Value of Post-therapy Whole Body Scintigraphy in Predicting the Need for Subsequent Radioactive Iodine Therapy in Patients with Well-differentiated Thyroid Carcinoma

Jerry M. Obaldo[1,2] and Ruben V. Ogbac[1,2]

[1]*Radioisotope Laboratory, Philippine General Hospital*
[2]*Section of Nuclear Medicine, Department of Medicine, College of Medicine and Philippine General Hospital, University of the Philippines Manila*

ABSTRACT

Introduction: Patients with well-differentiated thyroid carcinoma (WDTC) may require more than one session of radioactive iodine therapy (RAIT). This study was conducted to determine if post-therapy whole body scintigraphy (PTWBS) can identify patients who will require repeat RAIT due to persistent disease.

Method: The records of patients with WDTC who were referred to the Philippine General Hospital for RAIT from 2005-2007 were reviewed in this retrospective cohort study. PTWBS results (number of remnants, area of remnants, and presence of metastasis) of patients who had repeat RAIT (based on laboratory and clinical evidence of persistent disease) were compared with those of patients who did not have repeat RAIT. Multiple logistic regression analysis was done.

Results: Forty-five of 99 patients in the study [45%, 95% Confidence Interval (CI): 35 – 55] had repeat RAIT. Thirty-six of 38 patients (95%) with metastases on PTWBS required repeat RAIT, while only 9 of 61 patients (15%) with no scan evidence of metastases required subsequent therapy. Controlling for age group (age≥57), the odds ratio was 102 (95% CI: 20 – 507). Using the model to predict repeat RAIT, the sensitivity was 80 (95% CI: 68-92); specificity was 94 (95% CI: 85 – 99). Positive and negative predictive values were 95 and 85% respectively. The same results were obtained using metastases alone as a predictor. Twenty-six patients had extra-cervical metastases by PTWBS and all required repeat RAIT. The number and aggregate size of thyroid remnants by PTWBS, however, were not found to be predictive of the need for repeat therapy.

Conclusion: The presence of functioning metastases seen on PTWBS was highly predictive of the need for repeat RAIT.

Keywords: radionuclide imaging, thyroid carcinoma, thyroid cancer, radioactive iodine, radioisotope therapy, nuclear medicine

Introduction

Treatment of well-differentiated thyroid carcinoma currently consists of total or near-total thyroidectomy followed by radioactive iodine therapy (RAIT) to remove remnant tissues.[1-8] However, a substantial proportion of patients undergoing RAIT will require repeat treatments to completely ablate residual or metastatic disease. Ablation success rates range from 43 – 90% in patients with localized disease,[9-13] depending on the dose and method of determining persistent disease. A meta-analysis performed by Hackshaw showed an approximately 79% ablation rate from the pooled studies, therefore, as much as 21% of patients may need repeat treatment. Higher activities of I-131 were associated with better success rates than lower activities.[14] Recent studies have shown that patients with metastases may have even lower ablation success rates. In one series, only 35% of patients with lymph node metastases became disease-free even after repeat RAIT,[15] while another study found that those with distant metastases rarely had complete eradication of the disease.[16]

Predicting which patients may require further RAIT is important since successful ablation is associated with better prognosis.[17] Both disease-free survival and thyroid cancer-related mortality are better in patients with completely ablated thyroid glands. Patients with recurrent disease have been found to have poorer prognosis and may require more aggressive treatment.[18]

A number of laboratory parameters have been studied in an attempt to predict who will need further treatment. Serum thyroglobulin and thyroid stimulating hormone (TSH) levels at the time of first RAIT, and their relationships, have been studied most commonly.[19-22] Generally, the level of serum thyroglobulin (a measure of tumor burden) correlated positively with persistence or recurrence after RAIT. Serum TSH levels were used to correct for suppression of serum thyroglobulin release. One study also correlated serum thyroglobulin and TSH with radioactive iodine (I-131) uptake and found that the parameter Tg/(TSH x 24-h I-131 uptake), predicted recurrence of disease better than other laboratory findings alone.[23] The histopathological findings were likewise used in conjunction with laboratory parameters such as thyroglobulin in order to further improve prognostic value.[24]

Serum thyroglobulin and radioactive iodine uptake are not routinely performed prior to the first session of RAIT, primarily because of cost considerations; therefore the above parameters are not readily available. On the other hand, whole body scintigraphy is now regularly performed after RAIT. Post-therapy whole body scintigraphy (PTWBS) is used to document uptake of the therapy dose by remnants and to check for metastasis. A number of investigators have shown that PTWBS can demonstrate lesions not visible in a pre-therapy WBS using diagnostic doses (usually 2-5 mCi) of I-131.[25-30]

The results of the PTWBS are usually discussed with the patient soon after RAIT, and prior to a long delay in follow-up of up to three to six months. The immediate post-RAIT period would therefore be a good time to determine prognosis and direct subsequent management. We propose that the PTWBS

Corresponding author: Jerry M. Obaldo, MD
Radioisotope Laboratory
Philippine General Hospital
Taft Avenue, Manila, 1000 Philippines
Telephone: +632 524-5133
Email: jerryobaldo@yahoo.com

may have prognostic value in terms of the need for additional sessions of RAIT. A review of the literature showed that there are insufficient studies on this topic. This study was therefore conducted to determine if PTWBS can identify patients with well-differentiated thyroid carcinoma who have undergone total or near total thyroidectomy and high dose RAIT, who will require repeat RAIT due to persistent disease.

Specific Objectives

1. To determine the percentage of patients who needed repeat RAIT
2. To determine the association of the following PTWBS findings with repeat RAIT:
    a. Number of remnants
    b. Area of remnants
    c. Presence and location of metastasis, if any

Methods

Research Design

This is a retrospective cohort study.

Patients

Records of consecutive patients referred to the Radioisotope Laboratory of the Philippine General Hospital for RAIT from 2005 to 2007, were reviewed. They were included in the study if they fulfilled the following criteria:

1. Patients with well-differentiated (papillary, papillary/follicular variant, or follicular) thyroid cancer who have undergone total or near total thyroidectomy;
2. Patients who have had RAIT (at least 3.7 GBq or 100 mCi);
3. Patients who have had whole body scanning three to seven days after RAIT;
4. Followed-up for at least 12 months after the first RAIT or had repeat RAIT within 12 months

Patients with no uptake on post-therapy WBS after the second RAIT session were excluded since this indicates a lack of persistent functioning thyroid tissue amenable to RAIT. This is to eliminate those patients with spuriously elevated thyroglobulin levels and those with thyroglobulin-forming, but non-iodine-concentrating tumors.

Data Collection

Patients' records were reviewed and data were obtained for the following:

Initial Therapy

All patients underwent total or near-total thyroidectomy by experienced surgeons. Neck dissection was performed together with total thyroidectomy in 20 patients. At least four weeks after surgery, radioactive iodine (I-131) was administered orally with the patient in a hypothyroid state. The I-131 activity used was based on a fixed protocol: 3.7 GBq (100 mCi) for localized disease (n = 63), 5.5 GBq (150 mCi) for patients with cervical lymph node metastases (n = 32), and 7.4 GBq (200 mCi) in those with known distant metastases (n = 4). Between surgery and RAIT, thyroid hormone therapy was withheld and iodine intake was reduced. Sodium iodide I-131 capsules were supplied by a single company (Assurance Controls Technologies).

Post-therapy whole body scintigraphy (PTWBS)

PTWBS was done between three and seven days after RAIT administration, when the patient's radiation exposure rate, one meter from the umbilicus, was below 2.5 mR/hr as measured by a properly calibrated survey meter.[31]

Whole body images were obtained using a commercially available gamma camera (Siemens Medical) equipped with a high-energy collimator. Standard quality assurance procedures were performed prior to use. Body scans were acquired using a continuous speed of 20 cm/min. Spot views of the neck (20 minute acquisitions with a pinhole collimator or high-energy parallel hole collimator) were likewise obtained to resolve lesions better, and to determine lesion dimensions. The number and aggregate area dimensions (in cm^2) of functioning remnants, as well as presence and location of local and distant metastases, were recorded. All images were analyzed by one experienced nuclear physician.

Follow-up examination

Patients were asked to return for follow-up clinical and laboratory examination every three to six months. They underwent at least one of the following tests: serum thyroglobulin, cervical ultrasound, chest x-ray, or whole body I-131 scan to determine the presence of persistent disease requiring repeat RAIT. Thyroid hormone was withdrawn in most cases about one month prior to serum thyroglobulin determination.

Patients were classified into the following two groups:

Group 1 – subsequently underwent repeat RAIT due to: a serum thyroglobulin level of at least 2 ng/ml while on thyroid hormone therapy, or at least 10 ng/ml off thyroid hormone therapy; functioning remnant or metastasis on 74 – 185 MBq (2 – 5 mCi) pre-therapy whole body I-131 scan performed at least six months after RAI therapy; palpable remnant or metastasis; positive chest x-ray or cervical ultrasound.

Group 2 – followed up for at least 12 months after RAIT; and has no indication for repeat RAIT for persistent disease based on clinical examination, serum thyroglobulin, cervical ultrasound, chest x-ray or whole body I-131 scan.

Patients who underwent repeat RAIT were usually given 5.5 – 7.4 GB (150 – 200 mCi) of I-131, and likewise had PTWBS.

Statistical analysis

The percentage of patients with repeat RAIT was estimated at a 95% confidence level. The association of PTWBS findings after first RAIT (number of remnants, aggregate area of remnants in cm^2, and presence and location of metastases) with repeat RAIT was determined by estimating the crude odds ratio at a 95% confidence interval.

The following variables related to repeat RAIT were studied, mainly as confounders: age at first RAIT, sex, extent of surgery, histopathology, TNM stage, presence and location of palpable metastases, and activity of I-131 used during first RAIT.

Quantitative data were described using means, standard deviations and the minimum and maximum values. Qualitative data were described by frequency distributions. Tests of differences among populations were done using the t-test (for quantitative data) and χ^2-test (for qualitative data). Level of significance was 0.05, 2-tailed.

To determine the value of PTWBS after initial RAIT in determining prognosis (repeat RAIT), controlling for the other factors cited above as confounders, multiple logistic regression analysis was done. The Stata 10 statistical package was used.

Results

A total of 99 patients were included based on the inclusion and exclusion criteria. Characteristics of, and treatment received by these patients are summarized in Table 1. Forty-five patients required repeat RAIT (45: 95% CI: 35% - 56%). Gender ratio and histopathological findings were comparable in both groups. The patients who received repeat RAIT (Group 1) were, on average, 6 years older, and had more advanced disease. As a result of the latter, Group 1 patients in general had more extensive surgery and received higher activities of iodine-131 during initial RAIT (Mean 5.1 GBq ± 1.1 SD(137 ± 31 mCi) versus Mean 3.9 ± 0.6 SD GBq (106 ± 17 mCi), p-value < 0.001). Most patients (64%) in Group 1 received 5.5 GBq (150 mCi) or more of I-131, while only 13% of Group 2 patients received 5.5 GBq (150 mCi) or more. Neck dissection was performed in 31% of Group 1 patients while only 11% of Group 2 patients had neck dissection. The decision to perform repeat RAIT was made primarily due to a positive pre-therapy diagnostic WBS using 74 – 185 MBq (2 – 5 mCi) of I-131 in five patients, a palpable metastasis in three patients, chest x-ray evidence of metastasis in one patient, and serum thyroglobulin level in the other 36 patients.

Table 1. Patient characteristics and initial treatment

	Group 1 (with repeat RAIT)	Group 2 (without repeat RAIT)	Crude Odds Ratio or Difference Between Means (95% Confidence Interval)
	n = 45	n = 54	
Sex, number (%)			
Female	35 (77.8)	46 (85.2)	0.61 (0.19-1.92)
Male	10 (22.2)	8 (14.8)	
Age, years			
Mean	45.3	39.1	6.2 (0.8 – 11.6)
Standard Dev.	13.9	12.9	
Min-Max	21-72	17-70	
Age, number (%)			
≥57	12 (26.7)	5 (9.3)	3.6 (1.1 – 11.1)
<57	33 (73.3)	49 (90.7)	
Palpable metastasis			5.5 (1.95 – 16.3)*
Extracervical	6 (13.3)	0	
Cervical	16 (35.6)	8 (14.8)	
None	23 (51.1)	46 (85.2)	
Histopathology			
Papillary/Follicular variant	5 (11.1)	8 (14.8)	0.80 (0.14-4.49)
Papillary	33 (73.3)	37 (68.5)	1.15 (0.34-4.06)
Follicular	7 (15.6)	9 (16.7)	
TNM Stage			
4	9 (20.0)	0	12.9 (2.3 – 127.1)*
3	1 (2.2)	2 (3.7)	
2	16 (35.6)	3 (5.6)	13.7 (3.3 – 79.2)
1	19 (42.2)	49 (90.7)	
Extent of surgery			
Neck dissection	14 (31.1)	6 (11.1)	7.8 (1.3 – 56.4)
Total thyroidectomy	28 (62.2)	38 (70.4)	
Near total thyroidectomy	3 (6.7)	10 (18.5)	2.4 (0.56 – 15.0)
I-131 activity (first RAIT)			
7.4 GB (200 mCi)	4 (8.9)	0	12.2 (4.1 – 38.5)*
5.5 GB (150 mCi)	25 (5.6)	7 (13.0)	
3.7 GB (100 mCi)	16 (35.6)	47 (87.0)	

*TNM Stage 3 and 4 were combined; I-131 activity 150 and 200 combined; extracervical and cervical combined

Table 2 shows the results of analysis of PTWBS findings. The number of remnant lesions seen was not significantly different between Groups 1 and 2, with the group requiring repeat RAIT having a slightly higher mean number of lesions. The aggregate sizes of the lesions were likewise similar in both groups (about 10 – 11 cm^2).

The presence of metastasis on PTWBS was strongly associated with the need for repeat RAIT. Thirty-six of 38 (95%) patients with metastases on PTWBS required repeat RAIT, and of these only 25 had metastases clinically. Only 9 of 61 (15%) patients with no evidence of metastases by scanning needed subsequent therapy. Twenty-one of 23 patients with cervical metastases on PTWBS required repeat RAIT. Twenty-six patients had extracervical metastases on PTWBS (only six had clinical evidence of extracervical metastases), and all required repeat RAIT.

Table 2. Results of Post-Therapy Whole Body Scintigraphy (PTWBS)

	Repeat RAIT		
	Group 1 With repeat RAIT	Group 2 No repeat RAIT	Crude Odds Ratio or Difference between means [95% Confidence Interval]
	n = 45	n = 54	
Number of remnant lesions on PTWBS			
Mean	1.9	2.0	0.07 (-0.34 to 0.47)
SD	1.1	0.9	
Min-Max	1-6	1-6	
Aggregate area of lesions on PTWBS (square cm)			
Mean	10.2	11.6	1.4 (-0.85 to 3.7)
SD	6.3	5.2	
Min-Max	2-26	2-23	
Metastases on PTWBS			
Both extracervical and neck	11 (24.4)	0	104 (19.6-958.2)*
Extracervical	15 (33.3)	0	
Neck	10 (22.2)	2 (3.7)	
None	9 (20.0)	52 (96.3)	

*compares metastasis versus no metastasis

Multiple logistic regression analysis was done to determine the association of PTWBS findings with repeat RAIT, controlling for the other patient variables as confounders. Table 3 shows the full model (Model 1) with all three PTWBS components (area and number of remnants, and presence of metastasis) and confounders included.

This model, however, did not have a good fit (Hosmer-Lemeshow Goodness-of-Fit test was statistically significant, p-value=0.024). Furthermore, some of the odds ratio estimates (especially the odds ratio for metastases) in the model were very imprecise indicating over-fitting.

Table 3. Results of multiple logistic regression to determine the association of PTWBS findings with repeat RAIT -- full model [all the 3 PTWBS components and confounders were included] -- Model 1

Patient Attribute	Adjusted Odds Ratio	95% Confidence Interval	
		Lower Limit	Upper Limit
PTWBS Results after first RAIT			
No. of Remnants	2.41	0.98	5.94
Area of Remnants (square cm)	1.19	1.01	1.40
Metastasis Present	487.54	29.52	8053.16
Confounders			
Age, years	1.02	0.93	1.13
Sex, Female	0.78	0.10	5.89
Surgery [reference is near total]			
Total	7.05	0.07	750.07
Total with Neck	11.21	0.08	1562.76
Histopathology [reference is follicular]			
Papillary	3.73	0.14	99.24
Papillary-Follicular	3.68	0.08	172.30
TNM Stage [reference is stage 1]			
Stage 2	0.94	0.03	27.13
Stage 3 or 4	0.98	0.02	47.09
Palpable Mass	11.35	0.58	223.42
I-131 Activity 150-200 [Reference is 100]	5.66	0.73	43.78

Table 4. Results of multiple logistic regression to determine the association of PTWBS findings with repeat RAIT -- reduced model [only the 3 PTWBS components included] -- Model 2

PTWBS Findings	Adjusted Odds Ratio	95% Confidence Interval	
		Lower Limit	Upper Limit
No. of Remnants	1.91	0.99	3.66
Area of Remnants	1.08	0.96	1.21
Metastasis Present	294.66	38.88	2233.07

To improve the fit and the clinical utility of the model, a reduced model (Model 2) containing only the PTWBS findings was derived. Table 4 shows the results.

This model had a very good fit (Hosmer-Lemeshow Goodness-of-Fit test was not statistically significant, p-value=0.99). However, the adjusted odds ratio for presence of any metastasis is still very imprecise.

Using Model 2, the probability of repeat RAIT can be calculated by the following equation:

$$\textit{Probability (Repeat RAIT)} = \frac{6}{1+e^{-(-4.29+646\,(\text{No. of remnants})+0.074\,(\text{Area of remnants})+5.686\,(\text{Metastasis present}))}}$$

A value of 1 is entered in the equation if metastasis is present, and 0 if there is no metastasis, by PTWBS. This model was used to classify the patients as those needing RAIT (predicted probability >=0.50) and those not (predicted probabilities < 0.50) and the results obtained are summarized in Table 5.

To further improve the clinical utility, another model incorporating only "Age" and "Presence of metastasis by PTWBS" was likewise derived (Model 3). Information for age is readily available and when patients were grouped according to age≥ 57 and < 57, crude analysis showed a statistically significant odds ratio of 3.6. Table 6 shows the results.

Table 5. Results of applying the derived equation for Model 2 on the patient data, and association with the need for repeat RAIT.

	Repeat RAIT		
Classification based on Model 2	Yes	No	Total
+ [Predicted Probability>=0.50]	37	3	40
-[Predicted Probability<0.50]	8	51	59
Total	45	54	99

The odds ratio of the presence of metastasis on PTWBS, controlling for age, was more precise. The model had a good fit (Hosmer-Lemeshow Goodness-of-Fit test was not statistically significant with p-value=0.60).

Table 6. Results of multiple logistic regression to determine the association of PTWBS findings with repeat RAIT -- reduced model [only Age and Presence of Metastasis on PTWBS] -- Model 3

Parameter	Adjusted Odds Ratio	95% Confidence Interval	
		Lower Limit	Upper Limit
Age ≥57	3.20	0.61	16.92
Presence of Metastasis on PTWBS	101.71	20.39	507.34

Table 7 shows results of applying Model 3 on the patient data, and association with the need for repeat RAIT. Thirty-six of 38 patients (95%) predicted by the model to require repeat RAIT subsequently underwent repeat RAIT, while 52 of 61 patients (85%) predicted by the model do not require repeat RAIT did not need subsequent therapy.

Table 7. Results of applying the Model 3 on the patient data, and association with the need for repeat RAIT.

	Repeat RAIT		
Classification based on Model 3	Yes	No	Total
+ [Predicted Probability>=0.50]	36	2	38
-[Predicted Probability<0.50]	9	52	61
Total	45	54	99

The utility of selected clinical and PTWBS findings (one at a time), as well as Models 2 and 3 derived from multiple logistic regression analysis, in predicting repeat RAIT were compared by determining their accuracies, sensitivities, specificities and predictive values (Table 8). The highest accuracy (88.9%) was obtained using either the presence of metastases on PTWBS as criterion, or Models 2 or 3. The other PTWBS parameters: number of remnants (at least two), and aggregate remnant size (at least 10 cm^2), had poor accuracy of 45.5% and 41.4%, respectively.

Discussion

The ability to identify which patients may require further RAIT is important because these patients are likely to have poorer prognosis and may need more aggressive

Table 8. Summary of clinical and post-therapy scan parameters with their accuracy in predicting the need for repeat radioactive iodine therapy taken one at a time, compared with Models 2 and 3 of the multiple logistic regression analysis

Parameter	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy	Positive Predictive Value	Negative Predictive Value
Age 57 years or more	26.7%	90.7%	61.6%	70.6%	59.8%
TNM Stage 2 or greater	57.8%	90.7%	75.8%	83.9%	72.1%
Palpable metastasis	48.9%	85.2%	68.7%	73.3%	66.7%
Any metastasis by PTWBS	80.0% (65.4 – 90.4)	96.3% (87.2 – 99.5)	88.9%	94.7%	85.2%
At least 2 remnants by PTWBS	60.0%	33.3%	45.5%	42.9%	50.0%
Remnant size of at least 10 cm2 by PTWBS	57.8%	27.8%	41.4%	40.0%	44.1%
Multiple logistic regression analysis (Model 2)	82.2% (67.9 -92.00)	94.4% (84.6 – 98.8)	88.9%	92.5%	86.4%
Multiple logistic regression analysis (Model 3)	80.0% (65.4 – 90.4)	96.3% (87.2 – 99.5)	88.9%	94.7%	85.2%

management.[17,18] Clinical parameters may not be sufficient to accurately predict those patients needing repeat radioiodine treatment. Investigators have been attempting to use laboratory findings to help identify patients with poor prognosis with varying success.[19-24]

Post-therapy WBS is potentially an ideal test for prognostication since this is currently done routinely in almost all medical centers in the Philippines. The results of the scan can be discussed with the patient soon after RAIT so that subsequent management over the next several months can be planned immediately.

This study investigated the potential of the following PTWBS components in predicting repeat RAIT: presence and location of metastasis, number of remnants, and aggregate area of the remnants.

Crude analysis shows that the number of remnants and the aggregate areal remnant dimensions are very similar for both groups. However, when adjusted for confounders (Model 1 – full model), the odds of repeat RAIT more than doubles (adjusted OR=2.41) with one more additional remnant on PTWBS. Likewise, for the aggregate area, the odds of repeat RAIT are increased by 0.2 for every cm^2 increase (adjusted OR 1.20). Similar results were obtained in Model 2. These finding were however, not statistically significant. The most important predictor is the presence of metastasis both on crude and adjusted analysis. The odds of patients with any metastasis subsequently requiring repeat RAIT was 104 times more than those of patients without metastasis. The adjusted odds ratio was even higher at 488. The estimate however is very imprecise suggesting overfitting (fitting a logistic regression model with too many predictors and confounders using a small data set). Simpler models were fitted and presence of metastases remains an important predictor.

Location of metastases is also important in prognosis. Ninety one and 100 percent of patients with cervical and extra-cervical metastases needed repeat therapy, respectively. The demonstration of metastasis alone had a positive predictive value of 95%. The corollary finding is also useful, with absence of metastasis having a negative predictive value for repeat therapy of 85%.

Our findings that metastases were associated with persistent disease were generally comparable with published results. Verburg et al. followed up patients presenting with lymph node metastases for a median follow-up of 84 months. Using thyroglobulin and iodine-131 scanning as parameters, 65% of patients were never free of detectable disease. If the initial treatment does not result in a disease-free status, chances are low that additional treatment will succeed in achieving it.[15] Sampson and co-workers studied differentiated thyroid cancer patients with distant metastases and found that only 16% were disease-free after repeated therapy and prolonged follow-up.[16] The three-year survival rate for patients with lung metastasis only was 77%, and for those with bone metastasis, only 56%. Lin et al. studied 119 patients with nodal metastases, and reported that 22% had persistent disease after RAIT.[32] Similarly, Beasley and others reviewed their experience with 118 patients with well-differentiated thyroid carcinoma who present with neck node metastases outside the central compartment of the neck, specifically to the lateral neck and mediastinum. They found that these patients have an approximately six-fold risk of developing recurrences after total thyroidectomy and routine postoperative iodine-131 ablation.[33] Using clinical parameters, another study in children and adolescents by Borson-Chazot et al. found that the presence of palpable cervical lymph nodes at diagnosis was a predictive factor of recurrence regardless of the extent of the initial surgery.[34]

Vassilopoulou-Sellin et al. found that distant or extranodal metastases do not concentrate radioactive iodine as well as localized disease. They are therefore expected to require further therapy and to have poorer prognosis.[18] Increasingly, surgery is being recognized as necessary to eradicate metastatic disease as neither repeated radioiodine therapy nor external beam radiotherapy result in cure in some patients.[35] Inadequate surgical management of cervical lymphadenopathy has been shown to be associated with locoregional recurrence.[36,37] Bone metastases are particularly poor responders to the usual doses of radioiodine and may require other approaches such as surgery and external beam radiation therapy.[38]

The reason why metastases tend to respond poorly to radioiodine is not clear, although reduced vascularity or the development of radioresistant subclones have been proposed. Also, the observation that radioiodine uptake decreases with the patient's age suggests an accumulation of biochemical defects in tumors arising in older patients.[38]

The role of the other scan parameters should be studied further. While patients in both groups had very similar values, adjusted analyses show trends. Some patients with multiple and/or large remnants in the thyroid bed responded completely with one session of radioiodine therapy. The need for repeat treatment was essentially due to persistent metastases, rather than remnants. This may be because most of the remnants were quite small. Also, areal dimensions may be misleading because these are planar measurements and may not reflect actual volume or mass of remnant tissues. Regardless of the possible reasons, the results bode well for the effectiveness of RAIT in patients with localized disease.

Aside from being inherently a more important predictor of repeat RAIT compared to age, stage or other clinical parameters, PTWBS had additional prognostic value based on its ability to uncover unknown metastasis.[25] For instance, for the predictor extracervical metastases (a strong predictor of RAIT), in this study only six patients were positive clinically but PTWBS was able to demonstrate the condition in 20 more patients (Figure 1). Overall, only 25 patients had clinical evidence of metastasis, and PTWBS identified an additional 13 patients, for a total of 38 patients with metastases. Of these, 36 required repeat RAIT. Table 8 summarizes the accuracy of the various parameters studied, demonstrating the value of PTWBS.

The results of multiple logistic regression analysis using all variables produced a model with a poor fit. This is probably due to the small sample size relative to the number of variables in the model. The model incorporating only the PTWBS findings (Model 2) had a good fit but the accuracy was only similar to that of using the presence of metastasis alone as parameter. The association of metastases with subsequent need for repeat RAIT was much stronger than the other parameters; thus, the contribution of areal dimension and number of remnants to the calculated probability was minimal. Age and presence of metastases on PTWBS were shown to be significantly different between those requiring repeat RAIT from the group that did not. Another model (Model 3), incorporating only age and presence of metastases on scan was derived. This model, however, still showed accuracy only similar to the presence of metastasis alone, and similar to Model 2.

Therefore, simply using the finding of metastasis on PTWBS had high accuracy for identifying patients who will need repeat RAIT, without the mathematical complexity of calculating the actual probability using the models. Furthermore, multiple logistic regression analysis models like those above need to be validated against a new set of patients before it can be recommended.

Some limitations have to be noted 1) Due to the small sample size the multiple logistic regression analysis including the potential confounders had a very poor fit and simple models have to be generated; 2) Patients who did not follow-up for at least 12 months were excluded in this study. Interpretation of the results of this study should take into account this subset of patients who were lost-to-follow up within the first year after RAIT; 3) Being a retrospective cohort, this study relied on the accuracy of recorded data. A prospective cohort study involving more patients is recommended to further investigate the role of the number and aggregate size of remnants as well as the other potential predictors of repeat RAIT.

Figure 1. Patient with no clinical metastases but with scan evidence of metastases to fronto-parietal and left humerus after first radioactive iodine therapy.

Conclusions and Recommendations

While the role of the number and aggregate size of remnants on PTWBS in predicting the need for repeat RAIT have to be further investigated, the presence of functioning metastases was found to be a very strong predictor of repeat RAIT among cases of well-differentiated thyroid carcinoma. PTWBS was also able to demonstrate additional metastases (particularly extra-cervical metastases, which are strongly associated with the need for repeat RAIT) not detected clinically. We propose that the PTWBS should be performed routinely to guide subsequent management of patients with differentiated thyroid cancer.

Acknowledgment
The authors wish to thank Professor Cynthia P. Cordero. Her invaluable contributions in the statistical analysis and manuscript editing were instrumental in shaping the paper into its final form.

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