A Quantitative Evaluation of Hepatic Uptake on I-131 Whole-Body Scintigraphy for Postablative Therapy of Thyroid Carcinoma

Michihiro Nakayama, MD, PhD, Atsutaka Okizaki, MD, PhD, Miki Sakaguchi, RT, PhM, Shunta Ishitoya, MD, PhD, Takahiro Uno, RT, Junichi Sato, RT, and Koji Takahashi, MD, PhD

Abstract: This study aimed to determine clinical association between quantitative hepatic uptake on postablative whole-body scan (WBS) with differentiated thyroid cancer (DTC) prognosis.

We analyzed 541 scans of 216 DTC patients who were divided into 3 groups based on radioactive iodine (I-131) WBS uptake and clinical follow-up: group 1 (completion of ablation), group 2 (abnormal uptake in the cervical region), and group 3 (abnormal uptake with distant metastases). For each group, we calculated the ratio of I-131 WBS hepatic uptake (H) to cranial uptake as background (B); this ratio was defined as H/B. Furthermore, we made a distinction between group 1, as having completed radioactive iodine therapy (RIT) (CR), and group 2 and 3, as requiring subsequent RIT (RR).

The average H/B scores were 1.34 (median, 1.36; range 1.00–2.1) for group 1; 1.89 (median, 1.75; range 1.41–4.20) for group 2; and 2.09 (median, 1.90; range 1.50–4.32) for group 3. Bonferroni multiple comparisons revealed significant differences in H/B among these groups. The H/B of group 1 was significantly smaller than that of other 2 groups (P < 0.0001). The precise cutoff value of H/B for therapeutic effect was ≤1.5. Moreover, 159 of 160 scans in the CR and 375 of 381 patients in the RR were correctly diagnosed using this cutoff value in the final outcome of RIT. Furthermore, we found that hepatic uptake on post-RIT scans appears as discrete lesions. 11 Organoiodine compounds are metabolized by the liver; therefore, hepatic uptake on post-RIT scan suggests the presence of organic iodine.12–15 Some authors considered diffuse hepatic uptake to be a sign of treatment benefit; however, others reported it to be a nonspecific finding.6–8 It is unclear whether the iodinated proteins observed are derived solely from thyroid tissue. Therefore, this study aimed to investigate whether the quantitative evaluation of hepatic uptake is associated with disease progression in DTC patients.

MATERIALS AND METHODS

Study Population

This was a retrospective review. Data were collected from the records of consecutive DTC patients at our hospital between April 2004 and January 2014. Exclusion criteria were as follows: missing biochemical and/or imaging parameters, presence of liver metastases, and/or abnormal liver function and/or follow-up of <6 months. All patients had primarily undergone total thyroidectomy and received I-131 ablation with a mean activity of 5.3 GBq (range 3.70–5.55 GBq) after the withdrawal of hormone therapy for at least 2 weeks. After the RIT, every patient was taken care of as an outpatient.

The study patients were classified into 3 groups by the visual assessment of I-131 WBS: group 1 = completion of ablation; group 2 = abnormal uptake of cervical region, including thyroid bed; and group 3 = that of metastasis, as independently rated by 2 experienced nuclear physicians. Representative cases are shown in Figure 1. A patient was considered to have completed ablation if thyroglobulin did not increase for at least 6 months of follow-up and if there were no imaging studies or clinical findings consistent with persistent or...
recurrent disease. Furthermore, we made a distinction between the groups by defining group 1 as those who completed RIT (CR) and groups 2 and 3 as those who required subsequent RIT (RR).

**Image Analysis**

WBS was performed 4 days after I-131 administration. An anterior planar projection was acquired using dual-head gamma cameras (Millennium VG, GE Medical System, Tokyo, Japan) equipped with high-energy medium-sensitivity collimators. Scan velocity was 15 cm/min. A matrix size of 256 × 1024 pixels and a symmetric window of 20% centered on a 364 keV photopeak were used for all acquisitions.

In the WBS anterior view, region of interests (ROIs) were set on the liver and on the cranial region to minimize individual variations caused by bone marrow and soft tissue on the background. The hepatic uptake ratio (H/B) was calculated using the following formula: H/B = (maximum hepatic uptake counts)/(maximum background counts). ROIs for the liver and background were defined manually by 2 experienced nuclear physicians and 1 radiology technician on the basis of a visual boundary. H/B was evaluated in blinded fashion and was calculated as the average of each value determined by those 3 experts. CT images were reviewed to facilitate ROI determination.

**Statistical Analysis**

Data analysis was conducted using statistical software (XLSTAT2014, Addinsoft, Paris, France). Measurements for the same lesion from these 3 readers were averaged and the mean values were used for further analyses. Differences in H/B were assessed by the Kruskal–Wallis test. Bonferroni multiple comparison was used to identify groups that were different from the others.

Differences in H/B between CR and RR were analyzed using the Wilcoxon signed-rank test. Receiver operating characteristic (ROC) curve was derived using the H/B of CR and RR. The sensitivity, specificity, and positive and negative predictive values were determined from the optimal cutoff values using the ROC curve. P values < 0.05 were considered statistically significant.

**Ethics**

Informed consent on secondary use of clinical information for research was obtained from all patients who participated in the study. This study was retrospective, and the data were analyzed anonymously; therefore, ethics committee approval was deemed unnecessary at our institution.

**RESULTS**

**Patient Characteristics**

During the analysis period, a total of 615 WBS were performed after treatment with I-131 for DTC. In this study,

**TABLE 1. Characteristics of Patients in Each Group Who Underwent I-131 WBS After RIT for DTC (N = 541)**

| Characteristics                  | Group 1 | Group 2 | Group 3 |
|----------------------------------|---------|---------|---------|
| Age at diagnosis (y), mean (range) | 61.0 (22–83) | 57.0 (19–82) | 68.0 (31–87) |
| Gender (female/male)             | 108/52  | 146/78  | 102/55  |
| Histology (total)                | 160  | 224  | 157  |
| Papillary thyroid carcinoma      | 155  | 216  | 145  |
| Follicular thyroid carcinoma     | 5  | 8  | 12  |
| TNM stage                        |         |         |         |
| I                                | 15  | 27  | 0  |
| II                               | 5  | 18  | 0  |
| III                              | 39  | 51  | 0  |
| IV A/B/C                         | 67/5/29 | 117/11/0 | 0/0/157 |
| I-131 dose (average ± standard deviation) | 144.9 ± 6.8 | 143.4 ± 11.8 | 143.3 ± 13.2 |

Group 1 = completion of ablation, Group 2 = abnormal uptake in the cervical region, including thyroid bed, and Group 3 = abnormal uptake with distant metastases. DTC = differentiated thyroid cancer, I-131 = radioactive iodine, RIT = radioactive iodine therapy, WBS = whole-body scan.
541 scans of 216 patients were included. Demographic data, histological types, and tumor-node-metastasis (TNM) classification are shown in Table 1. Pathological classification of thyroid tumors was according to the TNM version 7 (2009).19

**Hepatic Uptake Ratio and Clinical Outcome**

The average H/B scores were 1.34 (median, 1.36; range 1.00–2.1) for group 1; 1.89 (median, 1.75; range 1.41–4.20) for group 2; and 2.09 (median, 1.90; range 1.50–4.32) for group 3. There were significant differences in H/B among these 3 groups \( P < 0.0001 \) and \( P < 0.00003 \). The H/B of group 2 was significantly greater than that of the other 2 groups \( P < 0.00001 \); the average H/B score of RR was 1.97 (median, 1.80; range 1.41–4.32), and that of CR was the same as that of group 1. There was a significant difference between CR and RR \( P < 0.00001 \). The box plots are shown in Figure 2 and Figure 3.

**ROC Analysis**

Detailed results from the final outcome of RIT are presented in Table 2. The precise cutoff value of H/B for therapeutic effect was \( \leq 1.5 \) (Figure 4). Moreover, 159 of 160 scans in the CR and 375 of 381 patients in the RR were correctly diagnosed using this cutoff value, yielding a sensitivity of 99.4%, specificity of 98.4%, positive predictive value of 96.4%, and negative predictive value of 99.7%. The area under the curve of H/B was 0.991.

**DISCUSSION**

DTC patients are evaluated by chest radiography, ultrasound, CT, I-131 WBS, and thyroglobulin concentration after total thyroidectomy. Post-RIT WBS provides the physician with important information, including the presence of metastatic disease and iodine avidity of residual thyroid tissue.20 As an extremely useful marker of metastasis and relapse, the concentration of serum thyroglobulin, which is synthesized by thyroid follicular cells, is widely used for tumor evaluation after total thyroidectomy for DTC. However, coexistent serum thyroglobulin autoantibodies (TgAb), which were reported in 7.5% to 25% of DTC patients,21–26 can underestimate thyroglobulin measurement by immunometric assays.27–30 Furthermore, Albert and Puliafito31 reported false-positive results of thyroglobulin tests. H/B may have limited clinical significance, but might be found to be clinically valuable when the patients have TgAb.

Iodine does not normally concentrate in the liver.19 The majority of thyroid hormones in the thyroid gland and plasma are levothyroxine. Most levothyroxine is converted to triiodothyronine,32 a more metabolically more active form, by deiodination in liver, skeletal muscle, kidney, brain, and other

| Cutoff Value H/B | Disease Positive | Disease Negative | Total |
|------------------|------------------|------------------|-------|
| Positive \( \leq 1.5 \) | True positive 159 | False positive 6 | 165 PPV 96.4% (159/165) |
| Negative          | False negative 1 | True negative 375 | 376 NPV 99.7% (375/376) |
| Total             | 160 sensitivity 99.4% (159/160) | 381 specificity 98.4% (375/381) | 541 accuracy 98.7% (534/541) |

CR = completed radioactive iodine therapy, H/B = hepatic uptake ratio, NPV = negative predictive value, PPV = positive predictive value, RR = required subsequent radioactive iodine therapy.
tissues, whereas the rest is conjugated with sulfate and glucuronic acid in the liver, excreted in bile, and partially hydrolyzed in the bowel. This could be a possible reason that diffuse hepatic uptake of radioiodine is frequently observed in WBS.33 Studies of physiologic radioiodine uptake in the liver are shown in Table 3. Some authors have reported diffuse hepatic uptake on I-131 WBSs.9,10,16,17,33–36 Chung et al16 found that I-131-labeled thyroglobulin was related to hepatic uptake, and that the presence of thyroid remnants, metastatic DTC lesions, which is in agreement with our current hypothesis. Furthermore, Jun et al9 reported that the hepatic uptake of radioiodine is frequently observed in WBS.33 A more recent study conducted by Lee et al10 revealed no correlation of hepatic uptake with thyroid remnant, and presence of distant metastatic foci. However, by visual score, the criteria used to determine the presence of hepatic uptake often depended on the physicians’ personal experience; therefore, the results are variable. Some studies indicated a correlation between liver uptake and I-131 dose16,17,37; however, no relationship with the dose administered to each group was observed in our study. However, H/B may have an advantage of not being dependent on dose and test date because it can normalize hepatic uptake by background.

In this study, we quantitatively evaluated hepatic uptake on I-131 WBS after RIT. H/B was associated with disease progression; moreover, if H/B fell below a certain level, DTC patients may have an extremely low risk for cancer recurrence. The area under the curve of H/B was 0.991 that led to high sensitivity and specificity. H/B and residual thyroid tissue or metastases were found to be associated, and this was likely the mechanism for diffuse hepatic uptake.

Maximum hepatic uptake was positively correlated with both liver volume and radioactivity per unit volume.38,39 Furthermore, the maximum value would probably not be affected by the digestive tract even if ROI settings were incomplete because I-131 intrahepatic distribution was relatively uniform.12,17,31

This study had several limitations. First, selection bias is inevitable because the present study is a retrospective single-center study. Second, the follow-up period of our study was relatively short. Third, because it was a single-center study, the number of subjects was relatively small, despite the fact that the data were collected from a 10-year period. As our institution is still performing RIT, a study with more patients and longer follow-up period can still be carried out in the future. Fourth, the occasional high uptakes from perspiration and/or intestinal tracts rendered difficult quantitative evaluations, necessitating patients to take a shower and/or use laxatives before the scan. Fifth, the cutoff value was based on data collected at our institution alone, and the value of H/B may have varied according to the imaging system used. We intend to address these issues by conducting similar comparisons at multiple institutions. Finally, in general, this assessment was performed three-dimensionally; therefore, the effects of absorptive scattering correction and liver morphology may have been ignored. However, even if such errors were overlooked, it appears to be an extremely easy to use index with sufficiently demonstrated results. In future, we plan to investigate on a hepatic uptake method that can be used for a more accurate quantitative evaluation.

### Table 3. Review of Diffuse Hepatic Uptake of Radioiodine

| Reference         | Incidence of Hepatic Visualization | Dose mCi (GBq), Scanning Time | Correlation With Residual or Metastatic Thyroid Tissue |
|-------------------|-----------------------------------|------------------------------|------------------------------------------------------|
| Zissmann et al (1987)17 | 74.7% (14/19)                     | 30–200 (1.1–7.4), 3–7 d      | Yes                                                  |
| Rosenbaum et al (1988)13 | 52.2% (15/29)                    | 80–150 (3.0–5.6), 7 d        | Not always                                           |
| Chung et al (1997)16  | 72.0% (580/806)                  | 30–200 (1.1–7.4), 3–5 d      | Yes                                                  |
| Ömür et al (2009)8   | 96.5% (863/894)                  | 75–200 (2.8–7.4), 6–13 d     | No                                                   |
| Ferris et al (2013)11 | 37.0% (20/54)                    | Not assessed, 6–8 d          | Yes                                                  |
| Lee et al (2015)10   | 33.4% (73/219)                   | 100–200 (3.7–7.4), 3 d       | No                                                   |
| Jun et al (2015)9    | 48.9% (23/47)                    | 30–200 (1.1–7.4), 5–8 d      | Yes                                                  |
CONCLUSIONS

Increased hepatic uptake on I-131 WBS may predict disease progression. In clinical practice, patients are usually taken off current treatment if they have disease progression/recurrence. When patients who received RIT were considered disease progression, they may select other treatment such as molecular targeted therapy. Thyroglobulin concentration cannot be used to determine treatment response in patients who are TgAb positive. In such a case, H/B might be presented to help us determine whether disease progression was observed or not.

REFERENCES

1. American Cancer Society. Cancer Facts & Figures 2014. Atlanta: American Cancer Society; 2014:21–22.
2. Carvalho MR, Ferreira TC, Leite V. Evaluation of whole-body retention of iodine-131 (131I) after postoperative remnant ablation for differentiated thyroid carcinoma—thyroxine withdrawal versus rhTSH administration: a retrospective comparison. Oncol Lett. 2012;3:617–620.
3. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med. 1994;97:418–428.
4. Utiger RD. Follow-up of patients with thyroid carcinoma. N Engl J Med. 1997;337:928–930.
5. Ozata M, Suzuki S, Miyamoto T, et al. Serum thyroglobulin in the follow-up of patients with treated differentiated thyroid cancer. J Clin Endocrinol Metab. 1994;79:98–105.
6. Tatar FA, Morita E, Ituarte PH, et al. Association between residual thyroid carcinoma and diffuse hepatic uptake of 131I following radioiodine ablation in postoperative total thyroidectomy patients. World J Surg. 2001;25:718–722.
7. Rosenbaum RC, Johnston GS, Valente WA. Frequency of hepatic visualization during I-131 imaging for metastatic thyroid carcinoma. Clin Nucl Med. 1988;13:657–660.
8. Ömür O, Akgün A, Ozcan Z, et al. Clinical implications of diffuse hepatic uptake observed in postablative and post-therapeutic I-131 scans. Clin Nucl Med. 2009;34:11–14.
9. Jun S, Lee JJ, Park SH, et al. Prediction of treatment response to 131I therapy by diffuse hepatic uptake intensity at 24, 48, and 72 hours after the administration of recombinant human thyroid-stimulating hormone to normal volunteers. Ann Nucl Med. 2015; Epub ahead of print. DOI: 10.1007/s12149-015-0983-5.
10. Lee JW, Lee SM, Choi J. Clinical significance of diffuse hepatic uptake on post-therapeutic early and delayed (131I) scans in differentiated thyroid cancer: a preliminary report. Ann Nucl Med. 2015;29:190–197.
11. Ferris HA, Williams G, Parker JA, et al. Therapeutic implications of diffuse hepatic uptake following I-131 therapy for differentiated thyroid carcinoma. Endocr Pract. 2013;19:263–267.
12. Pochin EE. Profile counting: medical radioisotope scanning. In: Pochin EE, ed. Medical radioisotope scanning. Philadelphia, PA: JB Lippincott; 1991:1138–1165.
13. Pacini F, Mariotti S, Formica N, et al. Thyroid autoantibodies in thyroid cancer: incidence and relationship with tumor outcome. Acta Endocrinol. 1994;119:373–380.
14. Mariotti S, Barbesino G, Catulregi P, et al. Assay of thyroglobulin in serum with thyroglobulin autoantibodies: an unobtainable goal? J Clin Endocrinol Metab. 1995;80:468–472.
15. Spencer CA, Takeuchi M, Kazarosyan M, et al. Serum thyroglobulin autoantibodies: prevalence, influence on serum thyroglobulin measurement, and prognostic significance in patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab. 1998;83:1121–1127.
16. Chung JK, Lee YJ, Jeong JM, et al. Clinical significance of hepatic visualization on iodine-131 whole-body scan in patients with thyroid carcinoma. J Nucl Med. 1997;38:1191–1195.
17. Ziessman HA, Bahar H, Fahey FH, et al. Hepatic visualization on iodine-131 whole-body thyroid cancer scans. J Nucl Med. 1987:28:1408–1411.
18. McDougall IR. Whole-body scintigraphy with radioiodine-131. A comprehensive list of false-positives with some examples. Clin Nucl Med. 1995;20:869–875.
19. Greene FL, Gospodarowicz M, Wittekind C. American Joint Committee on Cancer (AJCC) Staging Manual. 7th ed. Philadelphia, PA: Springer; 2009.
20. Mazzaferri EL. Carcinoma of follicular epithelium: radioiodine and other treatment and outcomes. In: Braverman LE, Utiger RD, eds. The Thyroid. Philadelphia, PA: JB Lippincott; 1991:1138–1165.
21. Pacini F, Mariotti S, Formica N, et al. Thyroid autoantibodies in thyroid cancer: incidence and relationship with tumor outcome. Acta Endocrinol. 1994;119:373–380.
22. Mariotti S, Barbesino G, Catulregi P, et al. Assay of thyroglobulin in serum with thyroglobulin autoantibodies: an unobtainable goal? J Clin Endocrinol Metab. 1995;80:468–472.
23. Spencer CA, Takeuchi M, Kazarosyan M, et al. Serum thyroglobulin autoantibodies: prevalence, influence on serum thyroglobulin measurement, and prognostic significance in patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab. 1998;83:1121–1127.
24. Chiovato L, Latrofa F, Braverman LE, et al. Disappearance of humoral thyroid autoimmunity after complete removal of thyroid antigens. Ann Intern Med. 2003;139:346–351.
25. Kumar A, Shah DH, Shiriari U, et al. Significance of antithyroglobulin autoantibodies in differentiated thyroid carcinoma. Thyroid. 1994:4:199–202.
26. Rubello D, Casara D, Girelli ME, et al. Clinical meaning of circulating antithyroglobulin antibodies in differentiated thyroid cancer—a prospective-study. J Nucl Med. 1992;33:1478–1480.
27. Schlumberger MJ. Papillary and follicular thyroid carcinoma. N Engl J Med. 1998;338:297–306.
28. Whitley RJ, Ain KB. Thyroglobulin: a specific serum marker for the management of thyroid carcinoma. Clin Lab Med. 2004;24:29–47.
29. Pena S, Arum S, Cross M, et al. I-123 thyroid uptake and thyroid size at 24, 48, and 72 hours after the administration of recombinant human thyroid-stimulating hormone to normal volunteers. J Clin Endocrinol Metab. 2006;91:506–510.
30. Spencer C, Petrovic I, Fatemi S. Current thyroglobulin autoantibody (TgAb) assays often fail to detect interfering TgAb that can result in the reporting of falsely low/undetectable serum Tg IMA values for patients with differentiated thyroid cancer. J Clin Endocrinol Metab. 2011;96:1283–1291.
31. Albert DM, Puliafito CA. Hepatic visualization after iodine-131 in patients with thyroid carcinoma [Letter]. N Engl J Med. 1977;28:1408–1411.
32. Oppenheimer JH. Thyroid hormones in liver. Mayo Clin Proc. 1972;47:854–863.
33. Jong-Ryoo, Byeong-Cheo Ahn. False-positive uptake on radioiodine whole-body scan in patients with thyroid carcinoma. J Nucl Med. 1990;31:1575–1576.
36. Maayan ML, Eisenberg J, Lopez EM, et al. Hepatic visualization after iodine-131 in patients with thyroid carcinoma. *N Engl J Med.* 1976;295:1258–1270.

37. Ramos-Gabatin A, Philips WT, Ware RW, et al. Significance of diffuse hepatic uptake on radioiodine (I-131): diagnostic and post therapy total body scans (TBS) in patients with well differentiated thyroid cancer [abstract]. *J Nucl Med.* 1989;30:4Ab.

38. Macey DJ, DeNardo GL, DeNardo SJ. Planar gamma camera quantitation of 123I, 99 mTc or 111In in the liver and spleen of an abdominal phantom. *Cancer Biother Radiopharm.* 1999;14:299–306.

39. van Rensburg AJ, Lotter MG, Heyns AD, et al. An evaluation of four methods of 111In planar image quantification. *Med Phys.* 1988;15:853–861.