Factors Associated with Dose Determination of Radioactive Iodine Therapy for Differentiated Thyroid Cancer

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Abstract

Radioactive iodine (RAI) therapy for differentiated thyroid cancer has been successfully used for more than 70 years. However, there is still plenty of controversy surrounding the use and doses of radioiodine. There is insufficient evidence to answer the questions. Recent American Thyroid Association (ATA) guidelines seem to favor low-dose RAI, based on recent clinical trials and meta-analyses. However, long-term follow-up data remains limited, and there are additional factors we should consider that might affect the efficacy of RAI therapy. Therefore, until sufficient data are available, it is necessary to remain cautious about determining RAI doses by considering multiple patient-specific variables.

Keywords Differentiated thyroid cancer · I-131 · Radioactive iodine · High dose · Low dose

Introduction

The incidence of differentiated thyroid cancer (DTC) has markedly increased over the years, but excellent prognosis is observed in most patients [1, 2]. Total thyroidectomy followed by radioactive iodine (RAI) therapy is the standard procedure for patients with DTC. RAI therapy can provide adequate therapeutic effect, even in patients with metastatic DTC [3]. Furthermore, we can expect complete remission in patients with disseminated lung micrometastases. Although complete remission is less often achieved in older patients, RAI therapy can control the disease without impairment of the patients' quality of life [4].

There are three major purposes of RAI therapy after total thyroidectomy in patients with DTC: RAI remnant ablation, RAI adjuvant therapy, and RAI therapy (Table 1) [5]. First, RAI remnant ablation is performed to achieve undetectable serum thyroglobulin (Tg) levels that Tg can be used as a tumor marker and enhance the sensitivity of diagnostic radioactive

iodine whole-body scans (WBSs). High RAI uptake in thyroid remnants may hamper the visualization of relatively lower uptake in metastatic lesions. Second, RAI adjuvant therapy is performed to improve disease-free survival through the destruction of suspected, but unproved, residual disease, particularly in those patients with a relatively high risk of recurrence. Third, RAI therapy can treat known persistent disease [5, 6].

ATA risk stratification system is widely adopted for decision making of RAI therapy. In low-risk patients, less than 1 cm of tumor without any evidence of high risk features is generally not considered for RAI therapy. However, patients with any kind of high risk features need to consider RAI therapy [5]. Not only pathologic features but also other features (such as, age, postoperative Tg) could be considered for determination of RAI therapy and dose determination.

Although the current treatment strategies available for the initial management of thyroid cancer are widely accepted, the appropriate dose of radioactivity is unclear and a wide range of recommended doses exist in major guidelines [5, 7, 8]. A major problem in determining the optimal dose of RAI is insufficient evidence. Most available evidence is based on retrospective studies, which is informative, but hampered by selection bias [3]. As patients with thyroid cancer survive relatively longer than other cancers, it is generally not feasible to prove survival benefit of certain treatment modalities with usual clinical studies. And, it might take more than decades to get optimal results about recurrence analysis. Therefore, many studies are performed to evaluate the ablation success or response criteria.

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Table 1 Purpose and dose of RAI therapy

	Purpose of RAI	2015 ATA risk stratification	Dose
RAI remnant ablation	To detect recurrent disease using serum thyroglobulin and RAI whole-body scans	Low risk	1.1–3.7 GBq (30–100 mCi)
RAI adjuvant therapy	To destroy suspected, but unconfirmed residual disease	Intermediate/high risk	1.1–5.5 GBq (30–150 mCi)
RAI therapy	To treat known persistent disease	High-risk patients with persistent disease	3.7–7.4 GBq (100–200 mCi) or dosimetry

RAI radioactive iodine, ATA American Thyroid Association

However, definition of ablation success is different depending on studies [9–11], and response criteria suggested by the 2015 ATA guidelines has ambiguous definition, such as nonspecific imaging findings and faint radioiodine uptake in thyroid bed [5]. These ambiguous definitions are aroused from ambiguous diagnosis of post-therapy whole-body scan. Recent advances of single-photon emission computed tomography/computed tomography (SPECT/CT) provide better diagnostic performance [12], which might provide better estimation of prognosis. Future response criteria might need to include SPECT/CT for clear definition and better performance.

In this review, we discussed difference of empiric low/high dose and dosimetry of RAI therapy; factors we need to consider for dose determination.

Low-Dose Versus High-Dose

It is generally assumed that high-dose RAI results in higher ablation success rates than low-dose RAI. Doi et al. performed a meta-analysis and demonstrated that high-dose RAI is more efficient than low-dose RAI for remnant ablation [13]. RAI uptake in DTC mainly relies on the differentiation status of the cancer, which decides the efficiency of trapping circulating RAI [14–17]. Samuel et al. showed that RAI uptake and its effective half-life in the target tissue are reduced compared with prior RAI therapy in patients who underwent multiple RAI therapies [18]. This result could be explained by the hypothesis that less differentiated cells, which have low RAI avidity, are more likely to survive during a course of RAI therapy with non-maximum activity [4]. In addition, patients who do not receive RAI with sufficient activity might undergo more frequent administrations of RAI, which might change the biokinetics of RAI in DTC [19]. Therefore, there is an argument for administering a higher dose of RAI initially, not only for remnant ablation but also for adjuvant therapy of hidden malignancy [20].

However, recent 2015 American Thyroid Association (ATA) guidelines seem to favor low-dose (1.1 GBq) RAI ablation in low- to intermediate-risk patients [5]. The use of low-dose RAI is based on results of recent multicenter studies that showed that low-dose (1.1 GBq) postoperative RAI ablation is

non-inferior to high-dose (3.7 GBq) in patients with low-risk thyroid cancer, with the added advantage of unnecessary hospitalization [10, 11]. Several meta-analyses supported similar ablation success rates of low-dose RAI compared to high-dose RAI [21–24], but one meta-analysis reported that high-dose RAI shows better results than low-dose [25]. Even though ablation success and ATA response criteria is related to the long-term outcome of the patients [26], we need to validate the long-term follow-up data in the future studies.

As limited long-term data on the impact of various activities for remnant ablation or adjuvant therapy are available, it is still difficult to conclude the optimal dose of RAI. Verburg et al. performed a retrospective database review of 1298 DTC patients with at least 5 years of follow-up [2]. They suggested caution in the usage of low-dose RAI (< 2 GBq) in older patients (aged ≥ 45 years). In older patients with low-risk DTC (pT1 or pT2, and no involved lymph nodes), those who underwent low-dose RAI (< 2 GBq) showed higher DTC-specific mortality compared with patients who were administered high-dose RAI. In older patients with high-risk M0 DTC, the recurrence rate and DTC-specific mortality were significantly higher in patients who underwent low-dose RAI (< 2 GBq). However, there was no difference in overall survival rate between these older patients who received either low- or high-dose RAI.

Welsh et al. reported that 49% of patients who received low-dose RAI (1.1 GBq) achieved successful ablation, while 51% of patients required additional RAI administration to achieve successful ablation [27]. Jeong et al. also reported that patients who underwent low-dose RAI ablation showed higher rates of incomplete biochemical and structural response compared to those who underwent high-dose RAI ablation. Patients who underwent low-dose RAI also tended to require additional RAI therapy compared to those who underwent high-dose RAI ablation [6].

Dosimetry

The empiric fixed dose method was widely used for a long time due to its simplicity. However, this method does not take individual variabilities into account, wherein there are possibilities of under- or over-treatment of patients [28]. Flux et al.

performed dosimetric analysis of patients who underwent 3 GBq RAI therapy, and the results showed that the variability in absorbed dose (7–570 Gy) to remnant tissue and ablation success are strongly dependent on the absorbed dose to thyroid remnants [29]. To address these concerns, two dosimetry-based approaches have been used: as high as safely administrable (AHASA) and as low as reasonably achievable (ALARA).

AHASA, sometimes referred to as maximum tolerated activity, was originally reported by Benua et al. [30]. This method targets safety, limiting the absorbed dose to the blood to 2 Gy and the whole-body activity of RAI in adults to 3 GBq (80 mCi) 48 h after administration [30]. The blood and bone marrow dosimetry can be determined with sufficient accuracy after oral administration of 10–15 MBq (0.27–0.41 mCi) I-131. Serial blood sampling and whole-body scan using gamma camera are needed until whole-body activity has decreased to less than 5% of the administered activity. Blood sampling and whole-body imaging are performed at 2, 6, 24, 96, and 144 h after the administration. After generating time-activity curve, we can calculate AHASA activity. A detailed description about the procedure is well described in the procedure guideline of the European Association of Nuclear Medicine (EANM) standard operating procedure for pre-therapeutic dosimetry [31].

AHASA could avoid severe damage to the hematopoietic and pulmonary systems. The theoretical rationale for implementing the AHASA approach is based on the concept that a maximal safe prescribed activity should have greater therapeutic benefit than multiple smaller empiric activities that may induce nonlethal changes in the cancer tissue with subsequent cellular repair [32]. One of recent meta-analysis showed correlation between the absorbed dose delivered and therapeutic response, indicating that dosimetry-based personalized treatments would improve outcome and increase survival [33].

The second approach, ALARA, which is referred to as lesion-based dosimetry, is focused on targeted efficacy to deliver a desired absorbed radiation dose to a targeted lesion. Maxon et al. considered the target absorbed dose to thyroid remnants as 300 Gy and to metastatic disease as 80 Gy [34]. To calculate the delivered dose to target tissue, serial imaging acquisition was performed for generating time-activity curve [35, 36], and sometimes assumption of biologic half-life was also used [37]. To obtain activity of target tissue, the lesions should be visualized for several days on imaging. Because of concern about stunning, only limited dose of RAI could be administered for the dosimetry. And, there are difficulties in estimating volume or mass of the small lesions, such as disseminated lung metastases in younger patients. Therefore, lesion-based dosimetry could be applied for larger lesions. More recent studies based on measurements with improved equipment support the hypothesis that therapeutic outcome correlates with the absorbed dose to the target tissue. Pretreatment I-124 positron emission tomography-computed tomography (PET/CT) scans shows excellent correlation with

I-131 uptake during RAI treatment [36, 38], and PET/magnetic resonance (MR) imaging also shows similar results to those of PET/CT [39]. As I-124 is not easily available in many countries, SPECT/CT using I-123 or I-131 is also applied for lesion-based analysis [29, 35, 40].

These dosimetric approaches help to decide appropriate RAI dose which is able to obtain effective therapeutic effect but avoid unnecessary radiation which could be hazard to patients. Even though these are advantages of using dosimetry, empiric fixed dose is more widely used due to the complexity of the methods. Recently, Deandreis et al. reported that there is no significant difference of outcome compared with empiric fixed dose and AHASA dosimetry [41], but many researchers against their approaches [42, 43].

Therefore, we need to select the patients who might have benefits using dosimetry. The dosimetry is especially helpful for pediatric patients and patients with unresectable metastatic lesions. In pediatric patients, there is special concern of secondary malignancies, but they show excellent prognosis after RAI therapy [44]. As young individuals usually show fast excretion of iodine, we need to optimize the dose of RAI. Patients with disseminated lung disease show good response to RAI therapy, but we need to prevent subsequent pulmonary fibrosis using dosimetry [19]. In addition, patients who are vulnerable to surgery or surgical complications might have advantages of lesion-based dosimetry.

Pathologic Factors for Dose Determination

In daily practice, dosimetric methods are reserved for complex clinical situations, such as in children, elderly patients, and patients with renal insufficiency and diffuse pulmonary metastases [45]. Doses of RAI are generally empirically determined, based on characteristics of patient and cancer status. Risk stratification system is widely used for guide the dose determination of RAI therapy.

The 2015 ATA guidelines adapt a three-tiered risk stratification system (low, intermediate, high) [5], and European Consensus Conference also suggests similar classification system (very low, low, high) [46]. Many factors are associated for classification (Table 2): tumors confined to thyroid gland (intrathyroidal), microscopic extrathyroidal extension, macroscopic invasion into perithyroidal structures, status of lymph node metastasis, number and size of metastatic lymph nodes, aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma), vascular invasion, and genetic mutations (BRAF, TERT, etc.) [5].

As there are many factors, only three classification categories are not enough to characterize each patient. The risk of recurrence within the individual risk categories can vary depending on the clinical features of each patient. Therefore, dose adjustment might be needed for patients in same risk classification.

Table 2 Influencing factors for empirical RAI dose determination

Factors	Ref.
Pathologic factors	[5]
Extrathyroidal extension	
Aggressive histology	
Vascular invasion	
Lymph node metastasis	
Genetic mutation (BRAF, TERT, etc.)	
Possible factors	
Surgeon's experience	[47–49]
Surgical procedure	[5, 48]
Postoperative thyroglobulin	[50, 51]
Status and methods of TSH stimulation	[52–54]
Low-iodine diet	[55, 56]
Age	[2, 57]

RAI radioactive iodine

Possible Factors for Dose Determination

As there are not enough prospective studies to effectively determine doses of RAI, there are controversies to determine the doses based on the pathologic factors. Furthermore, there might be additional factors we should consider for dose determination (Table 2).

Experience of surgeons is an important factor for surgical completeness and ablation success rate [47–49]. Pre-ablation RAI scans demonstrated the relationship between the surgical volume and size of thyroid remnants, and there were significant differences in remnant size after surgery performed by endocrine and general surgeons [49]. High-volume surgeons resulted in smaller remnant sizes compared with low-volume surgeons [48]. In addition, high-volume surgeons conferred significantly lower complication rates and shorter hospital stays [58]. However, over 80% of thyroid resections are performed by low- and intermediate-volume surgeons (< 100 thyroid cases per year) in the USA [59]. Therefore, different approaches for each center might be needed, before following the guidelines based on the studies performed at international centers of excellence [47].

Surgical procedures also affect remnant size in patients. Oltmann et al. reported that patients who underwent single total thyroidectomy showed less remnant uptake compared with patients who underwent complete thyroidectomy followed by a staging operation [48]. Patients who received less than the total or near-total thyroidectomy might need higher RAI doses [5].

The postoperative Tg value can be influenced by a wide variety of factors, including the amount of thyroid remnant and/or residual thyroid cancer. Multiple studies showed that postoperative TSH-stimulated Tg is related to risk of recurrence [50, 51]. Elevated postoperative Tg levels are also related to ablation failure after 1.1 GBq of RAI administration [60].

TSH values for RAI therapy are arbitrarily determined, and no definitive evidence is available, but > 30 mIU/L is widely considered as optimal TSH levels for RAI therapy [5]. Fallahi et al. reported that TSH value before TSH > 25 mIU/L was significantly associated with the ablation success [61]. Some studies did not show significant relationship between TSH level and ablation success [62, 63], but they are not sufficient to conclude that TSH elevation is unnecessary. Because they already performed that thyroid hormone withdrawal and TSH level below 30 mIU/L are generally not considered for RAI therapy in these studies. Age, body surface area, body mass index, and creatinine show a relationship with TSH elevation, and creatinine is the most powerful predictor [52]. Although recombinant human TSH (rhTSH) has been approved for remnant ablation only, patients who cannot achieve sufficient elevation of TSH might need rhTSH injection for treatment of distant metastasis. There are some evidences of faster washout of radioiodine in metastatic lesions using rhTSH compared to the thyroid hormone withdrawal (THW) [53, 54] that dose escalation could be considered according to the TSH status and methods of stimulation.

Although there is insufficient evidence of a relationship between a low-iodine diet (LID) and recurrence, excessive iodine intake has been reported to be associated with poor RAI ablation outcomes [55]. In iodine-rich countries, such as Korea and Japan, a strict LID is very difficult to maintain and energy intake during a LID is significantly reduced [56]. Therefore, special concern for patients in iodine-replete countries might be needed.

Age is an important factor for the American Joint Committee on Cancer staging but not included in risk stratification system of ATA. However, age is also an important factor for dose determination. Verburg et al. reported that older patients (≥ 45 years) showed benefits in their database of receiving > 2 GBq of RAI [2]. Tuttle et al. reported that elderly patients (≥ 70 years) who received more than 7.4 GBq of RAI frequently exceed the calculated maximum tolerable dose [57]. However, < 5.18 GBq of RAI rarely exceeds the tolerable dose. Most young patients may be able to receive much higher RAI doses relative to the empiric dose, thereby delivering potentially higher absorbed dose to the metastases without exceeding tolerable dose. Therefore, special concern for very old patients and young patients with metastatic disease is needed to determine an optimal RAI dose.

Adverse Effects and Dose of RAI

Short-term side effects (such as nausea, neck pain, lacrimal gland dysfunction, salivary gland dysfunction, and altered tastes) in the weeks following RAI remnant ablation have been reported to be more frequent in patients treated with 3.7 GBq as compared to 1.1 GBq in recent multi-center

randomized trials [10, 11]. As most of the short-term side effects are reversible and can be managed with the attention of physicians, the long-term irreversible adverse effects of RAI ablation including secondary primary malignancy, xerostomia, and infertility should be more carefully considered [45]. Weighting risks versus benefits of low-dose and high-dose RAI ablation for individual patients is warranted for deciding on an optimal personalized RAI dose.

Most long-term follow-up studies variably report a very low risk of secondary malignancies in long-term survivors. A meta-analysis showed that the relative risk of second malignancies and leukemia increases in patients treated with RAI, although the absolute increase in second primary malignancy risk attributable to RAI is considered to be trivial [64]. Rubino et al. reported that the risk of secondary malignancies is dose-related, with an excess absolute risk of 14.4 solid cancers and of 0.8 leukemias per GBq of I-131 at 10,000 person-years [65]. Another study showed that 9% of patients with RAI-treated DTC were diagnosed with a secondary malignancy, while this proportion was 10.5% in patients with non-RAI-treated DTC [66]. There is no direct evidence of increased risk of secondary malignancies after a single administration of low-dose or high-dose RAI. The risk is clearly increased in patients who have been treated with a large cumulative RAI dose that is higher than 600 mCi [65].

Xerostomia is a common side effect of RAI therapy, which hampers the quality of life of patients. The reported incidence of xerostomia is variable; there were no significant differences in xerostomia symptoms between 1.1-GBq and 3.7-GBq RAI therapy in two prospective randomized clinical trials [10, 11]. However, the incidence and severity were increased in patients who underwent 5.5 GBq of RAI therapy compared with the patients who underwent 3.7-GBq RAI therapy [67]. Therefore, in patients who need high-dose RAI therapy, an emphasis should be placed on appropriate protection of the salivary gland [68, 69].

Infertility is another major concern of RAI therapy. Wu et al. performed a retrospective cohort study of 25,333 DTC patients [70]. RAI ablation is associated with delayed child-bearing in women aged 20–39 years, and with decreased birth rate in women aged 35–39 years; however, it was not clear whether these findings were the result of physician recommendations to delay pregnancy or an actual biologic effect of RAI administration. Approximately 1 year of earlier menopause might be associated with ovarian damage due to RAI therapy, but there is no significant association with cumulative dose or age at the time of RAI therapy [71]. Permanent male infertility is unlikely with a single ablative activity of RAI, and evidence suggests that RAI-induced azoospermia is mainly reversible [5, 45]. During 21 years of median follow-up, patients who underwent RAI therapy (cumulative dose, 3–44 GBq) did not show any evidence of long-term infertility or increased risk of birth defects [72].

Conclusion

RAI therapy for DTC has been successfully used for more than 70 years; however, there are still many controversies surrounding RAI dose determination due to insufficient evidence. Therefore, until sufficient data are available, it is necessary to be cautious about determining RAI dose by considering multiple patient-specific variables. To optimize the dose of RAI, understanding of radiation effect and course of DTC is necessary. Just following the guideline might not be optimal for treating individual DTC patient. Nuclear medicine physicians need to be state of the art with balancing the therapeutic effects and side effects of RAI therapy by considering radiation-related factors.

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Compliance with Ethical Standards

Conflict of Interest Chae Moon Hong and Byeong-Cheol Ahn declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with animals or human participants performed by any of the authors.

Informed Consent None.

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