Review

Low-Risk Differentiated Thyroid Cancer and Radioiodine Remnant Ablation: A Systematic Review of the Literature

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Background: Radioiodine remnant ablation (RRA) has traditionally been one of the cornerstones of differentiated thyroid cancer (DTC) treatment. The decision to use RRA in low-risk (LR) and intermediate-risk (IR) patients is controversial. The aim of this review is to examine the evidence of RRA benefit in the staging, follow-up, and recurrence prevention in LR and IR DTC patients.

Methods: From a PubMed search, we selected original papers (OPs) using the following inclusion criteria: 1) DTC; 2) LR and IR patients; 3) non-RRA-treated patients or RRA-treated vs non-RRA-treated groups; 4) a report of the outcome of cancer recurrence; and 5) publication since 2008.

Results: Neck ultrasonography is superior to whole-body scan for disease detection in the neck. A rising or declining serum thyroglobulin level over time provides an excellent positive or negative predictive value, respectively, even in non-RRA-treated patients. No OP demonstrating RRA benefit on recurrence in LR patients was found; two OPs found no evidence of benefit. We found 11 OPs that observed some benefit in reducing recurrence rates with RRA in IR patients and 13 OPs that failed to show benefit from RRA in this group.

Conclusions: Neck ultrasonography and serum thyroglobulin measurement are equivalent or superior in detecting and localizing residual disease compared to post-therapy whole-body scan. There is no evidence of RRA benefit in recurrence prevention for LR patients. There are conflicting data on IR patients and only a few studies with homogenous and properly stratified populations. A careful evaluation of tumor pathological features and patient characteristics and preferences should guide RRA decision making. **(*J Clin Endocrinol Metab* 100: 1748–1761, 2015)**

Over the last several decades, the incidence of differentiated thyroid cancer (DTC) has risen worldwide, mainly due to the diagnosis of small, subclinical, localized papillary thyroid cancer (PTC) (1, 2). Today, clinicians are faced with a growing number of patients with low-risk (LR) PTC, and there is a need for safe, efficient, and cost-effective management strategies, avoiding overtreatment and preserving quality of life (QoL). Risk-stratified categories and treatment strategies have been developed (3–6) for LR and intermediate-risk (IR) disease.

The American Joint Committee on Cancer (AJCC) tumor node metastasis (TNM) staging is the most accepted staging system to predict the risk of death (Table 1). Because death rates in LR and IR DTC patients are extremely low (7), the prevention of recurrent disease has become the focus of contemporary management and research. The American Thyroid Association (ATA) Guidelines on DTC identify three disease recurrence (DR) risk categories (low, intermediate, and high) (Table 1), which have been validated in several recent retrospective studies (8, 9).

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Abbreviations: CT, computed tomography; DFS, disease-free survival; DR, disease recurrence; DSM, disease-specific mortality; DTC, differentiated thyroid cancer; DxWBS, diagnostic WBS; FTC, follicular thyroid carcinoma; F/U, follow-up; mPTC, micro PTC; OP, original paper; PTC, papillary thyroid cancer; QoL, quality of life; RAT, radioiodine adjuvant therapy; RRA, radioiodine remnant ablation; RxWBS, post-therapy WBS; SPECT, single photon emission computed tomography; Tg, thyroglobulin; TNM, tumor node metastasis; US, ultrasonography; WBS, whole-body scan.

Table 1. AJCC TNM Staging, ATA Risk Classification, and RRA Recommendations According to ATA 2009 and 2015 Previews

T	N	M	Additional Features	Stage ≥ 45 y	Stage < 45 y	2009 ATA Risk	2009 RRA Recommended	2014 ATA Risk	2014 RRA Recommended[a]
1a	0	0		I	I	L	No	L	No
1b-2	0	0		I-II	I	L	Selective use	L	Not routine
1–2	0	0	Multifocal[b]	I-II	I	L	Selective use	L	Not routine
1–3 (size)	0	0	FTC minimal vascular invasion	I-II	I	L	Selective use	L	Not routine
3 (size)	0	0		III	I	L	Yes	L	Not routine
1–3 (size)	1a	0	≤ 5 microscopic N1 (< 2 mm)	III	I	I	Selective use	L	Not routine
1–3	1a	0		III	I	I	Selective use	I	Consider
1–3	1a	0	> 5 N1 of < 3 cm	III	I	I	Selective use	I	Consider
1b-3	0	0	BRAF mutation	I-III	I	I	Selective use	I	Consider
3	0	0	Microscopic extrathyroidal invasion[b]	III	I	I	Selective use	I	Consider[c]
1–3	1b	0		IVa	I	I	Selective use	I	Consider
1–3	0–1b	0	Aggressive histology[b]	I-IVa	I	I	Selective use	I	Consider
1–3	0–1b	0	Uptake outside thyroid bed on RxWBS	I-IVa	I	I	Selective use	I	Consider
1–3	0–1b	0	Vascular invasion[b]	I-IVa	I	I	Selective use	I	Consider
1–3	0	0	FTC > 4 foci of vascular invasion	I-III	I	I	Selective use	H	Yes
1–3	1a-b	0	N1 > 3 cm	III-IVa	I	I	Selective use	H	Yes
4a	0	0		IVa	I	H	Yes	H	Yes
4a	1a-b	0		IVa	I	H	Yes	H	Yes
4b	Any N	0		IVb	I	H	Yes	H	Yes
Any T	Any N	1		IVc	II	H	Yes	H	Yes
Any T	Any N	0	Incomplete tumor resection		I	H	Yes	H	Yes
Any T	Any N	0	Tg out of proportion with RxWBS findings		I	H		H	Yes

Abbreviations: ATA, American Thyroid Association; L, low; I, intermediate; H, high.

[a] 2015 ATA guidelines recommendations are taken from an ATA Satellite meeting in Chicago in June 2014 and may differ from the final published version.

[b] Aggressive histology (eg, tall cell, columnar, insular and poorly differentiated), vascular invasion and multifocal foci in combination with size, lymph node status, and age can increase the risk of the patient and may be an argument for RRA for ATA 2009 guidelines.

[c] May be deferred for small tumors.

Despite the continuing controversies surrounding its use, radioiodine remnant ablation (RRA) has traditionally been one of the cornerstones of DTC treatment. The aim of this review is to examine the evidence of RRA benefit in staging, follow-up (F/U), and DR prevention in LR and IR DTC, which comprise most DTC patients in the 21st century.

Search Strategy

We performed PubMed research using the following search strategy: "low risk"[tiab] OR "low-risk"[tiab] AND (radioiodine[tiab] OR "radioactive iodine"[tiab] OR "iodine 131"[tiab] OR "iodine-131"[tiab]); "intermediate risk"[tiab] OR "intermediate-risk"[tiab] AND (radioiodine[tiab] OR "radioactive iodine"[tiab] OR "iodine 131"[tiab] OR "iodine-131"[tiab]); Filters: Abstract available, From 2008/01/01 until 2014/03/01, English. From the 149 results obtained, we selected 26 original papers (OPs) using the following inclusion criteria:

- DTC (either follicular or papillary)
- LR and IR patients
- Non-RRA-treated patients or RRA-treated vs non-RRA-treated groups
- Reporting of the outcome of cancer recurrence (local relapse, regional, or metastasis)

We chose to review literature starting from 2008 in order to update the evidence on which the 2009 and 2014 ATA guidelines are based. In addition, a meta-analysis by

Sawka et al (10) focused on effectiveness of RRA in DTC and included papers published from 2002 until 2007, and a narrative review by Sachs et al (11) examined the literature through April 2008.

What Are the Rationales for RRA?

RRA consists of the oral administration of ^{131}Iodine, with the following goals (3): 1) to facilitate a patient's staging by revealing possible metastatic disease on the post-treatment scan and thereby detect early disease persistence; 2) to destroy thyroid remnants in order to facilitate F/U by enabling stimulated thyroglobulin (Tg) testing; and 3) to treat microscopic or "occult" persistent disease, fulfilling the role of adjuvant therapy.

RRA improves disease-free survival (DFS) and disease-specific mortality (DSM) for high-risk patients (12), but advantages in DFS and DSM are less clear for IR patients, and there is little evidence for benefit among LR patients. Current ATA RRA recommendations are summarized in Table 1. We will examine each of the rationales for RRA and discuss each in detail.

Critical Examination of the Uses of RRA in LR and IR Patients

Goal 1: to facilitate a patient's staging by revealing possible metastatic disease on the post-treatment scan and thereby detect early disease persistence

One of the main theoretical reasons to perform RRA is to facilitate staging through early disease detection. In LR and IR patients, however, the risk of persistent disease is about 2.5 and 11%, respectively, ranging from $<$ 1 to 20% according to the different pathological features (7, 13) (B. Haugen, oral communication; and http://www.thyroid.org/members-only/member-resources/ata-draft-guidelines accessed 9/23/14). The disease is usually confined to the neck, whereas the occurrence of distant metastases (M1) is uncommon, with a 10-year distant DR rate of 1.3% in PTC patients (10). Therefore, the main target in LR and IR patients is the early detection of locoregional disease. Radioiodine whole-body scan (WBS) has very high specificity (up to 100%) for disease detection but low sensitivity (51–55%), with a global accuracy of 90–92% (14, 15). The post-therapy (RxWBS) is more sensitive than the diagnostic WBS (DxWBS) (16) but suffers from low specificity, being prone to false-positive results (17). In optimal conditions, RxWBS can detect lesions of $<$ 0.2 g (a few millimeters), and DxWBS can detect lesions of $>$ 0.2 g (18). The frequency of post-RRA RxWBS that are suspicious for cervical lymph node metastases (N1) varies among different studies, ranging from 36% in a 2001 series by Mazzaferri and Kloos to 2% in a more recent report from Rosario et al (19–21). Some may argue that more precise localization techniques such as single photon emission computed tomography (SPECT)/computed tomography (CT) are now routine in clinical practice, with a gain of information in 20–50% of patients (22–25). WBS and SPECT/CT may also reveal mediastinal N1. A recent study by Gallicchio et al (25) suggests that it is possible that SPECT/CT could identify lesions not detectable on neck ultrasonography (US). However, to our knowledge, there are no studies that directly compare SPECT/CT and neck US with regard to detection accuracy of N1 disease, and the report from Gallicchio et al (25) is the only study in favor of SPECT/CT. Currently, neck US is the most sensitive technique for N1 detection, with a global accuracy of US + fine-needle aspiration biopsy of 100% as discussed below in "Which diagnostic tools can be used in non-RRA patients?" (26). In a series of 359 DTC patients, RxWBS and neck US were compared in their ability to detect N1 in 116 patients who underwent neck US at the time of RRA. N1 were found on neck US in 18 patients, all of whom were WBS negative (14). A 100% negative predictive value of an undetectable Tg and negative neck US has been observed (21). All patients with metastases detected by RxWBS but not by US had stimulated Tg levels of $>$ 10 ng/mL (21). The presence of M1 can be suspected by the finding of elevated levels of Tg (3), typically above 5 ng/mL (27). Only about 1% of patients with radiologically detectable M1 have undetectable Tg values (27), and there are probably fewer with new ultrasensitive Tg assays.

On the basis of the foregoing discussion, it appears that neck US and serum Tg measurement are equivalent or superior in detecting and localizing residual disease compared to RxWBS. In any case, it is doubtful that early detection of microscopic locoregional metastases will impact on a patient's outcome (28).

Goal 2: to destroy thyroid remnants in order to facilitate F/U by enabling stimulated Tg testing

The main purpose of the postoperative F/U of patients with DTC is to identify those individuals with persistent or recurrent tumor (the minority) and those without evidence of disease, who are probably cured (the vast majority) (7). In this regard, the ATA (3) and the European Thyroid Association (4) agree that Tg measurement fulfills both functions, with detectable and undetectable serum Tg levels regarded as markers of disease and disease-free status, respectively. Radioiodine administration is essential to increase Tg specificity, by eliminating any residual normal

thyroid tissue that may contribute to Tg production and Tg sensitivity, allowing for TSH-mediated stimulation. As for the latter, endogenous or exogenous TSH stimulation is warranted to enable the detection of any residual microscopic foci of thyroid cancer cells, which may not be detected under suppressed or even normal TSH levels (29, 30). A similar approach is usually recommended in those patients who have received RRA (3, 4). Under these conditions, undetectable TSH-stimulated Tg levels have the highest sensitivity to accurately detect disease-free patients, with a negative predictive value of almost 100% (26, 31). That being said, the need for TSH stimulation is expected to decline after the increasing use of ultrasensitive Tg assays (32–34), although the cutoff offering the best balance between sensitivity and specificity still needs to be validated in larger prospective studies.

Which diagnostic tools can be used in non-RRA patients?

As discussed above, basal and stimulated serum Tg assessments are considered the cornerstone of postoperative surveillance programs for patients with DTC (3, 4). Indeed, for individuals who have undergone surgery and postoperative RRA, detectable Tg levels are a highly specific marker of residual or recurrent disease, provided all of the normal thyroid tissue has been eliminated. However, for those who have not received RRA, the clinical significance of Tg assay positivity is unclear because Tg production may well originate from remnants of normal thyroid cells. In these patients, there are no reliable cutoffs that optimally distinguish Tg production from benign and malignant residual thyroid tissues. Serum Tg levels are directly related to the volume of normal thyroid remnant. Total thyroidectomy, especially in experienced hands, can leave only minimal or no remnants, rendering serum Tg very low or even undetectable. However, whereas initial serum Tg measurement is a less specific marker in nonablated patients, serial Tg determinations are informative during long-term surveillance. This issue has been specifically addressed in a recent study exploring the natural history of postoperative Tg production in a cohort of 290 LR PTC patients who were not treated with RRA (35). One year after total thyroidectomy, serum Tg levels had dropped below the assay detection threshold of 0.2 ng/mL in about 60% of the patients, in the absence of TSH suppression and anti-thyroglobulin. In the remaining cases, Tg levels spontaneously declined over time, so that at the fifth year of F/U, 80% of patients had undetectable Tg levels. Thus, almost all of the patients spontaneously achieved the target Tg associated with radioiodine administration. Notably, all of these patients remained disease-free after a median F/U of 5 years. DR was detected in a single patient in whom rising serum levels of Tg were observed during F/U. A similar experience was subsequently reported in a retrospective study showing that thyroidectomy alone was followed by a fairly rapid decline in serum Tg; by 6 months, Tg levels fell to < 0.5 ng/mL (functional assay sensitivity, ≤ 0.10 ng/mL) in 61% of patients (36). Overall, these data highlight that Tg measurement is useful in monitoring DTC patients who have not undergone RRA. Some (but not all) patients not receiving RRA have detectable Tg levels during the early phase of F/U, and this undeniably reduces the diagnostic value of Tg as a marker of residual disease. However, the temporal trend of serial Tg determinations yields an excellent negative (declining values) or positive (rising values) predictive value for thyroid cancer DR. In this regard, Miyauchi et al (37) suggested a postoperative serum Tg doubling-time of less than 1 year as a reliable predictive marker of locoregional and distant DR, irrespective of radioiodine administration.

This approach may result in somewhat later identification of DR. However, based on 2004–2010 data from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute, the vast majority of DTC metastases are confined to the neck (86.7%) (38). Indeed, neck US has been repeatedly proven to be a highly sensitive tool in detecting cervical node involvement, regardless of whether patients had (26, 39–41) or had not (42–44) received RRA and irrespective of Tg values. Three different studies exploring the outcome of nonablated patients with LR and IR reported a structural DR rate of 0.3–4.1% (35, 42, 43). In all cases, DR was confined to the neck and was detected by US. Moreover, a recent study demonstrated that early neck US (within 6 mo from initial treatment) is accurate and is an independent predictor of DR (45). Sonographic criteria for identifying N1 are well-established (46).

Thus, considering the increasingly large proportion of patients with DTC who do not undergo RRA, neck US is becoming the main tool of the early postoperative F/U, when Tg assay results are difficult to interpret. The diagnostic value of serum Tg determination increases with time as serial measurements accumulate and allow reliable predictions of disease status.

Goal 3: to treat microscopic or "occult" persistent disease fulfilling the role of adjuvant therapy

Radioiodine benefit for treating microscopic persistent disease: radioiodine adjuvant therapy (RAT)

Radioiodine can potentially treat microscopic persistent disease (3), and its efficacy to improve survival and DR in higher stage disease (12) probably depends on this adjuvant effect. We now review the current evidence for

RAT benefit on DR prevention in LR and IR patients, where the evidence for efficacy is less clear.

RAT benefit in LR patients

To the best of our knowledge, there are no OPs or systematic reviews that demonstrate a benefit from RAT in DR prevention in LR patients published since 2008. In contrast, two OPs found no evidence of benefit (Supplemental Table A) (44, 47). Retrospective and nonrandomized trials are prone to selection bias, and LR patients have very low DR rates. Any difference in DR rates in LR patients is difficult to demonstrate in this setting. On the other hand, the absence of a difference in DR rates in radioiodine- and nonradioiodine-treated patients may suggest the non-inferiority of the two approaches. Patients with microcarcinoma (tumors $\leq$ 10 mm) will be discussed first, followed by a review of the data in patients with macrocarcinoma.

LR microcarcinomas. Only one study on micro PTC (mPTC) without any aggressive features was found. In this retrospective series of 312 patients with unifocal mPTC, without aggressive histology, extrathyroidal invasion, or N1 or M1, patients received or did not receive RAT based on of their physicians' preferences (44). No clinical or radiological recurrences were found in either the RAT or non-RAT group. In F/U, all patients in the RAT group had basal Tg $\leq$ 1 ng/mL. In the non-radioiodine-treated group, 12 of 175 (7%) had basal Tg $>$ 1.0 ng/mL (1.3–6 ng/mL), and in these patients Tg levels were stable or decreasing over time (44). The clinical significance of a detectable Tg in this setting is uncertain because all imaging was negative and only a rising Tg is a reliable marker of persistent/recurrent disease (3).

LR macrocarcinomas. There is a similar lack of evidence of benefit from RAT in patients with LR macrocarcinomas. In a series of 965 LR DTC patients with a median F/U of 10.3 years, no impact of RAT on overall survival and on DFS was found after stratification by propensity score; age and gender were the only independent risk factors for overall survival and DFS (47). Biochemical persistence of disease, ie, high Tg level or persistent anti-thyroglobulin, was not considered to be a relapse without evidence of structural disease (47).

RAT benefit in IR patients and patients with other possible "risk modifiers"

We will now focus on IR patients. The presence of one or more of the following features defines IR: minimal extrathyroidal extension, aggressive histology (eg, tall cell, columnar, or diffuse sclerosing variants), vascular invasion, N1, and uptake outside the thyroid bed on DxWBS or RxWBS (3). Other potential higher risk features, such as multifocality or the V600E BRAF mutation, may also play a role in the decision to recommend RRA. We found 10 OPs (48–57) that observed some benefit in reducing DR rates with RAT in IR patients and 14 OPs (43, 58–70) that failed to show benefit from RRA in similar groups of patients (Tables 2, 3, 4, and 5 and Supplemental Table B). Microcarcinomas will be discussed first, followed by macrocarcinomas.

IR microcarcinoma. In a series of 704 mPTC patients, of whom 480 were IR, six had DR and all had received RAT (67). No difference in DFS was found between RAT-treated and non-RAT-treated patients (67). RAT-treated patients had a significantly higher TNM stage compared to non-RAT-treated patients, but no differences were found among the other pathological and demographic features (67).

Specific risk modifiers that are used to support RAT in IR microcarcinoma patients. Factors that have been considered to be risk modifiers for microPTC include: multifocality (50, 53, 56, 59, 60), minimal extrathyroidal invasion (50, 53), presence of N1 (49, 50, 53, 54, 56, 59, 60), and BRAF status (70) (see Tables 2–5). For multifocality, two OPs found no difference in DR rates (59, 60), whereas three OPs found some benefit from RAT (50, 53, 56). For N1 status, 2 OPs found no difference (59, 60). N1 status was an independent risk factor of DR in five OPs (49, 50, 53, 54, 56), but no N1 stratified analysis for RAT benefit in DR prevention was done. RAT was considered of some benefit in mPTC with minimal extrathyroidal invasion in two OPs (50, 53). No difference was found in RAT-treated and non-RAT-treated BRAF V600E patients (70).

IR macrocarcinomas. No difference between RAT-treated and non-RAT-treated IR patients with macrocarcinoma was observed in three OPs (58, 62, 64), and three OPs observed very low DR rates in non-RAT-treated patients (43, 61, 63). In nonrandomized studies such as these, one could argue that the RAT achieved its goal, actually reducing the number of recurrences that would have occurred had it not been given to these higher risk patients.

Specific risk modifiers that are used to support RAT in IR macrocarcinoma patients. Factors that have been considered to be risk modifiers for IR macrocarcinomas include: minimal extrathyroidal invasion (58, 66), aggressive histology (48, 51, 65), presence of N1 (55, 68, 69), BRAF status (52), and other primary malignancy before DTC diagnosis (57) (see Tables 2–5 and Supplemental Table B).

Table 2. Review of Evidence of RAT Benefit in IR Patients or Patients With Risk Modifiers from 2008 to 2011, No Evidence of Benefit

First Author, Year (Ref)	Design	Population	Non-RAT-Treated, %	Risk Stratification	Event No.	F/U Tools (Median F/U)	Results
Pelttari, 2008 (58)	RSC	495 DTC (median age, 40.6 y); 7% T4, 12.5% N1, 0.2% M1	20	MACIS stage	Cancer death,1 (0.2%); recurrences, 44 (8%)	Tg and neck US (11.6 y, range 5–19)	No difference in RAT- and non-RAT-treated for tumor recurrence ($P = .8$). Independent risk factors of recurrence: age, gender, and local infiltration
Hay, 2008 (59)	RSC	900 mPTC (mean age, 46 y), pT1a, 30% N1, 3% M1	87	No	Cancer death, 3 (0.3%); 40 y recurrence rate, 8%	NA (17.2 y, range 0.1–54)	No significant improvement in RAT- vs non-RAT-treated patients for local and distant recurrence ($P = .34$ and $P = .84$, respectively). Recurrence more likely in multifocal tumors (11 vs 4%; $P = .002$) and N1 patients (16 vs 0.8%; $P < .001$), but no effect of RAT
Ross, 2009 (60)	Registry	611 mPTC (46% < 45 y old); pT1a, 22% N1	56	N1 and multifocality	Cancer death,1 (<0.1%); recurrences, 38 (6%)	Tg + imaging (3 y, range 0–18)	No significant improvement in RAT- vs non-RAT-treated patients for recurrence, even after adjusting for N1 status and multifocality. In the non-RAT-treated group, recurrence was more frequent in multifocal mPTC ($P = .02$)
Ito, 2010 (61)	RSC	2638 PTC (mean age, 51 y); cT1 cN0, 26% T3, 57% N1	100	TNM	Cancer death,1 (< 0.1%); recurrences, 62 (2%) (4 M1)	Tg + imaging (CRx, US, CT scan) (7.5 y, range 0.5–20)	10-y DFS, 97%; 10-y DFS in N1 patients, 96%; recurrence rate, 2%; 1% thyroid bed recurrence in patients treated with lobectomy
Vaisman, 2011 (43)	RSC	289 DTC (median age, 44 y) 10% T3, 7% N1a, 2% N1b	100	ATA	Recurrences, 8 (3%)	Tg + neck US (5 y, range 0.5–34)	Very low rate of recurrence: 2.3% with total thyroidectomy and 4% with lobectomy

Abbreviations: CRx, chest radiography; DSS, disease-specific survival; NA, not available; RSC, retrospective single center.

For minimal extrathyroidal invasion, two OPs found no difference in DR rates (58, 66). RAT was found effective in preventing DR in aggressive variants of PTC (51) and was recommended for angioinvasive minimally invasive follicular thyroid carcinoma (FTC) and widely invasive FTC in two OPs (48, 65). RAT was considered of some benefit in N1 patients in one OP (55), whereas two OPs found no benefit (68, 69). BRAF V600E was proposed as a tool for RAT decision making (52). DTC developing in the setting of a prior malignancy was associated with a worse overall survival, and RAT in these patients was associated with better overall survival (57).

Adverse Effects of Radioiodine in the Context of RRA

Side effects of radioiodine

Because the benefits of RRA are unproven in LR patients and in some IR patients, the risk of adverse effects should play an important role in the decision-making process. The most common side effects of radioiodine are listed in Table 6. With typical ablative activities of radioiodine (ie, 30–100 mCi), the most frequent acute side effects are nausea, transient sialoadenitis, and transient change in taste and smell (71, 72). Subclinical abnormalities in blood count, lacrimal function, and gonadal function have also been observed (73–76). Chronic side effects are uncommon with low activity RRA, involve mainly salivary and lacrimal function (74, 77), and have a linear correlation with the cumulative administered radioiodine activity (74). An increased risk of a second primary malignancy has been observed for thyroid cancer patients in general, but the risk was significantly higher in patients treated with ^{131}I (78). A linear correlation was found for the risk of a second malignancy and the administered radioiodine activity; it was estimated that 100 mCi (3.7 GBq) of radioiodine will cause an excess of 53 solid malignancies and three leukemias in 10 000 patients over 10 years of F/U (79). Brown et al (78) noted that the period of highest risk for a second malignancy was in the first 5 years after radioiodine exposure, and that younger patients were particularly susceptible. However, the risk of a sec-

Table 3. Review of Evidence of RAT Benefit in IR Patients or Patients With Risk Modifiers From 2012 to 2014, No Evidence of Benefit

First Author, Year (Ref)	Design	Population	Non-RAT-Treated, %	Risk Stratification	Events No.	F/U Tools (Median F/U)	Results
Nixon, 2012 (62)	RSC	532 PTC (median age, 46 y), 21% T3, 10% T4, 38% N1	29	GAMES, TNM, ATA, MSKCC	Recurrences, 27 (5%)	NA (4.2 y, range 0.1–23.5)	No difference in RAT- and non-RAT-treated patients for recurrence ($P = .2$); N1 only significant predictor of poor outcome
Rosario, 2012 (63)	PSC	136 PTC with TSH/Tg < 1 ng/mL (median age, 47 y), 56% pT1b-2, 44% pT3	100	TNM	Recurrences, 2 (1%)	Tg + neck US (3.6 y, range 1–6)	Only two patients experienced recurrent disease (one recurrence in cervical lymph nodes and one AbTg increase)
Ibrahimpasic, 2012 (64)	RSC	298 PTC with basal Tg < 1 ng/mL (57% age < 45 y), 23% T3, 2% T4, 34% N1	43	ATA, GAMES	Recurrences, 8 (3%)	Tg + neck US (5 y, range 0.2–9.6)	No difference in recurrence risk for RAT- vs non-RAT-treated patients with Tg < 1 ng/mL (97 vs 96%; $P = .2$)
Jeon, 2013 (66)	RSC	229 PTC $>$ 45y (median age, 52 y), pT3N0M0 < 4 cm	47	ATA	Recurrences, 23 (10%)	Neck US + Tg + PET + CT scan (7.2 y, range 2–12)	No difference in RAT- and non-RAT-treated patients for recurrence ($P = .44$) (even after adjusting for age, gender, multifocality, vascular and lymphatic invasion, tumor size). Size was the only prognostic factor
Kim, 2013 (67)	RSC	704 mPTC (mean age, 47 y), 46% T3, 24% N1	18	TNM, ATA	Recurrences, 6 ($<$ 0.1%)	Tg + neck US (5.3 y, range 0.1–15.4)	No difference in RAT- and non-RAT-treated patients, in particular for IR ($P = .5$). All recurrences occurred in RAT-treated patients
Nixon, 2013 (68)	RSC	1129 PTC (median age, 46 y); 32% T3, 7% T4, 42% N1	39	TNM, ATA, MSKCC	Cancer death, 18 (2%); recurrences, 84 (7%)	Imaging ± Tg (5.3 y, range 0.1–23.5)	No difference in RAT- and non-RAT-treated patients for survival or recurrence. No difference in young (< 45 y) N1 patients
Momesso, 2014 (69)	RSC	176 DTC < 20 mm (mean age, 40.2 y), 28.4% T3, 27% N1, 3.4% M1	43	No	Cancer death, 2 (1%); recurrences, 28 (16%), 9 M1	Tg + neck US (mean, 14 ± 4.5 y)	No difference in RAT- and non-RAT-treated patients for recurrence ($P = .13$). Risk factors for recurrence: multifocality, extrathyroidal invasion, N1
Walczyk, 2014 (70)	RSC	113 mPTC (mean, 49.9 y), pT1aN0/x	60	TNM	Recurrences, 0 (0%)	Neck US + Tg ± WBS (mean, 4.8 y; range, 0.3–12)	No recurrences occurred in the RAT and non-RAT groups and in the BRAF mut and wt

Abbreviations: AbTg, anti-Tg antibodies; BRAF mut, BRAF mutated; NA, not available; PSC, prospective single center; RSC, retrospective single center; TSH/Tg, stimulated Tg; wt, wild type.

ond malignancy is significantly increased with high cumulative activities (>500–600 mCi) (79). With increased RRA use in LR patients, a troubling increase in the frequency of second malignancies, especially leukemia, has recently been observed (80). Although the occurrence of adverse effects, including second malignancies, is likely to be uncommon with low administered activities, recent data unfortunately indicate that relatively large administered activities are still being used for RRA (81), with no evidence of benefit beyond that achieved with 30–50 mCi (82–84).

Effects of RRA on QoL

Although a decreased rate of DR is an important goal in the management of DTC in LR and IR patients, RRA may provide little benefit and actually diminish health-related QoL. In a comprehensive systematic review of the literature, which included the results of randomized trials, thyroid hormone withdrawal for remnant ablation was associated with a transient worsening of health-related QoL compared to the use of recombinant human TSH (85). Similar results were found in two more recent large multicenter randomized trials (86, 87). In another study that examined patients' perceptions of their illness using a validated illness perception questionnaire, there was a statistically significant correlation between the number of radioiodine therapies and the perception of illness, especially indices of negative disease perception: illness identity, severity of consequences, and a negative response to illness (88). Interestingly, there was no correlation of these factors with the number of surgeries, and patients with a lower educational achievement had a worse perception of their disease. The authors proposed that the relationship

Table 4. Review of Evidence of RAT Benefit in IR Patients or Patients With Risk Modifiers on 2012, Evidence of Benefit

First Author, Year (Ref)	Design	Population	Non-RAT-Treated	Risk Stratification	Event No. (Rate)	F/U Tools (Median F/U)	Results
Creach, 2012 (49)	RSC	407 mPTC (median age, 45 y); 16.7% T3, 38% N1	14%	No	Recurrences, 40 (10%), 3 M1	Tg + DxWBS (5 y, range 0.2–51)	5-y DFS of RAT-treated patient was 95% vs 28.6% of the non-RAT-treated ($P <$ .0001); 5-y DFS for positive lymph node metastases and no RAT, 42.9% vs 93.2% of RAT-treated ($P <$ .0001). Independent predictors for recurrence: size > 8 mm, lymph node metastases, and RAT
Buffet, 2012 (50)	RSC	1669 mPTC (mean age, 47 y), 11% T3	22%	No	Recurrences, 58 (3%)	Tg + neck US (4.7 y, range 0.1–38)	Authors recommend RAT for N1, pT1a(m) with sum of larger tumor diameter ≥ 20 mm and/or T3 mPTC, but RAT was not associated with DFS ($P = .8$). Independent risk factors for recurrence: multifocality, N1, and male sex. Multifocal foci sum is a significant predictor for recurrence ($P = .009$; HR, 1.2; 95% CI, 1.05–1.4) with threshold of ≥ 20 mm. Recurrence-free probability was worse for T3 vs T1a mPTC ($P = .02$)
Kazaure, 2012 (51)	SEER database	423 738 PTC (mean age, 48.5 y DSV; 55 y TCV; 47 y PTC); DSV and TCV, 47%; T3, 68%; N1, 10% M1	52% DSV, 43% TCV, 51% PTC	No	Cancer death, 1158 (0.3%)	NA (4 y DSV, 3 y TCV, 5 y PTC; range NA)	RAT independent risk factor for cancer death. DSV patients were 4.9 times more likely to die (HR, 1.8; 95% CI, 1.2–2.7; $P = .007$), and TCV patients, 2.1 times (HR, 1.9; 95% CI, 1.4–2.5; $P <$ .001) if they did not receive RAT
Elisei, 2012 (52)	PSC	319 PTC (median age, 43 y), pT1–2 N0 M0	12%	TNM	Recurrences, 24 (8%)	Tg + neck US (mean 5.3 ± 0.8 y)	More relapse in BRAF mut vs wt ($P =$ .0001), not significant in pT1a. RAT is recommended in all but LR RAT wt patients. No recurrence observed in non-RAT-treated BRAF mut or wt. Vascular invasion associated to relapse ($P = .03$) on univariate analysis

Abbreviations: BRAF mut, BRAF mutated; CI, confidence interval; CRx, chest radiography; DSV, diffuse sclerosing variant of PTC; HR, hazard ratio; NA, not available; PSC, prospective single center; RSC, retrospective single center; SEER, Surveillance Epidemiology and End Results Program; TCV, tall cell variant of PTC; wt, wild type.

between radioiodine therapy and negative perception of illness could be linked to the fact that all the patients in the study had been withdrawn from thyroid hormone for RRA, the need for isolation following therapy, or both.

Factors that currently influence RRA usage

Somewhat surprisingly, given the paucity of evidence of benefit, an increased use of RRA has paralleled the increase in LR DTC incidence (81). In the United States, the use of RRA increased for all tumor sizes from 40.5% in 1990 to 65% in 2008, and a greater likelihood of receiving RRA was observed for younger patients in multivariate analysis (odds ratio, 2.15; 95% confidence interval, 2.04–2.26) (89). A large hospital-based variation was also observed, with patient and tumor characteristics explaining only 21% of this variation; hospitals with higher numbers of thyroid cancer cases were associated with higher RRA use (89). In LR patients, young age (90) and multiple tumor foci (80) were associated with increased RRA use. Higher socioeconomic status has also been associated with greater RRA use and lower AJCC stage (91). Moreover, in the United States, RRA use is influenced by geographic region, especially for LR patients (variation from 28 to 47%) (92).

In a recent survey of over 500 providers, most whom were endocrinologists, factors considered important in the decision to use RRA in LR and IR patients included not only prognostic factors and the patient's willingness to receive RRA, but also the patient and physician degree of worry about cancer death (93). Because the death rate in LR thyroid cancer is close to zero and is not much worse in many IR patients, these data reveal a significant knowledge gap.

In an in-depth study of 16 thyroid cancer patients' attitudes and experiences regarding radioiodine therapy after surgical treatment of thyroid cancer, patients reported receiving contradictory information about radioiodine therapy from various sources, including their own primary care physicians, endocrinologists, and the Internet. Patients regretted not having received simple information about potential risks and benefits and uncertainties re-

Table 5. Review of Evidence of RAT Benefit in IR Patients or Patients With Risk Modifiers From 2013 to 2014, Evidence of Benefit

First Author, Year (Ref)	Design	Population	Non-RAT-Treated	Risk Stratification	Event No.	F/U Tools (Median F/U)	Results
Mihailovic 2013 (54)	RSC	130 mDTC (mean age, 44 y); 36% N1, 2% M1	52%	No	Cancer death,4 (3%); recurrences, 14 (11%)	Tg + DxWBS ± neck US (10 y, range 1–25)	RAT improves recurrence ($P = .005$). Risk factors for recurrence: N1, radioiodine treatment, initial treatment (TT + RAT, TT or NTT, lobectomy)
Lee, 2013 (55)	RSC	3347 PTC (mean age, 45 y); 57% T3, 3% T4, 33% N1a, 13% N1b, 1% M1	58%	No	Recurrences, 134 (4%)	Tg + imaging (NA, ≥2 y, range NA-15)	RAT prognostic factor for DSS in univariate analysis (data not shown). Independent risk factor for recurrence: number of N1
Ardito, 2013 (53)	RSC	149 mPTC (44% age < 45 y); 13% T3, 10% N1, 1% M1	67%	No	Cancer death,1 (0.6%); recurrences, 28 (19%)	Tg + DxWBS ± imaging (5.4 y, range 5–11)	27/28 recurrences in RAT-treated patients. Independent risk factors for recurrence: multifocality, extrathyroidal invasion, solid pattern, absence of capsule. RAT is recommended in patients with these risk factors
Pedrazzini, 2013 (56)	RSC	231 mPTC (mean age, 45.7 y); 32% N1, 0.4% M1	43%	NA	Recurrences, 15 (6%)	Tg + neck US (12 y, range 5–35)	Independent risk factors for recurrence: age < 45 y, N1 at presentation. RAT is recommended in young patients with multifocal tumor or N1
Goldfarb, 2014 (57)	National cancer data base	42 062 TC patients (all < 45 y); 1349 with prior malignancies	55% TC as 1st cancer; 50% in TC as 2nd cancer	Variables that contribute to risk stratification	Cancer death, NA	NA (mean, 2.9 ± 2 y)	OS was improved by female sex and RAT and decreased by secondary malignancy status, Hispanic ethnicity, low SES, age 35–39 y, N1 and distant metastases

Abbreviations: DSS, disease-specific survival; mDTC, micro DTC; NA, not available; OS, overall survival; RSC, retrospective single center; SES, socioeconomic status; TC, thyroid cancer; TT, total thyroidectomy; NTT, near TT.

garding RRA, and they were particularly emphatic about the need to disclose the possibility of DR despite RRA (94). Patients in the study made four recommendations for physician counseling about RRA: 1) provide an explanation of the rationale for or against RRA using the patient's clinical status in the discussion; 2) in plain language, provide the risks and benefits of RRA as well as the uncertainties and the possibility of DR despite RRA; 3) provide a multidisciplinary team-based approach and individualized care; and 4) provide information pertinent to their care that is present in current clinical practice guidelines (94).

Strategies for Sparing Patients From RRA

Together with ATA risk class, additional criteria have been utilized to help in the decision whether to administer an ablative dose of radioiodine. A pretreatment DxWBS with no uptake is one traditional criterion to exclude patients from RRA. ATA guidelines recommend pretreatment DxWBS only: 1) when the extent of the thyroid remnant cannot be ascertained from the surgical report or with neck US; or 2) if the results would alter the decision to perform RRA or the administered RRA activity (3). However, DxWBS is often not performed because of high cost and the concern about stunning when ^{131}I (but not ^{123}I) is used (3). Undetectable Tg has been proposed as a criterion to spare patients from RRA. In one study, patients with stimulated Tg ≤ 1 ng/mL had very low rates of DR despite not receiving RRA (63), and in another study, RRA-treated and non-RRA-treated patients with nonstimulated undetectable Tg (defined as a Tg < 1 ng/mL) had no difference in DR (64).

Conclusions

In reviewing the rationales for RRA in LR and IR patients, the arguments for early staging and facilitation of F/U with Tg levels are not convincingly supported by the available data. With regard to early staging, RxWBS discloses few metastatic foci in cervical nodes, whereas neck US has shown excellent negative predictive value and accuracy (26, 42, 45, 46). Furthermore, the occurrence of M1 in LR and IR patients is rare, and high or rising levels of Tg will suggest the need for further investigation in such patients. The prevention of DR remains a valid argument for radioiodine in an adjuvant role, but no benefit from RAT has been shown for LR patients. In IR patients, or in the presence of risk modifiers such as multifocality or an adverse genetic profile, the benefit of RRA in DR prevention remains controversial. Several studies suggest that in selected patients, DR rates are similar between RRA-treated and non-RRA-treated patients (44, 59, 60, 62, 64, 66–68), suggesting the non-inferiority of the two approaches. Selected series of non-RRA-treated patients report very low rates of DR (61, 63). On the other hand, the proportion of LR and IR patients varies widely among the dif-

Table 6. Adverse Effects of Radioiodine and RRA

Site	Description	Frequency, %	Activity Range, mCi	First Author, Year (Ref)	Comment
Eye	Inflammation of lacrimal glands and xerophthalmia	16	80–600	Zettinig, 2002 (74), Alexander, 1998 (77)	92% of patients had at least one altered lacrimal test but lacrimal test alterations were not related to patients symptoms
	Obstruction of lacrimal duct and epiphora	11	80–600		
	Conjunctivitis (chronic or recurrent)	23	100–1900		
Salivary glands	Sialoadenitis, acute	2–67	100–1300	Van Nostrand, 1986 (71); Lin, 1996 (72); Alexander, 1998 (77)	Linear correlation with cumulative activity; more than half of patients develop xerostomia in the absence of acute post-treatment symptoms; 5% developed xerostomia with 40 mCi
	Sialoadenitis, chronic (xerostomia, obstruction)	2–43	40–1300		
Taste and smell	Transient loss/change in taste and smell	2–58	100–1300	Van Nostrand, 1986 (71); Alexander, 1998 (77)	Dependent on administered activity
Nose	Pain	Rare	>200	Van Nostrand, 1986 (71)	
	Epistaxis				—
Thyroid	Radiation thyroiditis, total thyroidectomy with large remnants	Rare	>75	Van Nostrand, 1986 (71)	
	Lobectomy	60			
Gastrointestinal system	Nausea	5–67	40–450	Van Nostrand, 1986 (71)	Correlation with administered activity. No symptoms with an activity of 30 mCi or less. Nausea starting from 40 mCi
	Vomiting	1–15	100–450	Lin, 1996 (72)	Vomiting 1% with < 100 mCi
Bone marrow	Any hematological abnormality	1–100	100–1040	Van Nostrand, 1986 (71); Alexander, 1998 (77); Dorn, 2003 (73),	Risk increases with cumulative dose and frequency of treatments. Grade > 3 or symptomatic abnormalities are rare
	Low WBC count	64			
	Low PLT count	68			
Fertility	Transient ovarian failure	8	30–1099	Sawka, 2008 (76); Sawka, 2008 (75)	No increased risk of long-term infertility
	Transient testicular failure	100	30–1335		
Second malignancy	Solid cancer and leukemia	Rare	54–1500	Rubino, 2003 (79); Brown, 2008 (78); Iyer, 2011 (80)	Linear correlation to dose; +27% increase in risk compared to general population

Abbreviations: PLT, platelet; WBC, white blood cell.

ferent series. Some analyses examining specific putative higher risk factors suggest that some features traditionally considered to be worrisome, such as microscopic extrathyroidal invasion, alone are not a sufficient argument for RRA (66). With regard to N1 status, the location, number, and size and the presence of extrathyroidal extension of metastatic lymph nodes, rather than the presence or absence of N1, are key features for DR risk estimates (28). The presence of a BRAF mutation in PTC has been associated with a worse outcome, but the association is not independent from other tumor features (95). Furthermore, iodine metabolism gene expression is compromised in BRAF-mutated tumors (96), and some reports have linked the BRAF mutation with radioiodine refractoriness (97, 98). Compared to the meta-analysis and the systematic review that examined literature until 2007–2008 (10, 11), our review of the more recent literature clearly shows no advantage of RRA in LR patients, but it was unable to provide conclusive data for or against RRA DR prevention in IR patients. From the previews of the newly revised ATA Thyroid Nodule and Thyroid Cancer guidelines (B. Haugen, oral communication; and http://www.thyroid.org/members-only/member-resources/ata-draft-guidelines/ accessed 9/23/14), we learn that the risk stratification will be enriched and the recommendations for RRA will be more selective (Table 1). However, for IR patients, no defined recommendation for or against RRA is made. The more thorough and dynamic risk stratification systems developed in the last few years will help to better identify LR and IR patients (Refs. 3–6 and 8; B. Haugen, oral communication; and http://www.thyroid.org/members-only/member-resources/ata-draft-guidelines/ accessed 9/23/14), and to create more homogeneous cohorts of patients, but in populations with low or very low RD rates, only prospective randomized trials can provide a reliable answer. Two prospective randomized trials comparing RRA-treated and non-RRA-treated patients are ongoing in Europe. Estimabl2 (Differentiated Thyroid Cancer: Is There a Need for Radioiodine Ablation in Low Risk Patients; trial no. NCT01837745) is a French non-inferiority study comparing LR patients treated with surgery (total thyroidectomy with or without neck dissection) plus RRA vs patients treated with surgery alone. Inclusion criteria are: DTC in the absence of aggressive histological subtypes, complete surgical tumor resection, surgical N0 or clinical N0 (assessed with neck US +/− fine-needle aspiration biopsy and Tg washout), unifocal pT1b tumors, multifocal tumors with sum of the maximum diameter of all tumor foci above 1 cm and equal or less than 2 cm. The primary objective is the 3-year DFS. The IoN study (Is Ablative Radio-iodine Necessary for Low Risk Differentiated Thyroid Cancer Patients; ClinicalTrials.gov identifier: NCT01398085) is a British non-inferiority study comparing LR patients and selected IR patients treated with total thyroidectomy and RRA vs patients treated

with total thyroidectomy alone. Inclusion criteria are: PTC of any size, absence of aggressive histology and extrathyroidal extension or multifocal tumor foci except from mPTC, N1 in central compartment, and FTC or Hurthle cell carcinoma less than 40 mm in size, without vascular invasion. The primary objective is the 5-year DFS. When the results of these trials become available, they will provide valuable data to inform this issue. Until then, a careful evaluation of the whole range of "aggressive" features of the tumor and patient characteristics (eg, age), rather than just a single element, should guide RRA decision making. Patients should be properly informed and should share in the decision to use RRA. When RRA is considered, low activities (eg, 30 mCi) and recombinant human TSH preparation should be preferred to minimize side effects and QoL impairment (87). The use of high radioiodine activities to reduce disease-specific death rates in LR patients (99) is at odds with the current literature and the tendency of the international evidence-based guidelines toward selective use of RRA with low activities. In this very recent study (99), higher initial activities of radioiodine for RRA (< 54 mCi [2000 MBq] vs > 81 mCi [81 mBq]) did not improve DFS or DSM in patients age < 45 years. However, in LR patients > 45 years of age, there were no differences in recurrence rates, but DSM was higher in those patients who initially received < 54 mCi (2000 MBq) vs those who received > 54 mCi, suggesting that patient age remains an important factor in the decision-making process.

In some patients, DxWBS or the use of basal or stimulated Tg may help to eliminate RRA from consideration. Careful and vigilant F/U with US and basal Tg measurement can be a reliable alternative to RRA. If Tg levels rise or suspicious findings on physical examination or neck US appear, restaging is warranted, and RRA could be considered. An undetectable serum Tg, especially in a high-sensitivity Tg assay, and negative neck US 6–12 months after surgery should enable many LR and IR patients to be categorized as being "free of disease," despite not having undergone RRA.

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