Original Article

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A Disease Progression Predictor by Quantitative Assessment of the Hepatic Accumulation on Postablative Iodine-131 Whole-Body Image in Differentiated Thyroid Cancer

Diferansiye Tiroid Kanserinde Postablatif İyot-131 Tüm Vücut Görüntüsünde Hepatik Birikiminin Kantitatif Değerlendirmesiyle Hastalık İlerlemesinin Tahmin Edilmesi

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Abstract

Objectives: A Iodine-131 (^{131}I) whole body scan (WBS) is performed to evaluate the treatment response after radioactive iodine (RAI) therapy. Despite the clinical relevance of RAI-refractory differentiated thyroid cancer, a consensus on its precise definition remains lacking.

This study investigates the potential utility of hepatic ^{131}I accumulation as an early predictor for tumor recurrence or progression after RAI administration.

Methods: Of 814 patients receiving care at our institution, we enrolled 225 patients who exhibited no accumulation of RAI in the remnant tissues or other lesions on ^{131}I WBS. We quantified the hepatic uptake ratio [defined as (hepatic uptake/background uptake (H/B)] from WBS. All patients were categorized into group A (H/B ≤1.5) and group B (H/B >1.5), and we assessed between-group differences. The Kaplan-Meier method and Log-rank test were used to analyze the progression-free survival (PFS). Using the Cox proportional hazards model, we identified independent prognostic factors from among the seven known prognostic factors, i.e., H/B, thyroglobulin, sex, age, stage, total ^{131}I dose, and final therapeutic dose.

Results: The 5-year and median PFS were 98.8% and 114.7 months in group A (n: 171) compared with 24.1% and 42.7% months in group B (n: 54), respectively. Group B showed a significant correlation with poor prognosis ($p<0.00001$). Of the seven prognostic factors, H/B exhibited the highest impact on patient outcomes (hazards ratio for recurrence/disease progression, 42.156; 95% confidence interval: 8.750-203.106).

Conclusion: Quantitative evaluation of hepatic uptake on ^{131}I WBS provides a marker that may help identify patients with differentiated thyroid cancer who are at a high risk of disease progression/recurrence immediately after RAI therapy.

Keywords: Radioactive iodine-refractory differentiated thyroid cancer, hepatic accumulation, radioactive iodine therapy, thyroglobulin, metabolically persistent disease

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Öz

Amaç: Radyoaktif iyot (RAİ) tedavisinden sonra tedaviye yanıtı değerlendirmek için İyot-131 (^{131}I) tüm vücut taraması (WBS) yapılır. RAİ-refrakter diferansiye tiroid kanseri klinik önemine rağmen, kesin tanımı konusunda bir fikir birliği henüz yoktur.

Bu çalışma, RAİ uygulamasından sonra tümör nüksü veya ilerlemesi için erken bir tahmin edici olarak hepatik ^{131}I birikiminin potansiyel faydasını araştırmaktadır.

Yöntem: Kurumumuzda tedavi gören 814 hastadan, ^{131}I WBS'de artık dokularda veya diğer lezyonlarda RAİ birikimi görülmeyen 225 hastayı çalışmaya dahil ettik. Hepatik alım oranını [(hepatik alım/arka plan alımı (H/B)] WBS'den nicelendirdik. Tüm hastaları grup A (H/B ≤1,5) ve grup B (H/B >1,5) olarak kategorize ettik ve gruplar arası farklılıkları değerlendirdik. Progresyonsuz sağkalımı (PFS) analiz etmek için Kaplan-Meier yöntemi ve Log-rank testi kullanıldı. Cox orantılı risk modelini kullanarak, bilinen yedi prognostik faktör arasından bağımsız prognostik faktörleri belirledik: H/B, tiroglobulin, cinsiyet, yaş, evre, toplam ^{131}I dozu ve son tedavi dozu.

Bulgular: Grup A'da (n: 171) 5 yıllık ve ortanca PFS sırasıyla %98,8 ve 114,7 ay iken, grup B'de (n: 54) sırasıyla %24,1 ve %42,7 ay idi. Grup B, kötü prognozla anlamlı bir korelasyon gösterdi (p<0,00001). Yedi prognostik faktör arasında H/B, hasta sonuçları üzerinde en yüksek etkiyi gösterdi (nüks/hastalığın ilerlemesi için risk oranı, 42,156; %95 güven aralığı: 8,750-203,106).

Sonuç: ^{131}I tüm vücut taramasında karaciğer tutulumunun kantitatif değerlendirmesi, RAİ tedavisinden hemen sonra hastalık ilerlemesi/nüksü riski yüksek olan diferansiye tiroid kanserli hastaların belirlenmesine yardımcı olabilecek bir belirteç sağlar.

Anahtar kelimeler: Radyoaktif iyota-dirençli diferansiye tiroid kanseri, karaciğer birikimi, radyoaktif iyot tedavisi, tiroglobulin, metabolik olarak kalıcı hastalık

Introduction

Thyroid cancer is the leading endocrine malignancy with a growing incidence in recent years (1,2). Total thyroidectomy is the gold standard for most patients with differentiated thyroid cancer (DTC) (3,4,5). Radioactive iodine (RAI) therapy is reportedly effective for patients with risk factors for recurrence (6,7). Patients who respond to RAI therapy exhibit excellent 10-year survival (92%) (8,9,10), compared with patients who do not respond to RAI therapy (10-year survival, 19%).

Although there is no standardized definition of radioactive iodine-refractory DTC (RR-DTC) at present, a general consensus exists that any patient with a known cancer lesion that does not display accumulation of RAI on Iodine-131 (^{131}I) whole body scan (WBS), or experiences growth of a lesion despite RAI uptake 6-12 months after RAI therapy, is considered RR-DTC (11,12,13,14). Until recently, limited effective treatment options were available for patients with RR-DTC besides suppression of thyroid-stimulating hormone. Presently, molecular-targeted therapy for RR-DTC is initiated in patients who exhibit disease progression within 12 months after diagnosis (15,16); however, such an approach may delay treatment.

The metabolism of organic iodine results in its hepatic uptake, which is captured on ^{131}I WBS and is also considered to show retention in thyrogenic cells. Previously, we reported that patients who exhibit positive results on ^{131}I WBS have a quantitatively high hepatic uptake/background uptake (H/B) (17). As the quantitative assessment of the hepatic uptake on ^{131}I WBS could reflect cancer status, we quantitatively assessed the hepatic uptake in patients who exhibited negative results on ^{131}I WBS, that is, those who had no clinically identified lesions that displayed ^{131}I uptake. This study intends to ascertain whether the risk of recurrence and disease progression can be predicted. Accordingly, the present study seeks to identify a hepatic uptake-based indicator on ^{131}I WBS for early assessment of the likelihood of disease progression or relapse following RAI administration.

Materials and Methods

Study Design

This study protocol adhered to the Declaration of Helsinki and was approved by the Asahikawa Medical University Research Ethics Committee (number: 15198, date: 09.03.2016). The requirement of informed consent was waived by the Ethics Committees because of the retrospective and non-invasive study design.

Study Population

Eight hundred fourteen consecutive patients were treated at our hospital. Two experienced nuclear medicine specialists independently evaluated that all patients enrolled in this study did not exhibit accumulation of RAI in the remnant tissues or other lesions on ^{131}I WBS after 4-day-treatment. Exclusion criteria based on previous studies (17) were inadequate biochemical and/or imaging parameters, presence of hepatic metastases and/or impaired liver function, or insufficient follow-up (<6 months). All patients had previously undergone total thyroidectomy, and were administered RAI therapy (3.70-5.55 GBq) following a minimum 2-week withdrawal from thyroid hormone replacement. Patients were considered to have completed ablation if they had no elevated thyroglobulin (Tg) levels

and no imaging or clinical evidence suggestive of persistent or recurrent disease during a follow-up period of at least 6 months.

Image Protocols

We acquired ^{131}I WBS images with a therapeutic radioactive dose 4 days after the RAI administration. Imaging was performed using a dual-head gamma camera with high-energy, medium-sensitivity collimators. The equipment used was Millennium VG (GE Medical Systems, Tokyo, Japan).

In the WBS, an anterior image was acquired at a speed of 15 cm/min, using a 256 1024 matrix and a 364-keV photopeak with a 20% window.

Region of Interest Setting and H/B Calculation

We set a region of interest (ROI) on the liver in the WBS anterior view. To reduce variability related to bone marrow activity among individuals, a background ROI was first positioned in the cranial region. Two board-certified nuclear medicine physicians then manually delineated the liver and background ROIs based on visual assessment. The H/B ratio defined as the hepatic accumulation divided by background accumulation was obtained from ^{131}I whole-body scintigraphy. The final H/B value was calculated as the mean of the two values independently determined by the blinded observers. Next, computed tomography images were also examined to support accurate ROI placement.

Previously, the receiver operating characteristic (ROC) curve was evaluated from the H/B values of the group that needed retreatment (abnormal accumulation in the neck and lung metastasis in ^{131}I WBS) and the group ascertained to not require retreatment; the optimal cut off value evaluated from the ROC curve was H/B $\leq$1.5, and the diagnostic ability of retreatment with this cut-off value was 99.4% sensitivity and 98.4% specificity (17). Thus, in this study, we evaluated the prognosis of RR-DTC by classifying patients, judged as accumulation-negative by ^{131}I WBS, based on the hepatic accumulation using this cut off value. We divided the study population into two groups based on our previous study: group A (H/B $\leq$1.5) and group B (H/B >1.5), and assessed between-group differences.

Statistical Analysis

In this study, we conducted statistical analyses using XLSTAT software (Addinsoft, Paris, France). We used the mean values of H/B for the analyses. Using the Kaplan-Meier method, we plotted the progression-free survival (PFS) curves. We then compared the groups using the Log-rank test to evaluate differences in survival outcomes. Additionally, the Cox proportional hazards model was used to determine independent prognostic factors among the already known factors (H/B, Tg, sex, age, stage, total ^{131}I dose, and final therapeutic dose). We considered $p<0.05$ as statistically significant.

Results

Of 814 patients treated at our institution during the study period, we enrolled 225 patients who tested negative for ^{131}I on WBS and were available for follow-up. An overview of patients' demographics, histologic subtypes, and tumor-node-metastasis (TNM) staging is presented in Table 1. A study using TNM version 8 (2017) pathological classification of thyroid tumors was performed (18). The median duration of follow-up was 114.7 months in group A [95% confidence interval (CI): 112.3-117.2] and 42.7 months in group B (95% CI: 31.9-53.5), as shown in Figure 1. The PFS rate at 5 years was 98.8% in group A compared to 24.1% in group B, with a statistically significant difference (Log-rank test, $p<0.00001$). Additionally, Tg, H/B, and age correlated with an increased hazard for the PFS. The analysis of the correlation between recurrence/disease progression and the seven prognostic factors using the Cox proportional hazards model revealed that H/B exhibited the highest impact on patient outcomes (hazard ratio: 42.156, 95% CI: 8.750-203.106; Table 2).

Table 1. The characteristics of the study population disaggregated by the study group (n: 225)

Characteristic	Group A (H/B ≤1.5)	Group B (H/B >1.5)
Gender		
Female	114	42
Male	57	12
Age (y)	58.9±14.1	61.9±13.2
Histological subtype		
Papillary thyroid cancer	166	53
Follicular thyroid cancer	5	1

Table 1. Continued		
Characteristic	**Group A (H/B ≤1.5)**	**Group B (H/B >1.5)**
TNM stage		
Stage 1	18	0
Stage 2	5	1
Stage 3	37	7
Stage 4A	74	23
Stage 4B	5	4
Stage 4C	32	19
Thyroglobulin (ng/mL)	83.5±191.6	231.5±286.5
Number of times of treatment	2.2±0.7	2.5±1.2
^{131}I dose in final RAI therapy (mCi)	142.8±15.5	144.8±8.8
TNM: Tumor, node, and metastasis, H/B: Hepatic uptake ratio, RAI: Radioactive iodine, ^{131}I: Iodine-131		

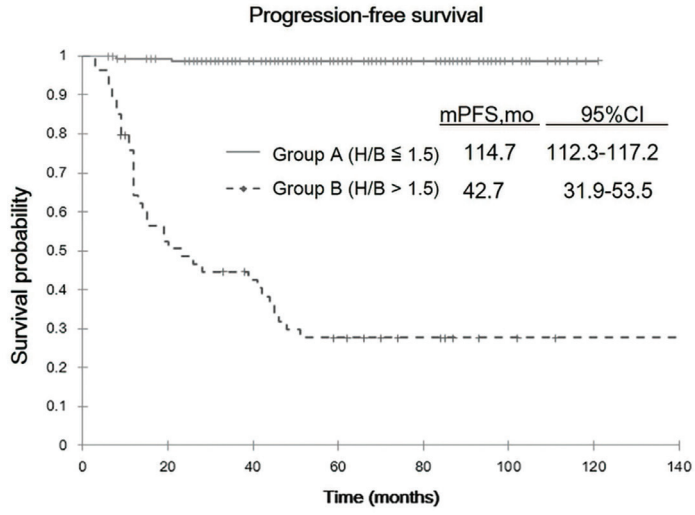

Figure 1. The Kaplan-Meier curves for the progression-free survival in groups A and B
CI: Confidence interval, H/B: Hepatic uptake ratio, mPFS: Mean progression-free survival

Table 2. The incidence of recurrence or metastases in relation to clinical, imaging, and biological variables						
Variable	**Regression coefficient**	**Standard error**	**p value**	**Hazard ratio**	**95% CI for hazard ratio**	
					Lower	**upper**
Tg: ≥35 ng/mL vs. <35 ng/mL	1.017	0.445	<0.03	2.765	1.157	6.610
H/B: >1.5 vs. ≤1.5	3.741	0.802	<0.0001	42.156	8.750	203.106
Female vs. male	0.204	0.410	N.S.	1.226	0.549	2.739
Age: >55 vs. ≤55	1.375	0.509	<0.01	3.954	1.458	10.724
Number of times of treatment: ≥4 (total 600 mCi) vs. <4	0.819	0.524	N.S.	2.269	0.812	6.342
Stage: 4C vs. 1-3, 4A and 4B	0.309	0.387	N.S.	1.362	0.638	2.908
^{131}I dose of final RAI therapy: 150 mCi vs. <50 mCi	0.320	0.356	N.S.	1.377	0.685	2.768
H/B: Hepatic uptake ratio, Tg: Thyroglobulin, CI: Confidence interval, RAI: Radioactive iodine, N.S.: Not significant, ^{131}I: Iodine-131						

Discussion

Recent developments in medical technology have facilitated a paradigm shift in the approach to cancer treatment; that is, a shift from individual decision making by physicians to a collaborative, multidisciplinary team approach. The treatment of thyroid cancer is no exception. With the advent of molecular-targeted drugs, patients with RR-DTC who previously had limited treatment options can now hope for better outcomes. The revised American Thyroid Association management guidelines (2015) highlight the significance of treatment response reclassification (19).

The SELECT and DECISION trials have already established the efficacy of molecular-targeted drugs; however, appropriate discretion should be exercised during the selection of candidate patients because of various potential adverse effects such as hypertension, hand-foot syndrome, and bleeding. Molecular-targeted drugs are suggested for advanced RR-DTC as well. The SELECT and DECISION trials defined RR-DTC as cancer progression (based on imaging findings and changes in serum levels of Tg and anti-Tg antibody) despite treatment with RAI at a cumulative dose of at least 22.2 GBq (600 mCi). The DECISION trial enrolled patients with RR-DTC who exhibited cancer progression within the past 14 months, whereas the SELECT trial enrolled those who presented cancer progression within the past 12 months (15-20).

Presently, there are no means available to estimate the prognosis of patients with RR-DTC, except close monitoring of their clinical course. Of note, not all patients with RR-DTC experience rapid deterioration; indeed, cancer progression is rather slow in many patients. Molecular-targeted therapy in such patients might be more harmful than beneficial. However, some patients have recurrent metastatic differentiated cancer that displays rapid progression and is eventually fatal. Hence, observation should be minimized before starting molecular-targeted drugs in these patients.

Per the American Thyroid Association guidelines, kinase inhibitor therapy should be considered for patients with RR-DTC who have metastatic, rapidly progressive, symptomatic, and/or imminently threatening disease not otherwise amenable to local control using other approaches (19). The National Comprehensive Cancer Network Guidelines (version 2.2015) recommend considering lenvatinib or sorafenib for progressive and/or symptomatic diseases with iodine-refractory metastases, except central nervous system metastases (21). Nevertheless, candidates should be comprehensively counseled on the risks and benefits of these therapies. Owing to the high frequency of adverse events, meticulous patient selection is imperative. Nonetheless, early detection and prompt intervention for RR-DTC are preferable due to the substantial therapeutic benefits of these agents (22).

The hepatic uptake on ^{131}I WBS might reflect the thyroid cancer status. Hepatic uptake on WBS occurs primarily due to the uptake of thyroxin, as organic iodine is typically metabolized in the liver, and inorganic iodine is eliminated from the kidneys via urine. Thus, the postoperative hepatic uptake on ^{131}I WBS for thyroid cancer is indicative of the possible presence of thyrogenic cells. In the literature, the reported efficacy of the hepatic uptake exhibited much variability, which was perhaps attributable to the visual assessment of the hepatic uptake. Following total thyroidectomy, any remaining thyroid tissue or DTC tissues are key sites for iodine metabolism. A hallmark of DTC is its ability to actively accumulate iodine for thyroid hormone synthesis (19).

Iodine metabolism begins with the transport of iodide from the bloodstream into thyroid follicular cells. This process, which occurs against both chemical and electrical gradients, is mediated by the sodium-iodide symporter located on the basolateral membrane of these cells (23). The second step involves the synthesis and secretion of Tg. Tg molecules contain approximately 140 tyrosine residues that act as precursors in thyroid hormone biosynthesis. In the next stage, iodide is enzymatically oxidised. Once inside the follicular cells, the iodide is transported towards the apical membrane and enters the follicular lumen. Iodination of the tyrosine residues on Tg occurs. The coupling of two diiodotyrosine (DIT) residues yields thyroxine (T4), while the combination of a monoiodotyrosine and a DIT yields triiodothyronine (T3). These hormones cross the basal membrane and enter the bloodstream. In the liver, T4 is rapidly converted to its active form, T3, by enzymatic deiodination. (24,25). This process is referred to as "radioactive iodide trapping" in the liver of RAI therapy-treated patients and is assumed to be a mechanism for hepatic accumulation (Figure 2).

Reportedly, the ^{131}I dose exhibits a positive correlation with the hepatic uptake grade (26,27,28,29). Typically, the radioiodine dose is determined according to the tumor, node, and metastasis stage. However, Jeon et al. (7) reported that patients with distant metastases who were administered 200 mCi exhibited low hepatic uptake, corroborating our findings. These findings indicate that elevated radioiodine dose does not directly correlate with higher hepatic uptake (30).

This study suggests that elevated H/B in patients who test negative on ^{131}I WBS designates the presence of organic iodine metabolized in the liver. The metabolic images of these patients might reflect the presence of a tumor (i.e.,

"metabolically persistent disease") (Figure 3). Although our study is single-center, the findings suggest that patients with elevated H/B tend to develop recurrence or disease progression during follow-up. Conversely, patients with low H/B do not experience disease progression, even if they have distant metastasis, perhaps, additional treatment is not needed in such patients.

The use of molecular-targeted drugs might not be practical in treatment-resistant patients, when they are asymptomatic. However, it is imperative to initiate treatment in a timely manner because the cancer is often quite advanced when symptoms manifest. Perhaps H/B could enable the identification of candidates for aggressive use of molecular-targeted drugs, especially when the selection of the optimal therapeutic option is not straightforward. Of note, no additional capital investment is needed, for the H/B assessment, because it can be ascertained with ^{131}I WBS, which is already used for assessing treatment efficacy. Hence, no physical or financial burden exists on patients. Perhaps clearly defining the H/B indications might decrease medical expenses in the future.

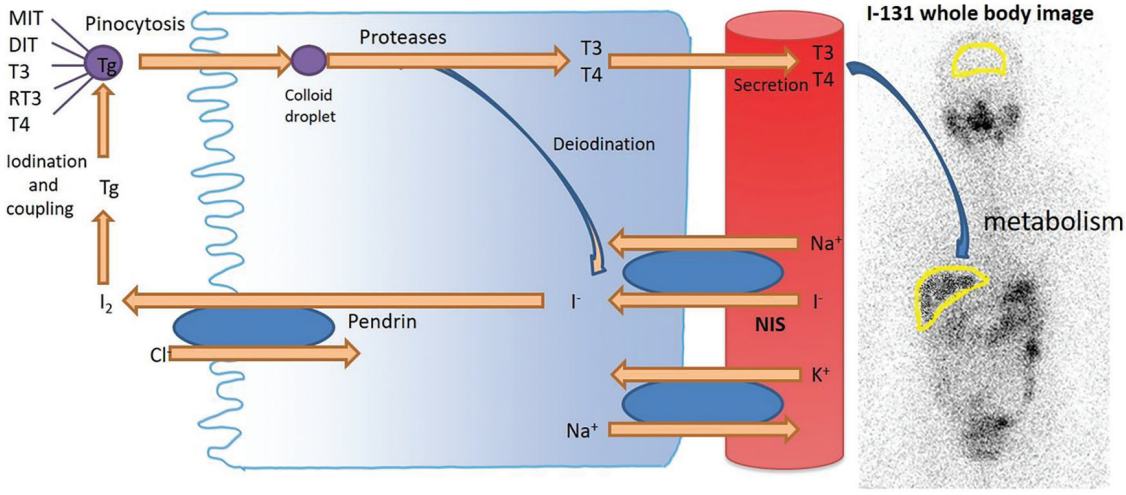

Figure 2. The thyroid hormone synthesis and the mechanism of liver accumulation in ^{131}I WBS
DIT: Diiodotyrosine, MIT: Monoiodotyrosine, NIS: Sodium iodide symporter, T3: Triiodothyronine, T4: Thyroxine, RT3: Reverse T3, WBC: Whole body scan

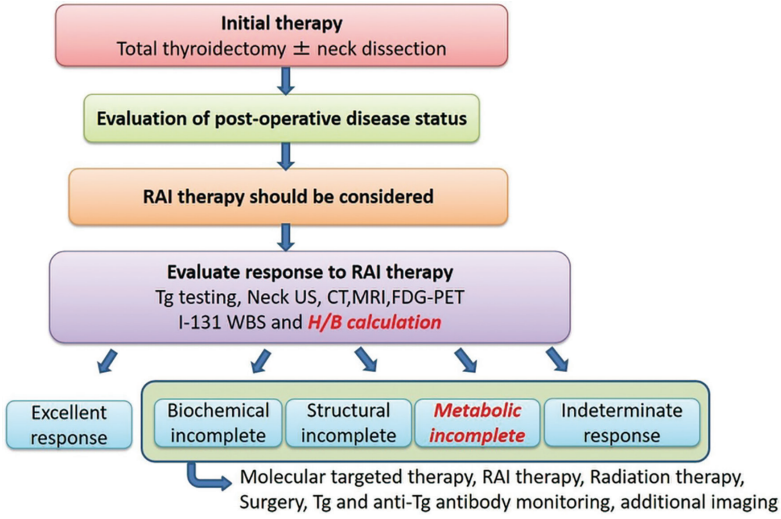

Figure 3. Clinical decision-making and management of patients with differentiated thyroid cancer after total thyroidectomy
CT: Computed tomography, FDG-PET: fluorodeoxyglucose positron emission tomography, H/B: Hepatic uptake ratio, MRI: Magnetic resonance imaging, US: Ultrasonography, RAI: Radioactive iodine, Tg: Thyroglobulin, WBS: Whole body scan, I-131: Iodine-131

Study Limitations

This study has several limitations. First, this is a single-center study. The optimized selection of the cut-off H/B could vary for each facility. Thus, it is essential to discuss and further clarify the optimized selection of the cut-off H/B. Additionally, it would be crucial to provide a recommended time window for ^{131}I WBS after RAI therapy, and discuss the potential impact of the time interval between ^{131}I WBS and RAI therapy on the results in multiple institutions. Hence, prospective research data from various institutions are warranted to validate the proposed idea.

Conclusion

In conclusion, this study suggests that H/B could be a useful marker that facilitates optimal treatment decision making and maximizes drug efficacy. Of note, H/B can be determined at various facilities by using the existing equipment. With the advent of molecular-targeted drugs, multidisciplinary healthcare teams comprising surgeons, medical oncologists, endocrinologists, and radiologists will be needed for thyroid cancer treatment. Furthermore, the use of H/B could help maximize the efficacy of molecular-targeted drugs, which are speculated to be used extensively in the near future, thereby further enhancing the outcomes in patients with thyroid cancer.

Ethics

Ethics Committee Approval: This study protocol adhered to the Declaration of Helsinki and was approved by the Asahikawa Medical University Research Ethics Committee (number: 15198, date: 09.03.2016).

Informed Consent: The requirement of informed consent was waived by the Ethics Committees because of the retrospective and non-invasive study design.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: M.N., K.N., S.K., Concept: M.N., K.N. Design: K.N. Data Collection or Processing: A.F., T.U., Analysis or Interpretation: S.K., I.Y., A.O., Literature Search: M.N., K.N., Writing: M.N.

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References

1. American Cancer Society. Cancer facts & figures 2025. Atlanta: American Cancer Society. 2025:24-25. Avaible from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2025/2025-cancer-facts-and-figures-acs.pdf
2. Burns WR, Zeiger MA. Differentiated thyroid cancer. Semin Oncol. 2010;37:557-566.
3. Carvalho MR, Ferreira TC, Leite V. Evaluation of whole-body retention of iodine-131 ((131)I) after postoperative remnant ablation for differentiated thyroid carcinoma - thyroxine withdrawal versus rhTSH administration: A retrospective comparison. Oncol Lett. 2012;3:617-620.
4. Rosenbaum MA, McHenry CR. Contemporary management of papillary carcinoma of the thyroid gland. Expert Rev Anticancer Ther. 2009;9:317-329.
5. Morrison SA, Suh H, Hodin RA. The surgical management of thyroid cancer. Rambam Maimonides Med J. 2014;5:e0008.
6. 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.
7. Jeon MJ, Kim WG, Choi YM, Kwon H, Lee YM, Sung TY, Yoon JH, Chung KW, Hong SJ, Kim TY, Shong YK, Song DE, Kim WB. Features predictive of distant metastasis in papillary thyroid microcarcinomas. Thyroid. 2016;26:161-168.
8. Durante C, Haddy N, Baudin E, Leboulleux S, Hartl D, Travagli JP, Caillou B, Ricard M, Lumbroso JD, De Vathaire F, Schlumberger M. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J Clin Endocrinol Metab. 2006;91:2892-2899.
9. Scott E, Learoyd D, Clifton-Bligh RJ. Therapeutic options in papillary thyroid carcinoma: current guidelines and future perspectives. Future Oncol. 2016;12:2603-2613.
10. Tuttle RM, Ball DW, Byrd D, Dilawari RA, Doherty GM, Duh QY, Ehya H, Farrar WB, Haddad RI, Kandeel F, Kloos RT, Kopp P, Lamonica DM, Loree TR, Lydiatt WM, McCaffrey JC, Olson JA Jr, Parks L, Ridge JA, Shah JP, Sherman SI, Sturgeon C, Waguespack SG, Wang TN, Wirth LJ. National Comprehensive Cancer Network. Thyroid carcinoma. J Natl Compr Canc Netw. 2010;8:1228-1274.
11. Robbins RJ, Wan Q, Grewal RK, Reibke R, Gonen M, Strauss HW, Tuttle RM, Drucker W, Larson SM. Real-time prognosis for metastatic thyroid carcinoma based on 2-[18F]fluoro-2-deoxy-D-glucose-positron emission tomography scanning. J Clin Endocrinol Metab. 2006;91:498-505.
12. Schlumberger M, Tubiana M, De Vathaire F, Hill C, Gardet P, Travagli JP, Fragu P, Lumbroso J, Caillou B, Parmentier C. Long-term results of treatment of 283 patients with lung and bone metastases from differentiated thyroid carcinoma. J Clin Endocrinol Metab. 1986;63:960-967.
13. Yen TC, Lin HD, Lee CH, Chang SL, Yeh SH. The role of technetium-99m sestamibi whole-body scans in diagnosing metastatic Hürthle cell carcinoma of the thyroid gland after total thyroidectomy: a comparison with iodine-131 and thallium-201 whole-body scans. Eur J Nucl Med. 1994;21:980-983.
14. Narayanan S, Colevas AD. Current standards in treatment of radioiodine refractory thyroid cancer. Curr Treat Options Oncol. 2016;17:30.
15. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, Habra MA, Newbold K, Shah MH, Hoff AO, Gianoukakis AG, Kiyota N, Taylor MH, Kim SB, Krzyzanowska MK, Dutcus CE, de las Heras B, Zhu J, Sherman SI. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med. 2015;372:621-630.
16. Faugeras L, Pirson AS, Donckier J, Michel L, Lemaire J, Vandervorst S, D'Hondt L. Refractory thyroid carcinoma: which systemic treatment to use? Ther Adv Med Oncol. 2018;10:1758834017752853.
17. Nakayama M, Okizaki A, Sakaguchi M, Ishitoya S, Uno T, Sato J, Takahashi K. A quantitative evaluation of hepatic uptake on I-131

whole-body scintigraphy for postablative therapy of thyroid carcinoma. Medicine (Baltimore). 2015;94:e1191.

18. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, Meyer L, Gress DM, Byrd DR, Winchester DP. The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017;67:93-99.
19. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 american thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the american thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016;26:1-133.
20. Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, de la Fouchardiere C, Pacini F, Paschke R, Shong YK, Sherman SI, Smit JW, Chung J, Kappeler C, Peña C, Molnár I, Schlumberger MJ; DECISION investigators. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet. 2014;384:319-328.
21. NCCN Clinical practice guidelines in oncology, thyroid carcinoma. 2015. Available from: https://pancan.org/facing-pancreatic-cancer/patient-services/nccn-guidelines/?gad_source=1&gad_campaignid=21995416780&gbraid=0AAAAD8O9VKyvXQarifK4YA-rcw8DUw5i&gclid=EAIaIQobChMI6qHBirvVjgMV7KSDBx17ygvbEAAYASAAEgIyyPD_BwE
22. Ito Y, Suzuki S, Ito K, Imai T, Okamoto T, Kitano H, Sugitani I, Sugino K, Tsutsui H, Hara H, Yoshida A, Shimizu K. Tyrosine-kinase inhibitors to treat radioiodine-refracted, metastatic, or recurred and progressive differentiated thyroid carcinoma [Review]. Endocr J. 2016;63:597-602..
23. Khurana I. Textbook of medical physiology. India: reed elsevier. Endocrinal System.2006;710-715.
24. Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR. Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. Endocr Rev. 2002;23:38-89.
25. Pal GK. Textbook of medical physiology. India: ahuja publishing house. Endocrine Physiology. 2007;3:346.
26. Ziessman HA, Bahar H, Fahey FH, Dubiansky V. Hepatic visualization on iodine-131 whole-body thyroid cancer scans. J Nucl Med. 1987;28:1408-1411.
27. Tatar FA, Morita E, Ituarte PH, Cavalieri RR, Duh QY, Price DC, Siperstein AE, Clark OH. 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.
28. Blum M. Hepatic visualization after 131I in patients with thyroid carcinoma. N Engl J Med. 1977;296:634.
29. Hung BT, Huang SH, Huang YE, Wang PW. Appropriate time for post-therapeutic I-131 whole body scan. Clin Nucl Med. 2009;34:339-342.
30. Kim K, Kim SJ, Kim IJ, Kim YK, Kim BS, Pak K. Clinical significance of diffuse hepatic visualization and thyroid bed uptake on post-ablative iodine-131 whole body scan in differentiated thyroid cancer. Onkologie. 2012;35:82-86.