

Current controversies in the use of radioactive-iodine remnant ablation in well-differentiated thyroid carcinoma

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Radioactive-iodine remnant ablation (RRA) is commonly performed as adjuvant therapy in the treatment of well-differentiated thyroid cancer. There is no long-term, randomized, controlled trial evidence to support the use of this intervention. This issue of *Endocrinology Rounds* reviews the existing observational evidence examining the benefits and risks of RRA. The issue also discusses several controversies in the use of RRA, including the use of this intervention in low-risk patients, radioiodine dosing, and the use of recombinant thyrotropin stimulation for ablation.

Case

A 38-year-old previously healthy woman presents with an asymptomatic thyroid nodule that is suspicious for papillary thyroid cancer on fine-needle aspiration biopsy. A few weeks previously, she had received a total thyroidectomy and a 1.6 cm, well-circumscribed papillary thyroid cancer was completely removed. No other lesions were noted in the thyroid and a limited lymph node dissection was negative for tumour. The cancer did not exhibit any tall cell variant, vascular invasion, lymphatic invasion, or extra-thyroidal extension. The resection margins were negative for tumour and no multifocality was noted. Pre-operatively, the patient had no clinical evidence of distant metastases and a chest X-ray was normal. The patient has never received any form of radiation therapy and her family history is unremarkable. Two questions arise from this case:

- Is RRA needed?
- If yes, what is the most appropriate dose of radioiodine for remnant ablation?

Epidemiology of well-differentiated thyroid carcinoma

Thyroid cancer is the most common endocrine malignancy; approximately 3,400 cases will be diagnosed in Canada in 2006.¹ Currently, in Canada, the incidence of thyroid carcinoma is increasing and the rate of increase in the total number of cases (increase in incidence burden) is greater than for any other malignancy.¹ The incidence of thyroid carcinoma is also increasing in the United States (US).^{2,3} The most frequent histologic subtype of thyroid carcinoma is papillary, which accounts for approximately 80% of cases, followed by follicular carcinoma (collectively referred to as well-differentiated thyroid carcinoma, WDTC).^{2,4} In a recent analysis of data from the US, the increase in incidence of thyroid carcinoma was entirely accounted for by an increase in cases of papillary thyroid carcinoma.³ Moreover, most newly-diagnosed cases were at an early stage, since 87% of primary tumours are <2 cm. in diameter.³ Most individuals diagnosed with thyroid carcinoma are relatively young; 58% of incident cases are aged < 50 years (median age at diagnosis 46 years).²

Deaths due to thyroid cancer are relatively infrequent. In Canada, 160 deaths will be attributed to thyroid cancer in 2006.^{1,3} Patients at low risk of thyroid cancer-related mortality are identifiable using various clinical-pathologic staging systems.⁵ Variables such as large primary tumour size, distant metastases at presentation, and advanced age are predictive of WDTC-related mortality.⁶ However, most patients diagnosed with thyroid cancer do not present at an advanced disease stage.⁷ Therefore, the long-term risks and benefits of any treatment for this disease must be considered very carefully, since most WDTC patients are likely to live many years with the diagnosis.



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Table 1: Guidelines pertaining to RRA: Treatment and dosage recommendations

Organization	Who should receive RRA	RAI dose for remnant ablation
AAACE/AAES¹¹ (2001)	The issue of RRA in low-risk patients remains unsettled; a case-by-case decision is recommended, guided by clinical judgment and experience.	Currently, no consensus exists about the most appropriate dose of RAI for ablation. The standard I ¹³¹ dose used in the past for RRA was from 75 to 150 mCi. In recent years, some US centers have used a low-dose regimen of 25 to 29.9 mCi, especially if the amount of thyroid remnant tissue is small.
ATA⁸ (2006)	RRA is recommended for patients with stage III and IV disease (AJCC, 6th edit), all patients with stage III disease aged ≥45 years, and selected patients with stage I disease, especially those with multifocal disease, nodal metastases, extrathyroidal or vascular invasion, and/or more aggressive histologies. RRA of a contralateral lobe is not recommended in lieu of completion thyroidectomy. <i>Women receiving RAI therapy should avoid pregnancy for 6 - 12 months. RAI should not be given to breast-feeding women.</i>	The minimum activity (30-100 mCi) necessary to achieve successful remnant ablation should be chosen, particularly in low-risk patients. If residual microscopic disease is suspected or documented, or if there is a more aggressive tumour histology (eg., tall cell, insular, columnar cell carcinoma), then higher activities (100-200 mCi) may be appropriate.
BTA¹² (2002)	Because of the safety and tolerability of I ¹³¹ ablation, it is recommended that well-differentiated thyroid cancers >1 cm in diameter receive post-operative I ¹³¹ ablation. <i>Pregnancy must be excluded before I¹³¹ therapy is started</i>	The usual ablation dose is 3.7 GBq. Some centres may use low-dose ablation (1100 MBq) or dosimetric assessment of RAI dosage, preferably within a trial or study setting.
ETCTF¹⁰ (2006)	No indication for RRA (low risk of relapse or cancer-specific mortality): Complete surgery, favourable histology, unifocal tumour ≤1 cm, NO, MO (AJCC staging system), no extrathyroidal extension Definite indication (use high activity >3.7 GBq [100 mCi] after thyroid hormone withdrawal): Distant metastases or incomplete tumour resection, or complete tumour resection, but high-risk for recurrence or mortality (ie, tumour extension beyond the thyroid capsule [T3 or T4 using the AJCC staging system] or lymph node involvement) Probable indication (use high or low activity (3.7 or 1.1 GBq [100 or 30 mCi]): Less than total thyroidectomy or no lymph node dissection or age <18 years or T1 >1 cm and T2, NO MO (AJCC staging system) or unfavourable histology, eg, papillary (tall-cell, columnar cell, diffuse sclerosing) or follicular (widely invasive or poorly differentiated) <i>Pregnancy must be excluded before I¹³¹ therapy is started</i>	Dose according to risk group as indicated in the preceding column
NCI⁹ (2006)	Stage I and II papillary and follicular thyroid carcinoma: Studies have shown that a postoperative course of therapeutic (ablative) doses of I ¹³¹ results in a decreased recurrence rate among high-risk patients with papillary and follicular carcinomas. It may be given in addition to exogenous thyroid hormone, but it is not considered routine. Patients presenting with papillary thyroid microcarcinomas (tumours <10 mm) have an excellent prognosis when treated surgically; additional therapy with I ¹³¹ is not expected to improve prognosis. Stage III papillary and follicular thyroid carcinoma: I ¹³¹ ablation following total thyroidectomy if the tumour demonstrates uptake of this isotope.	Not reported.

Note: To covert GBq to mCi, divide by 0.037 (eg. 3.7 GBq = 100 mCi)
RRA = radioactive-iodine remnant ablation, RAI= radioactive iodine, AJCC = American Joint Committee on Cancer

The goals of RRA treatment and the controversy surrounding its use in low-risk patients

The first-line of treatment for thyroid cancer is thyroidectomy; most commonly, a total or near-total thyroidectomy is recommended.⁸⁻¹² Conventionally, adjuvant RRA is recommended after bilateral thyroidectomy (Table 1).⁸⁻¹² RRA refers to the destruction of residual, macroscopically normal thyroid tissue after a complete gross surgical resection of cancer. The following discussion is

limited to those who have had gross surgical resection of WDTC and not patients with known persistent or recurrent disease, who would usually receive radioactive iodine (RAI) therapy (as opposed to adjuvant ablation). The theoretical goals of RRA are:

- to destroy any residual microscopic thyroid carcinoma
- to facilitate follow-up and early detection of recurrent or metastatic disease by measurement of serum thyroglobulin (with or without stimulation by recombinant

thyrotropin) or by RAI scanning (thereby enabling earlier treatment of recurrent disease).

Thyrotropin stimulation is required for RRA.⁸⁻¹² The alternative to RRA is close medical follow-up (including periodic measurements of thyroglobulin in the blood, imaging of the neck, and chest X-rays). Thyroid hormone (TH) therapy is generally administered after thyroidectomy, typically in doses sufficient for some suppression of endogenous thyrotropin secretion.⁸⁻¹²

In the US, approximately 38% of patients with WDTC are reported to have received RAI ablation or therapy (from 1973 to 1999).² In a survey of members of the American Thyroid Association published in 1996, 61% of respondents recommended RRA for a hypothetical low-risk papillary cancer case (a 39-year-old woman with a 2-cm primary tumour and no prior radiation exposure).¹³ Canadian patterns of RRA use are not known. As a result, at the University Health Network and Mount Sinai Hospital in Toronto, we are currently conducting a survey of Canadian physicians caring for patients with WDTC, to characterize RRA-related practice patterns. The sample case described above has been included in this survey.

As noted in Table 1, recommendations about which WDTC patients should receive RRA are varied.⁸⁻¹² The main controversy relates to the use of RRA in patients considered at low-risk of dying from WDTC. These patients are classified as early stage WDTC by current clinical-pathologic staging systems and the controversy stems from the lack of a long-term, randomized, controlled trial proving the benefit of RRA in decreasing WDTC-related recurrence or death in such patients.¹⁴

In a systematic review of cohort studies comparing thyroid cancer-related outcomes in predominantly low-risk RRA-treated patients with outcomes in untreated patients, significant heterogeneity was observed in the effects of RRA on decreased WDTC-related mortality.¹⁴ Moreover, the 10-year mortality rate exclusively among papillary cancer patients was relatively low, at 1.7%.¹⁴ Given this low thyroid cancer-related mortality rate in low-risk papillary patients, it is not surprising that an obvious benefit of this intervention in decreasing deaths was not clearly noted in the majority of studies.¹⁴ Additionally, this review found no statistically significant treatment benefit of RRA in decreasing WDTC-related mortality in follicular cancer patients.¹⁴ However, pooled analyses were suggestive of a statistically significant treatment effect in favour of RRA for the following 10-year WDTC outcomes: local-regional recurrence (relative risk 0.31, 95% confidence interval [CI], 0.20–0.49) and distant metastases (absolute decrease in risk 3%, 95% CI, 1%–4%).¹⁴ The incremental benefit of RRA in decreasing thyroid cancer-related outcomes after TH-suppressive therapy could not be determined in this study because the degree of TH suppression was not reported in the majority of cohort studies.¹⁴ Furthermore, many of the included cohort studies did not report the details of radioiodine dosing used for RRA. In studies reporting radioiodine dosing, the doses ranged from 28 to 200 mCi.¹⁴

It should be acknowledged that this meta-analysis is subject to bias and inaccuracy since the included studies were not randomized controlled trials and most had high

losses in follow-up.¹⁴ Moreover, most of the studies did not report the short- and long-term side effects of RRA or the impact of RRA on long-term health-related quality of life.¹⁴ After publication of this systematic review, an update of a Canadian cohort study of patients with WDTC was published by Brierley et al.¹⁵ This group observed no statistically significant benefit of RRA for cause-specific survival or local-regional recurrence rate in patients aged ≤ 45 years who were at American Joint Committee on Cancer (AJCC) stage I at the time of surgery.¹⁵ However, a statistically significant benefit in cause-specific survival and local-regional recurrence rate was noted in RRA-treated patients who were ≥ 45 years of age and at AJCC stage I, II, and III (without distant metastases and gross residual disease).¹⁵ In patients aged ≥ 45 years with no evidence of distant metastases, gross residual disease, or lymph node involvement at the time of surgery (AJCC Stage I or II), there was a statistically significant benefit of RRA for the outcome of local-regional recurrence, but not for cause-specific survival.¹⁵

It is thought that only a long-term, randomized, controlled trial of RRA will definitively prove the benefit of this intervention, particularly in low-risk groups;¹⁴ however, the feasibility of such a trial has been questioned.¹⁶ Challenges to the dosing and implementation of a randomized controlled trial of RRA include the low mortality rate of this malignancy (if mortality is used as a primary outcome) and the routine use of “sensitive follow-up paradigms” (eg, measurement of stimulated thyroglobulin) in WDTC patients after remnant ablation.¹⁶

Dosage recommendations for RRA

If remnant ablation is chosen, the optimal dose for RRA suggested by subspecialty organizations varies from “no firm dose”^{9,11} to fixed doses of 30 to 100 mCi (Table 1).^{8,10,12}

- The American Thyroid Association recommends that “minimum activity” radioiodine is needed for successful remnant ablation, with higher doses used in selected higher risk cases (eg, suspected residual microscopic disease or aggressive tumour histology).⁸
- In contrast, the British Thyroid Association recommends a “usual” dose of 100 mCi of radioiodine (with lower doses used in a study setting).¹²
- The European Thyroid Cancer Task Force recommends variable dosages according to the stage of disease.¹⁰

The result is a lack of consensus among thyroid and cancer subspecialty organizations on the optimum dose of RRA.

There are no long-term randomized controlled trials examining thyroid cancer-related recurrence or mortality using low-dose RRA compared to high-dose RRA. Theoretical advantages of low-dose ablation include a potentially lower risk of radiation-related side effects and outpatient therapy (in institutions where doses >29.9 mCi are given to inpatients). The short-term efficacy of a single low-dose of RRA (approximately 30 mCi) has been compared to a single higher dose of RRA (~ 75 to 100 mCi) for achieving complete ablation (thyroidal uptake on RAI scans) in a systematic review and meta-analysis.¹⁷ This review was limited because the authors chose to pool data from randomized controlled trials with data from cohort

studies.¹⁷ The authors found that the average failure of a single low-dose of RRA to achieve complete ablation was 46%.¹⁷ The relative risk of ablation failure was 27% lower with high-dose RRA than with low-dose RRA.¹⁷ However, in sensitivity analyses in which data from randomized controlled trials were pooled separately from the observational studies, a statistically significant treatment benefit of high-dose ablation was observed only in the pooled analysis of observational studies.¹⁷

Subsequently, Bal et al reported the results of a controlled trial in 565 patients randomized to 8 different doses of RRA, ranging from 5 mCi to 50 mCi (in 5 mCi increments).¹⁸ This study was designed to be an equivalence study and data from 509 patients were analyzed in a per protocol analysis.¹⁸ In this study, the rate of successful ablation was significantly higher in patients treated with radioiodine doses >25 mCi (81.6%) compared with those receiving lower doses (61.8%).¹⁸ It was not clear whether the comparison at a 25 mCi dose cut-off was planned *a priori* in the study as a primary analysis or whether this was a *post hoc* secondary comparison, since multiple comparisons were undertaken. Therefore, the optimum minimum dose for successful remnant ablation remains unclear. Moreover, it is not known whether the repeated doses of RAI required to complete initially unsuccessful ablation have any impact on long-term WDTC outcomes or quality of life.

Thyrotropin stimulation for RRA

In preparation for RRA, thyrotropin stimulation is required. This is accomplished endogenously by TH withdrawal or exogenously with the use of recombinant human thyrotropin (rhTSH). TH withdrawal has traditionally been recommended prior to remnant ablation.^{8,10,12} More recently, administration of rhTSH prior to RRA has been suggested as an alternative to TH withdrawal.^{8,10} Dietary iodine restriction for several weeks prior to RRA has also been traditionally recommended.^{8,10}

The advantages of using rhTSH prior to remnant ablation are the avoidance of clinical hypothyroidism, with its associated cognitive, emotional, and physical impairments or the complications of co-morbid conditions.¹⁹ Several single-centre comparative observational studies²⁰⁻²² and one multicentre, randomized, controlled trial,²³ have examined the use of rhTSH in preparation for RRA. They revealed no statistically significant differences between the TH-withdrawal group and the rhTSH group at the whole body I¹³¹ scan follow-up; the protocol for rhTSH included 2 consecutive days of 0.9 mg intramuscular dosing, followed 24-hours later by therapeutic RAI administration.²¹⁻²³ The doses of RAI administered after rhTSH ranged from fixed doses of 30 mCi^{20,21} or 100 mCi²³ to variable doses determined by dosimetry.²²

In the open-label, multicentre, randomized controlled trial of rhTSH compared with TH withdrawal pre-RRA, 100 mCi of I¹³¹ was administered 24-hours

after the second injection of rhTSH, with a successful ablation rate of 100% in both groups (28 patients randomized to TH withdrawal and 32 patients to rhTSH).²³ This 100% success rate in remnant ablation is higher than results observed in most prior studies using similar I¹³¹ activity after TH withdrawal.¹⁷ Health-related quality of life around the time of ablation was a secondary outcome examined in this trial; inferior scores were observed in several domains in the TH-withdrawal group using the Billewicz and SF-36 scales.²³ Another secondary analysis examined RAI kinetics; I¹³¹ activity was found to be lower in the blood of patients receiving rhTSH compared with those in the TH-withdrawal group.²³ The authors of this trial concluded that comparable remnant ablation rates may be obtained with 100 mCi of I¹³¹ in patients pre-treated with rhTSH compared to TH withdrawal and a higher quality of life is maintained (around the time of the procedure) with less radiation exposure.²³ Currently, there are no long-term randomized controlled trials comparing long-term thyroid cancer-related outcomes, long-term quality of life, or the long-term side effects of RAI in patients pre-treated with rhTSH compared to TH withdrawal for RRA.

Short- and long-term side effects of RAI and associated preparation for remnant ablation

The side effects of RAI therapy are generally dose-dependent and include acute and long-term effects. Some acute side effects of RAI (within 1-2 weeks after therapy) are caused by acute inflammation or tissue destruction and may include: uptake neck pain (in the region of the thyroid bed),²⁴ salivary gland pain,^{24,25} dry mouth,²⁴ change in taste,²⁴ abdominal pain (due to radiation gastritis),²⁴ and bladder irritation (due to radiation cystitis).¹² Changes in taste and salivary function may be variably persistent for different lengths of time. Some patients may experience acute nausea after administration of RAI, possibly a form of radiation sickness.²⁴ RAI therapy has also been associated with transient impairments in gonadal function in men²⁶ and women.^{27,28} The pregnancy miscarriage rate is reported to be as high as 40% in women who became pregnant within a year of RAI administration.²⁹ Blood count abnormalities are also observed in a small proportion of individuals treated with typical ablation doses of RAI, although these are considered clinically significant in only ~1% of cases.³⁰

In considering the short-term side effects of administering therapeutic RAI, the symptoms of TH-withdrawal preparation and the inconvenience of a low-iodine diet should also be considered. Symptoms of hypothyroidism at the time of ablation are expected and may include, fatigue, muscle cramps, edema, constipation, mood changes, weight gain, and cognitive changes. Hypothyroid symptoms are avoided by using rhTSH.²³ A low-iodine diet for several weeks prior to ablation is often advised to improve the efficacy of ablation.^{8,10,31} Some patients may find this diet

inconvenient and unpalatable. In a retrospective study from the Netherlands, the success rate for ablation was 65% in patients treated with a low-iodine diet, compared with 48% in patients without this diet.³² However, the stringency of a low-iodine diet has been questioned, given the relatively low North American dietary iodine intake.³³

An important consideration in the use of RAI is the risk of secondary malignancies, including solid tumours and leukemia.³⁴ Rubino et al, pooled cohort data from 6,841 thyroid cancer patients in Sweden, Italy, and France, who were diagnosed between 1934 and 1995 (mean age 44 years at diagnosis).³⁴ Compared with the general European population, an excess absolute risk of 14.4 solid cancers and 0.8 leukemias per GBq (27 mCi) of RAI and 100,000 person-years of follow-up was observed.³⁴ A relationship was also noted between RAI administration and the occurrence of bone and soft tissue, colorectal, and salivary gland cancers.³⁴ In this study, the mean time interval between thyroid cancer diagnosis and secondary malignancy was 15 years and the mean age at the time of secondary malignancy diagnosis was 64 years.³⁴

There are several other potential long-term consequences of RAI therapy. Long-term pancytopenia has been observed in some bone marrow biopsies of thyroid cancer survivors who received RAI.³⁵ Long-term cytopenias in the peripheral blood are largely dose-dependent, relative to the administered radioactive iodine dose.³⁶ Infertility is a theoretical concern after RAI therapy, but this risk is not thought to be higher than in the general population for both women and men.^{26,29,37-40} The risk of birth defects in children of thyroid cancer survivors who received RAI prior to conception are generally not thought to be higher than in the general population,^{29,37-39} although an increased risk of congenital anomalies was suggested in 1 small study.⁴¹

Long-term decreases in salivary flow rates and consequent xerostomia may also be a long-term complication of RAI therapy.^{42,43} The impact of RAI on salivary gland function is dose-dependent.⁴⁴ Nasolacrimal duct obstruction has been observed as a long-term complication of RAI treatment.⁴⁵ The increased risk of nasolacrimal drainage obstruction after RAI therapy may be partly explained by the known expression of the sodium-iodine symporter in the lacrimal sac and nasolacrimal duct.⁴⁶

Conclusion

The current epidemiology of well-differentiated thyroid cancer reflects the fact that more cases are being diagnosed at an earlier stage. Most patients diagnosed with early stage thyroid cancer have a low risk of death from this disease, so careful consideration of therapies such as RAI ablation is needed to balance potential risks and benefits. Although the use of RRA may facilitate follow-up using sensitive follow-up paradigms (eg, incorporating measurements of stimulated

thyroglobulin), it is not known if such strategies improve long-term thyroid cancer-related outcomes and quality of life in most low-risk thyroid cancer patients. Further prospective studies, ideally including randomized controlled trials, are needed to better define the role of current and future therapeutic interventions in this disease. In the absence of such trials, it seems reasonable for physicians and patients to consider the currently available clinical practice guidelines, acknowledging the uncertainty in the observational evidence upon which they are largely based, and the variability in recommendations from various organizations. In recent clinical practice guidelines such as those from the National Cancer Institute, RRA is no longer considered a "routine" requirement for all low-risk patients.⁹ Therefore, in many circumstances of low-risk WDTC, either RRA or careful surveillance without RRA may be considered reasonable options. Furthermore, if RRA is considered, the optimal dose is currently unclear. These issues are exemplified in the sample case for which there are really no clear "correct" answers for the questions posed.

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