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Review Article on Asian and Western Practice in Thyroid Pathology: Similarities and Differences

Radioactive iodine treatment of papillary thyroid carcinoma in Japan

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Abstract: We have a unique history of using radioactive iodine (RAI) therapy and surgical treatment for thyroid cancer in Japan. Less than total thyroidectomy without RAI therapy was the most common management of papillary thyroid carcinoma (PTC) in the past. Limited availability of dedicated facilities for the RAI administration due to the strict regulations and insufficient coverage of the expenses were the major reasons that impacted on the management decisions. Following the publication of the Japanese clinical practice guidelines for thyroid tumors in 2010, the risk-adapted approach has become a standard where the high-risk and selected intermediate-risk PTC patients undergo total thyroidectomy followed by RAI therapy and thyrotropin suppression therapy. We are on the shoulders of pioneers who made every effort to bring the interventions closer to an ideal environment for patients. Armed with the revised clinical practice guidelines 2018 and devised inpatient/outpatient RAI therapy, Japanese physicians are ready to proceed to more rational management that would improve patients' outcomes. Directions for the future include further advancement of relevant clinical research to fill the gaps between current evidence and recommendations in the guidelines, and obtaining approval for high-dose RAI therapy on an outpatient basis to improve its effectiveness in both adjuvant and treatment settings.

Keywords: Radioactive iodine (RAI); outpatient-based ablation; papillary thyroid carcinoma (PTC); risk classification; clinical practice guidelines

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Introduction

Radioactive iodine (RAI) therapy is one of the mainstays for managing patients with differentiated thyroid carcinoma (DTC) and has a definitive role in selected cases with distant metastases (1). However, the effectiveness of ablative or adjuvant RAI therapy for preventing oncologic events in surgically curable diseases has been controversial (2-4), and it has not been widely used in Japan (5-7). For example, only 1.5% of patients received RAI therapy for papillary thyroid carcinoma (PTC) in our department between 1981 and 1991, even though 35% of the cohort were deemed to have high-risk PTC (8). As Higashi *et al*. described, there are several reasons for this, including "radiophobia" among Japanese individuals, surgeons' belief in the effectiveness of less than total thyroidectomy (i.e., subtotal thyroidectomy or lobectomy) which precluded use of RAI, and limited availability of facilities for RAI therapy (7).

Availability of RAI therapy

In Japan, RAI therapy has not been readily provided in

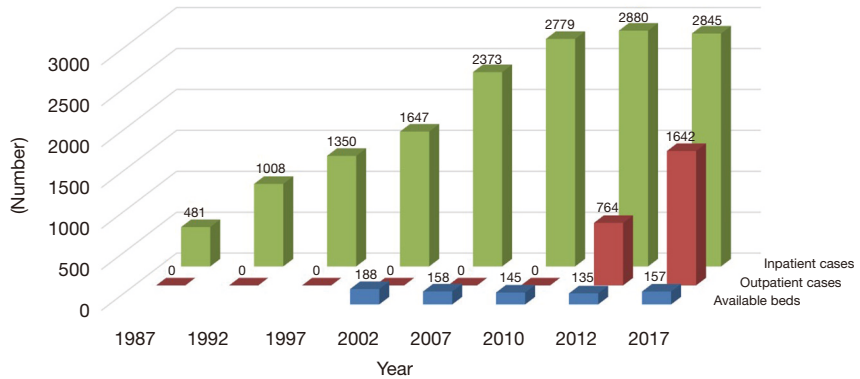


Figure 1 Time trends of the numbers of available beds, outpatient cases, and inpatient cases of RAI therapy for thyroid cancer.

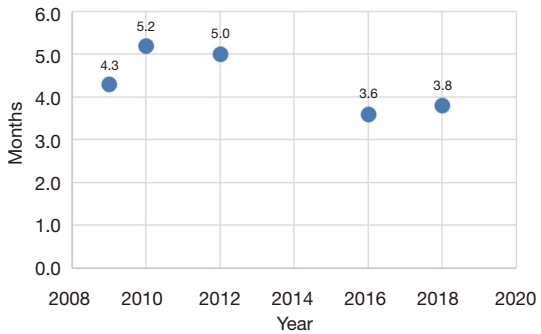


Figure 2 Average waiting time (months) to receive RAI therapy for thyroid cancer.

a timely manner to patients in need (6,7). Successive nationwide surveys on the status quo of RAI therapy for DTC in Japan have revealed that the number of beds dedicated to inpatient care has decreased. In contrast, the number of inpatient cases treated with RAI for adjuvant or therapeutic purposes has increased to nearly 3,000 during the past two decades (*Figure 1*) (9-14). There are two reasons for the decline in available beds (5-7). First, the Ministry of Health, Labour and Welfare of Japan has established fairly stringent and comprehensive regulations on the use of radioactive materials and release of patients following RAI therapy. Medical institutions have been spending a considerable amount to equip and maintain exclusive facilities, such as shield rooms, local air exhausters, filters, drainage, and waste disposal tanks, to observe the rules. However, the second reason is that the Japanese health insurance system does not fully reimburse the actual expenses. More than 90% of respondents in the nationwide survey felt that coverage was insufficient (12). Therefore, several hospitals had to abandon RAI therapy because of the financial load (7).

Another problem is that patients with recurrent disease have to wait for a long time to receive RAI therapy. Although the average waiting time decreased from 5.2 months in 2010 to 3.8 months in 2018, there is still room for improvement (*Figure 2*) (9-13). In fact, the distribution and availability of medical facilities vary across the country, and some patients have to wait for >9 months to receive treatment for their metastatic lesions (13). This observation posed serious concerns on the potential effects of such a long waiting period on the oncologic outcomes. Higashi *et al*. reported that delayed RAI therapy for metastatic DTC was significantly associated with poor disease-specific survival, and the hazard ratio of the interval from surgery to initial RAI therapy ≥180 days compared to that of <180 days was 4.22 (95% CI, 1.55–11.5) (15).

To overcome the potential harm caused by the shortage of dedicated facilities, Japanese experts initiated thyroid remnant ablation for DTC with a dose of 1,110 MBq of RAI in an outpatient clinic, following a pivotal study that examined the safety of the procedure. Kusakabe *et al*. of the Japanese Society of Nuclear Medicine concluded that outpatient-based ablation with 1,110 MBq of RAI after total thyroidectomy in patients with DTC was safe if applied under appropriate supervision and guidance by experts with specific qualifications (16). The number of patients treated with ablative RAI therapy in an outpatient basis increased from 764 in 2012 to 1,642 in 2017, according to the surveys (*Figure 1*) (14). In contrast, the number of inpatient cases remained at the same level, and the waiting time did not show a significant change (*Figures 1,2*). The need for RAI therapy for metastatic lesions can be expected to increase

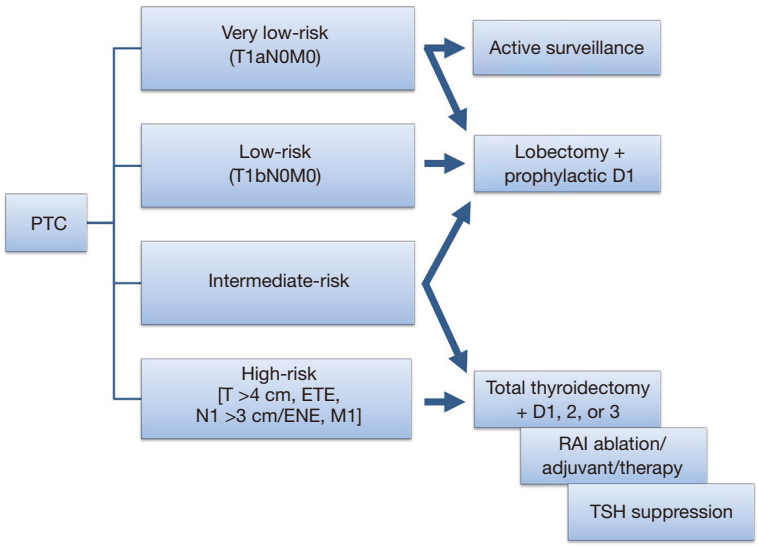


Figure 3 Flowchart of the initial management of PTC (the revised Japanese clinical practice guidelines for thyroid tumors) (20,21). PTC, papillary thyroid carcinoma; ETE, extrathyroidal extension; ENE, extranodal extension; D1, lymph node dissection of the central neck area; D2, lymph node dissection of the unilateral neck area; D3, lymph node dissection of the bilateral neck area.

because patients with PTC with high-risk features have sustained hazard of developing recurrence, even ≥10 years after initial treatment (8). Moreover, it is recommended that RAI therapy be performed first for unresectable progressive DTC, and molecular-targeted drugs are indicated only when the lesions are refractory to the treatment.

Clinical practice guidelines for thyroid cancer

Following the initial development of the clinical practice guidelines for thyroid tumors in 2010 (17-19), the Japan Association of Endocrine Surgeons (JAES) and the Japanese Society of Thyroid Surgeons (JSTS) revised the guidelines in 2018 (20,21). The guidelines set four risk categories as an initial assessment of PTC based on the pre- or intraoperative findings according to the UICC TNM classification (22): very low-risk PTC measuring ≤1 cm without any metastases (T1aN0M0); low-risk PTC measuring 1.1–2 cm without any metastases (T1bN0M0); high-risk PTC having at least one of the features including tumor size >4 cm, extrathyroidal extension or extranodal extension to adjacent structures except for the sternothyroid muscle, clinical node metastasis >3 cm, and M1; and intermediate-risk PTC, which indicates a tumor that does not meet any of the definitions for the very low-, low-, or high-risk categories (17-21). The guidelines are unique in that the management strategies are recommended according to the risk categories (*Figure 3*). Active surveillance without surgery can be an option for patients with very low-risk PTC, while lobectomy, along with prophylactic central node dissection, is a treatment of choice for very low- and low-risk PTC. Total thyroidectomy plus appropriate central/lateral lymph node dissection followed by RAI therapy and thyrotropin suppression therapy is recommended for high-risk PTC. For intermediate-risk PTC, sound judgment is required to determine the extent of thyroidectomy and lymph node dissection by considering each patient's characteristics and prognostic factors.

Considering the poor prognosis associated with high-risk PTC (8), Japanese experts reached a consensus that employing all available treatments would be necessary to reduce oncologic events. This recommendation must have been reflected in the rise of ablative RAI therapy on an outpatient basis during the past decade (*Figure 1*). However, so far, there is no substantial evidence to support the advantages of total thyroidectomy, ablative RAI therapy, and thyrotropin suppression therapy (21).

RAI therapy: definitions, goals, and evidence

The Japanese guidelines classify RAI therapy into three categories in line with those set by the latest guidelines developed by the American Thyroid Association (ATA) in 2015: ablation, adjuvant therapy, and treatment (*Figure 4*) (23).

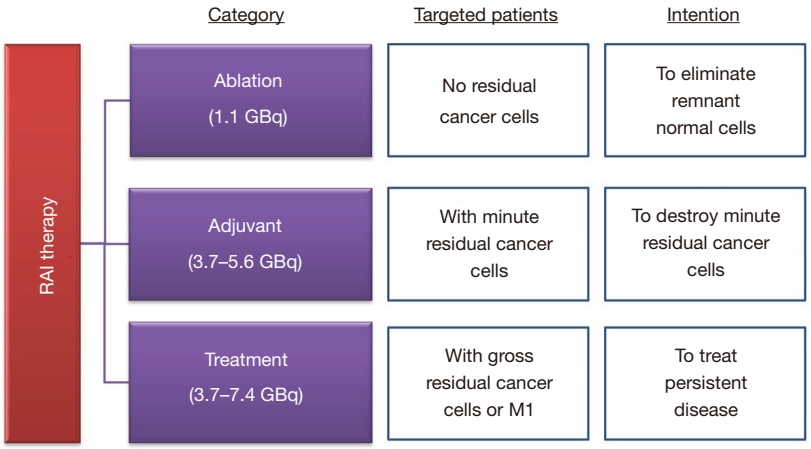


Figure 4 Category, targeted patients, and intention of RAI therapy (the revised Japanese clinical practice guidelines for thyroid tumors) (20,21).

Ablation aims to eliminate remnant normal follicular cells to facilitate the detection of recurrence by measuring thyroglobulin (Tg) levels. Adjuvant therapy is expected to improve recurrence-free and disease-specific survival by destroying microscopic residual cancer cells. RAI treatment is a therapy for a persistent disease that is not suitable for surgical therapy. Although the recommended dose of RAI for adjuvant therapy is 3,700–5,600 MBq (100–150 mCi), it is not attainable in Japan because the dedicated resources have been quite limited, as described above. Some patients who are candidates for adjuvant RAI therapy have been treated with 1,110 MBq (30 mCi) of RAI under "ablation."

Ablation

Recently, researchers from three institutions in Japan reported the efficacy of ablation using RAI 1,110 MBq (*Figure 5*) (24-26). Ablation success was achieved in 53% (95% CI, 38–68%) at Gunma University, 74% (95% CI, 61–83%) at Kyoto University, and 23% (95% CI, 15–33%) at Tokyo Women's Medical University. Several factors may explain the observed differences. The criteria in assessing a diagnostic whole-body scan (DxWBS) and the definitions of ablation success were different among the three reports. Particularly, Abe *et al*. used the most stringent definition for ablation success comprising of negative DxWBS and stimulated Tg level <2 ng/mL compared to that used by the other two studies (26). Study populations were also different in terms of the risk class of PTC. The proportion of patients with high-risk PTC was 23% at Gunma University, 34% at Kyoto University, and 45% at Tokyo Women's Medical University, whereas that of patients with low-risk PTC was 13%, 0%, and 0%, respectively. Furthermore, the investigators from Gunma and Kyoto University classified patients according to the ATA 2015 guidelines, while the authors at the Tokyo Women's Medical University referred to the Japanese 2018 guidelines. The two guidelines differ in some respects in defining the risk class for PTC (*Figure 6*). The Japanese classification is based on the pre- and intraoperative assessment, while the ATA classification uses pathological evaluation. For example, T3a (>4 cm) PTC without lymph node metastasis would be classified as high-risk based on the Japanese guidelines, but it would be classified as low-risk based on the ATA guidelines. In contrast, T1b PTC with more than five microscopic lymph node metastases would still be classified as low-risk in Japan, but it would be classified as intermediate-risk in the United States. Nonetheless, all three studies observed that the serum Tg level, either pretreatment or at the time of treatment, is associated with the success or failure of ablation (24-26).

Adjuvant therapy

Finding relevant studies showing evidence of effectiveness, harms, and patients' views were vital in formulating recommendations for RAI adjuvant therapy during the revision of the Japanese guidelines. However, the development encountered a few difficulties as follows (20,21): first, some studies included both PTC and FTC under the name "differentiated thyroid carcinoma (DTC)" in the study population. Moreover, the definitions of risk

	Gunma Univ. (n=47)	Kyoto Univ. (n=119)	Tokyo Women's Medical Univ. (n=119)
Female/male	34/13	80/39	74/45
Age (range)	Median 55 (25–79)	Median 54 (9–78)	Median 51 (24–76)
TgAb + ve	NA	14 (12%)	24 (20%)
Histopathology	PTC 47 (100%)	PTC 115 (97%) Others 4 (3%)	PTC 119 (100%)
PTC risk class	ATA 2015 guidelines: Low-risk 13 (28%) Intermediate-risk 23 (49%) High-risk 11 (23%)	ATA 2015 guidelines: Low-risk 0 (0%) Intermediate-risk 79 (66%) High-risk 40 (34%)	JPN 2018 guidelines: Low-risk 0 (0%) Intermediate-risk 65 (55%) High-risk 54 (45%)
Time from surgery to RAI	NA	NA	Median 122 days (35–840)
Ablation dose	1,110 MBq 47 (100%)	1,110 MBq 68 (57%) 2,960–3,700 MBq 51 (43%)	1,110 MBq 119 (100%)
Time from ablation to DxWBS	(6 months)		Median 261 days (148–560)
DxWBS dose	370 MBq 47 (100%)	370 MBq 119 (100%)	370 or 1,110 MBq 119 (100%)
DxWBS assessment	• No/faint uptake • Medium uptake • High uptake	• Negative scan: <0.1% uptake on the basis of the region-of-interest method	• Negative: negative ~ equivocal • Positive: probably ~ definitively positive
Ablation success	• Negative DxWBS and stimulated (TSH >30) Tg ≤5 ng/mL 25 (53%)	Negative DxWBS & *unstimulated* Tg <2.0 ng/mL • Low dose: 50 (74%) • High dose: 36 (71%)	a. Negative DxWBS 69 (58%) b. Stimulated (TSH >30) Tg <2.0 ng/mL 35 (37%)* c. a+b 22 (23%)*

Figure 5 Efficacy of ablation using 1,110 MBq in Japan. TgAb, anti-thyroglobulin antibody; PTC, papillary thyroid carcinoma; ATA, American Thyroid Association; JPN, Japanese; NA, not available; DxWBS, diagnostic whole-body scan; Tg, thyroglobulin.

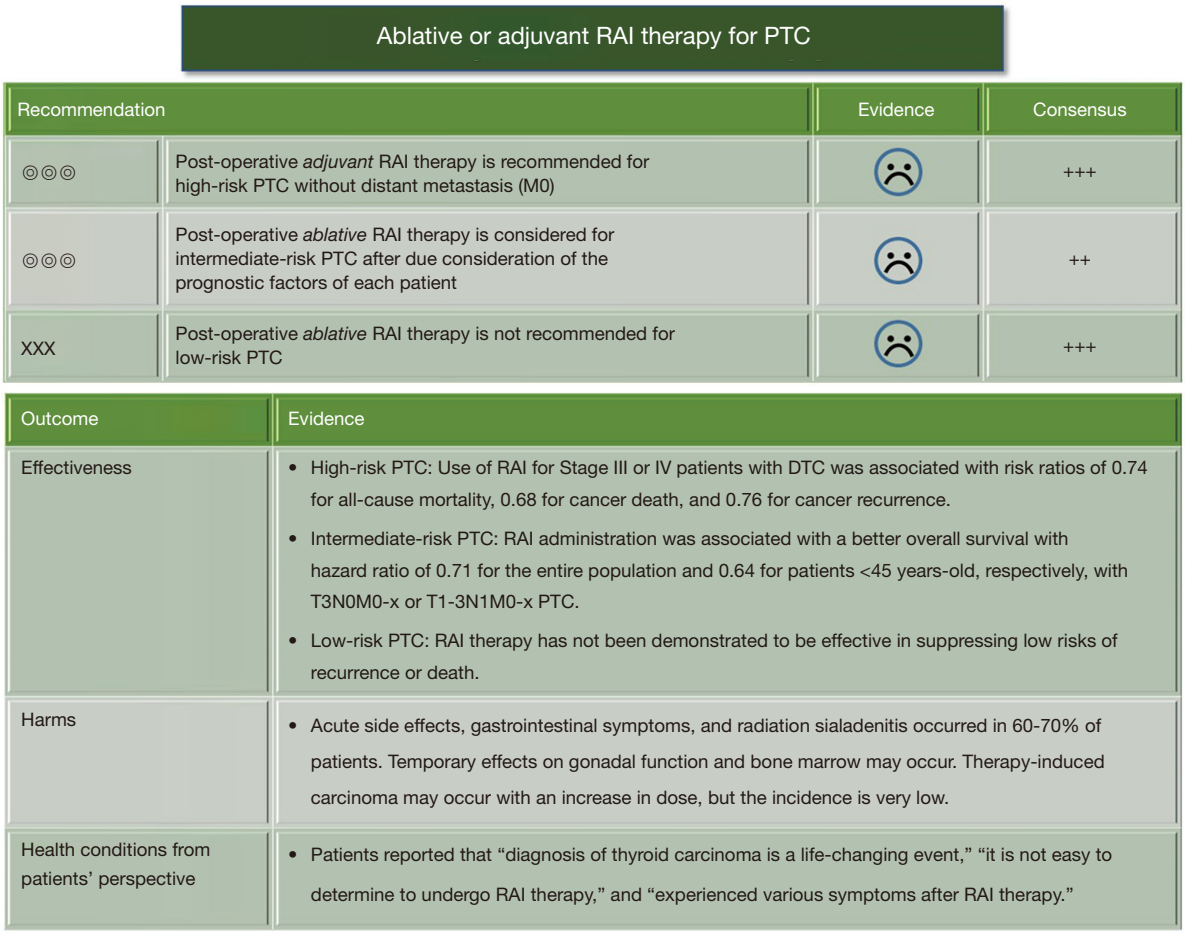
Risk classification of PTC (M0)

JPN 2018 GIs	cN0	cN1 (≤3 cm) & no ENE	cN1 (>3 cm) & ENE
T1a (≤1 cm)	Very low	Intermediate	High
T1b (1~2 cm)	Low	Intermediate	High
T2 (2<~4 cm)	Intermediate	Intermediate	High
T3a (>4 cm)	High	High	High
T4 (ETE)	High	High	High

ATA 2015 GLs	pN0	pN1 (≤5 mets)	pN1 (>5 mets)	pN1 (>3 cm)
No ETE	Low	Low	Intermediate*	High
Microscopic ETE	Intermediate*	Intermediate*	Intermediate*	High
Macroscopic ETE	High	High	High	High
Incomplete tumor resection	High	High	High	High

*intermediate-risk: also aggressive histology (tall cell, hobnail, columnar cell) or vascular invasion
ETE: extra-thyroidal extension

Figure 6 Risk classification of PTC. PTC, papillary thyroid carcinoma; ETE, extrathyroidal extension; ENE, extranodal extension.



Ablative or adjuvant RAI therapy for PTC

Recommendation		Evidence	Consensus
◎◎◎	Post-operative *adjuvant* RAI therapy is recommended for high-risk PTC without distant metastasis (M0)	☹	+++
◎◎◎	Post-operative *ablative* RAI therapy is considered for intermediate-risk PTC after due consideration of the prognostic factors of each patient	☹	++
XXX	Post-operative *ablative* RAI therapy is not recommended for low-risk PTC	☹	+++

Outcome	Evidence
Effectiveness	• High-risk PTC: Use of RAI for Stage III or IV patients with DTC was associated with risk ratios of 0.74 for all-cause mortality, 0.68 for cancer death, and 0.76 for cancer recurrence. • Intermediate-risk PTC: RAI administration was associated with a better overall survival with hazard ratio of 0.71 for the entire population and 0.64 for patients <45 years-old, respectively, with T3N0M0-x or T1-3N1M0-x PTC. • Low-risk PTC: RAI therapy has not been demonstrated to be effective in suppressing low risks of recurrence or death.
Harms	• Acute side effects, gastrointestinal symptoms, and radiation sialadenitis occurred in 60-70% of patients. Temporary effects on gonadal function and bone marrow may occur. Therapy-induced carcinoma may occur with an increase in dose, but the incidence is very low.
Health conditions from patients' perspective	• Patients reported that "diagnosis of thyroid carcinoma is a life-changing event," "it is not easy to determine to undergo RAI therapy," and "experienced various symptoms after RAI therapy."

Figure 7 Ablative or adjuvant RAI therapy for PTC (the revised Japanese clinical practice guidelines for thyroid tumors) (20,21). PTC, papillary thyroid carcinoma.

class varied among studies and were different from those in the revised Japanese guidelines. Second, the distinction between "ablation", "adjuvant", and "treatment" was not always made accordingly, even in the relevant literature. Finally, there was a wide variation in the RAI doses among the studies.

Figure 7 summarizes the recommendations and evidence of ablative or adjuvant therapy for PTC presented in the Japanese 2018 guidelines (20,21). The optimal extent of thyroidectomy for low-risk PTC is lobectomy. Thus, RAI ablation is not recommended. There were no reports in which the study population fit the classification of intermediate-risk PTC defined by the Japanese 2018 guidelines. Ruel *et al*. demonstrated the association between RAI administration and all-cause mortality in 21,870 cases of intermediate-risk PTC (pT3N0cM0-x, pT1-3N1cM0-x) registered in the National Cancer Database in the United States (27). The hazard ratio of adding RAI therapy was 0.71 (95% CI, 0.62–0.82) for the entire population and 0.64 (95% CI, 0.45–0.92) for patients aged <45 years. However, the absolute risk differences were quite small [1.9% (95% CI, 1.2–2.6%) for the entire population and 0.6% (95% CI, 0.1–1.1%)] for patients aged <45 years). Jonklaas *et al*. defined Stages III or IV DTC as high-risk disease and reported that adjuvant RAI therapy was associated with improved survival. The estimated risk ratios were 0.74 (95% CI, 0.63–0.91) for all-cause mortality, 0.68 (95% CI, 0.53–0.88) for carcinoma death, and 0.76 (95% CI, 0.60–0.68) for carcinoma recurrence (28). The literature does not demonstrate that the use of adjuvant RAI therapy is effective in preventing oncologic outcomes in patients with high-risk PTC defined by the Japanese 2018 guidelines. Therefore, the quality of evidence supporting each recommendation was marked with representing poor evidence (20,21).

RAI treatment for recurrent PTC

Recommendation		Evidence	Consensus
◎◎◎	RAI therapy is strongly recommended for lung metastasis.	☹	+++
◎◎◎	RAI therapy is strongly recommended for bone metastasis.	☹	++
◎	RAI therapy is weakly recommended for either local recurrence or lymph node metastasis that is inoperable but requires therapy.	☹	++
XXX	RAI therapy is not recommended for brain metastasis.	☹	+++

Outcome	Evidence
Effectiveness	• The response rate for lung metastasis showing iodine accumulation has been estimated to be 17% for complete response (CR), 44% for partial response (PR), 33% for stable disease (SD), and 6% for progressive disease (PD). • 5-year, 10-year, and 15-year survival rates of cases with lung metastasis showing iodine accumulation have been estimated at 87%, 69%, and 56%, respectively. • 5-year, 10-year, and 15-year survival rates of cases with lung metastasis without iodine accumulation have been estimated at 70%, 38%, and 21%, respectively. • The rate of CR for bone metastasis was 50% in 8 cases aged 45 years or younger, and 21% for 99 cases older than 45 years.
Harms	• The incidence of blood system disorders was reported as 37%.
Health conditions from patients' perspective	• No reports have inquired about the patients' perspective.

Figure 8 RAI treatment for recurrent PTC (the revised Japanese clinical practice guidelines for thyroid tumors) (20,21). PTC, papillary thyroid carcinoma.

Treatment

RAI therapy is strongly recommended for lung or bone metastasis, while it is weakly recommended either local recurrence or lymph node metastasis that is inoperable for some reason but requires therapy. Although the Japanese 2018 guidelines cited some numerical data from the literature regarding the effectiveness of the treatment (*Figure 8*), the validity of such estimates is unsatisfactory because of the retrospective nature of their designs, limited number of subjects, and concomitant interventions that made patients' clinical courses complex (20,21).

Dynamic evaluations and decisions

The definitions of RAI ablative or adjuvant therapy are apparent. However, clinical judgments may change according to the findings of imaging studies and serum Tg levels (*Figure 9*). When a patient is found to have residual accumulations outside the thyroid beds on the whole-body scan following RAI administration and the lesions are confirmed by other imaging modalities, the individual must have treatments with either RAI ≥3,700 MBq or salvage surgery. In contrast, if the scan shows I-131 accumulation in the thyroid bed alone, then a decision will be made based on a follow-up diagnostic scan (DxWBS) and serum Tg level at 6–12 months. A patient has no residual disease when the DxWBS shows no accumulation of RAI and stimulated Tg level <2 ng/mL. In patients with uncertain responses defined by either a positive DxWBS scan at the thyroid bed or stimulated Tg level ≥2 ng/mL, a second administration of RAI ≥1,110 MBq needs to be considered.

Future directions

While RAI treatment is a crucial element in the management of differentiated thyroid carcinoma throughout

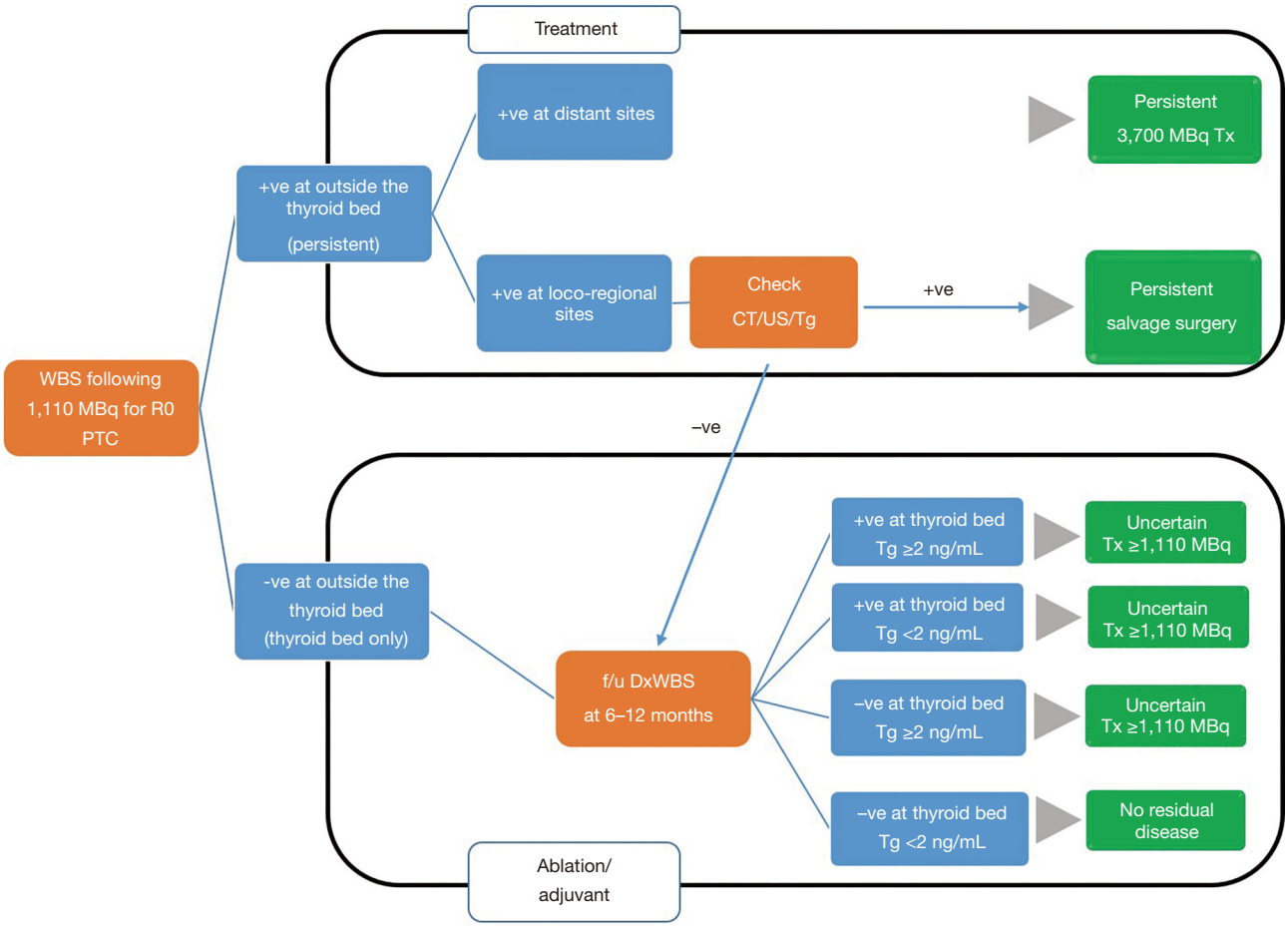


Figure 9 Dynamic evaluations and decisions on ablative or adjuvant RAI therapy. WBS, whole-body scan; R0, curative resection; +ve, positive; -ve, negative; DxWBS, diagnostic whole-body scan; CT, computed tomography; US, ultrasonography; Tg, serum thyroglobulin level.

the world, its use in Japan has been unique as compared to that in other countries due to various reasons. Now thanks to an evidence-based approach, we recognize no apparent differences in the recommendations for RAI use between in our latest guidelines and those in western ones (23).

The objective of the JAES 2018 guidelines is to improve health-related outcomes in patients with thyroid tumors by minimizing gaps in knowledge among physicians. However, further clinical research is needed to make shared decision more evidence based. It is vital to conduct studies to examine the long-term outcomes of patients with intermediate- or high-risk PTC in Japan, yet such reports have never been published. The ablation success rate can be an alternative measure to determine the efficacy of RAI therapy using 1,110 MBq. Abe *et al.* concluded that low-dose RAI therapy might be inadequate in achieving successful ablation based on their observations (26). To this end, we are still facing the barrier to provide RAI therapy to patients as appropriate. Japanese experts in nuclear medicine have been making efforts to obtain approval for high-dose RAI administration on an outpatient basis to overcome the limited availability of resources for therapy (29). All relevant health professionals need to work closely in practice and research to ameliorate the current situation to care for patients with thyroid cancer.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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