THEMATIC REVIEW

Tailoring the approach to radioactive iodine treatment in thyroid cancer

Sarah E Mayson¹, Christine M Chan² and Bryan R Haugen^{1,3}¹Division of Endocrinology, Metabolism and Diabetes, University of Colorado School of Medicine, Aurora, Colorado, USA²Section of Endocrinology, Department of Pediatrics, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, Colorado, USA³University of Colorado Cancer Center, Aurora, Colorado, USACorrespondence should be addressed to S E Mayson: Sarah.Mayson@cuanschutz.edu

This paper is part of a thematic review section celebrating 80 Years of the Use of Radioiodine. The guest editor for this section was Christopher John McCabe.

Abstract

The treatment of differentiated thyroid cancer continues to move away from a 'one size fits all' approach to a process of tailored therapeutic decision-making that incorporates disease-specific factors and individual patient preferences. Management options range from active surveillance to thyroid lobectomy to total thyroidectomy with or without the use of postoperative radioactive iodine (RAI). RAI may be administered for one or more reasons: Thyroid remnant ablation, adjuvant therapy, or therapy for persistent structural disease. It is important to be cognizant of the therapeutic intent of RAI and weigh the risks and benefits of treatment for each individual patient. Risk stratification should be used to identify those patients who are most likely to benefit from RAI and guide therapeutic choices. Available data suggest that RAI can be safely deferred for most patients considered at low risk for structural recurrence, while adjuvant RAI is associated with improved disease-free survival in patients with higher-risk disease. Although progress has been made, many areas of uncertainty related to the use of RAI remain. These include: (1) The appropriate selection of intermediate-risk patients to receive adjuvant RAI, (2) the superiority or inferiority of different RAI dosing activities, (3) the optimal approach to the use of RAI in special populations, including patients with end-stage renal disease and children, and (4) the management of patients with RAI-refractory disease.

Key Words

- ▶ thyroid cancer
- ▶ radioactive iodine
- ▶ remnant ablation
- ▶ adjuvant therapy

Endocrine-Related Cancer
(2021) **28**, T125–T140

Introduction

The first radioisotope of iodine produced was ¹²⁸I in the late 1930s by irradiating ethyl iodide with a radon-beryllium neutron source (Borges de Souza & McCabe 2021). By September 1937, collaborative efforts between Saul Hertz, Arthur Roberts, Howard Means, and Robley Evans led to an efficient method of ¹²⁸I production, which had a short half-life of approximately 25 min (Hertz 1938). Subsequent cyclotron technology using deuteron bombardment of tellurium led to the production of ¹³⁰I and a small amount of ¹³¹I. Hyperthyroidism was first treated with ¹³⁰I in the

late 1930s, but it was Samuel Seidlin who first reported the use of ¹³¹I to treat thyroid cancer in 1946 (Seidlin *et al.* 1946). A pivotal report in 1963 described a 14-year follow-up of 200 patients with thyroid cancer treated with ¹³¹I (Haynie *et al.* 1963). More than half of the patients with distant metastases were rendered disease-free. Radioiodine (RAI) is likely the first 'targeted therapy' for cancer.

There are 37 known isotopes of iodine, and ¹²⁷I is the only one that is not radioactive. The two main forms of radiation emitted from ¹³¹I are beta particles and

gamma rays. The beta particles, lacking in ^{123}I , confer the therapeutic benefit of ^{131}I . These beta particles have a maximum energy of 0.61 MeV, a range in the tissue of only 0.8 mm, and a decay half-life of approximately 8 days (Mumtaz *et al.* 2009).

The three basic considerations for using RAI (^{131}I) in patients with differentiated thyroid cancer (DTC) are remnant ablation, adjuvant therapy, and therapy (Table 1) (Haugen *et al.* 2016). These three categorical definitions are supported by a joint statement from the American Thyroid Association, European Association of Nuclear Medicine, Society of Nuclear Medicine and Molecular Imaging, and European Thyroid Association (Tuttle *et al.* 2019). It is important for those who treat patients with thyroid cancer to consider these three treatment categories and the risk/benefit for the use and administered activity of RAI in each patient.

Logistical considerations

When considering whether to give RAI to patients with DTC or which administered activity to give, we must consider the intent of the treatment, noted above, as well as the stage of disease and risk of recurrent disease. The AJCC/TNM 8th edition staging system dramatically changed in 2018, raising the age from 45 to 55 years and limiting older patients with lymph nodes metastases to stage II, among other changes (Table 2) (Tuttle *et al.* 2017a,b). The 8th edition of this staging classification is equal or superior to the 7th edition at separating survival between the four stages and reclassifies many patients into stage I (Pontius *et al.* 2017, Kim *et al.* 2018, Tam *et al.* 2018, van Velsen *et al.* 2018). While staging is a good predictor of overall survival and disease-specific survival, it is not a good predictor of disease recurrence or recurrence-free survival. The American Thyroid Association (ATA) developed and refined a recurrence risk stratification system into low-risk, intermediate-risk, and high-risk categories (Table 3) (Haugen *et al.* 2016).

The basic oncologic principles when considering any treatment, in this case RAI, are a risk/benefit assessment for improved survival, decreased recurrence, or ability to

more accurately monitor patients for disease recurrence. The risks of RAI therapy are discussed later in this chapter. There is no evidence that RAI adjuvant therapy improves survival in patients with stage I or stage II DTC. One potential caveat is patients <55 years old with distant metastatic disease (stage II). Generally, these patients are considered in the 'therapy' category, and most experts agree that RAI likely improves disease-specific survival. Some have suggested this subgroup be reclassified as stage III (Tam *et al.* 2018). Most patients with stage I or II DTC should not be considered for RAI adjuvant therapy if the intent is to improve survival.

The primary oncologic intent when considering RAI adjuvant therapy in most patients with DTC is to decrease the risk of recurrent disease, which is discussed in detail in the next sections. Finally, patients with DTC at low risk for disease recurrence may be considered for remnant ablation to more accurately monitor for response to therapy, using diagnostic RAI whole-body scans (WBS) and serum thyroglobulin tumor marker. There is growing evidence that diagnostic RAI WBS are generally not needed to monitor patients with the low-risk disease since the sensitivity of the scan in this situation is quite low (Pacini *et al.* 2002). Serum thyroglobulin is generally low (<1 ng/mL) after thyroidectomy in low-risk patients and can be monitored without RAI in most patients. It is our practice to measure serum thyroglobulin preoperatively to determine if postoperative serum thyroglobulin may be a reliable marker of disease persistence or recurrence and assess for the presence of anti-thyroglobulin antibodies. If the preoperative serum thyroglobulin is low normal, it may not be a sensitive marker for persistent or recurrent disease. One study showed that preoperative serum thyroglobulin levels above 30 and 63 ng/mL, were associated with contralateral lymph node metastases and distant metastases, respectively, although sensitivity and specificity are not optimal (Kim *et al.* 2020).

When should one consider a postoperative diagnostic RAI WBS? The simple answer is to perform a postoperative diagnostic RAI WBS if there is a high likelihood that it will change the use or administered activity of RAI treatment. The use of single-photon emission computed tomography

Table 1 Categories for consideration of the use of RAI in patients with DTC.

RAI considered for	Intention of treatment
Remnant ablation	To ablate any remaining normal thyroid cells to help facilitate detection of recurrent or persistent disease using thyroglobulin or diagnostics whole-body RAI scans
Adjuvant therapy	To improve disease-free survival in patients with no known residual disease but who are at intermediate or high risk for recurrent disease
Therapy	To treat known disease to improve disease-specific and disease-free survival

Table 2 AJCC/TNM 8th edition staging system.

	Stage	Description	Expected 10-year DSS
Younger patients	I	<55 years old No distant metastases	98–100%
	II	<55 years old Distant metastases	85–95%
Older patients	I	≥55 years old ≤4 cm tumor Confined to thyroid	98–100%
	II	≥55 years old >4 cm tumor <u>or</u> Lymph node metastases <u>or</u> Gross extrathyroid extension into strap muscles	85–95%
	III	≥55 years old Tumors of any size with gross extrathyroid extension into subcutaneous tissue, larynx, trachea, esophagus or RLN	60–70%
	IV	≥55 years old Any tumor with gross extrathyroid extension into prevertebral fascia, encasing major vessels (IVA) <u>or</u> Distant metastases (IVB)	<50%

Data from Tuttle *et al.* (2017a).

DSS, disease-specific survival; RLN, recurrent laryngeal nerve.

(SPECT) imaging has greatly improved the utility of RAI WBS, and this should be used instead of planar imaging where available (Van Nostrand 2017). There is still controversy in the literature as to when one should use a postoperative diagnostic WBS. We generally consider it for younger patients (<20 years old) who may have a higher likelihood of small pulmonary metastases and patients who have high postoperative serum thyroglobulin. There is some evidence that higher administered activities of ¹³¹I (≥4–5 mCi) may lead to less effective subsequent treatment

(Hu *et al.* 2004). If a postoperative RAI WBS with SPECT imaging is considered, ¹²³I (1.5–3 mCi) should be used, or ¹³¹I (1–3 mCi) should be used if ¹²³I is not available or feasible (cost) (Haugen *et al.* 2016).

Patient preparation for RAI treatment or diagnostic testing has two important components, the low iodine diet (LID) and TSH stimulation. The recommended daily dietary allowance for iodine is 150 µg for US adults. According to the National Health and Nutrition Examination Survey (NHANES) 2011–2014, the median urinary iodine

Table 3 American Thyroid Association (ATA) risk stratification for recurrent disease.

ATA risk	Description
Low	All macroscopic tumor has been resected <u>and</u> No extrathyroid extension <u>and</u> No aggressive histology (tall cell, columnar, insular, hobnail) <u>and</u> No vascular invasion <u>and</u> No distant metastases <u>and</u> If RAI is given, no uptake outside thyroid bed region <u>and</u> N0 or low volume LN mets (≤5 pN1 micrometastases) Intrathyroidal FTC with no or minimal (<4 foci) vascular invasion
Intermediate	Aggressive histology (see above) Microscopic extrathyroid extension PTC with vascular invasion Clinical N1 or >5 pN1 LN <3 cm or extranodal extension RAI-avid metastatic foci in neck (if RAI given)
High	Gross extrathyroid extension N1 disease with any involved LN ≥ 3 cm FTC with extensive vascular invasion (> 4 foci) Incomplete tumor resection Distant metastases Elevated postoperative serum thyroglobulin

Data from Haugen *et al.* (2016). Patients with LN metastases can be in low-, intermediate-, or high-risk groups.

N0, no metastatic LN; pN1, metastatic LN only identified at pathology assessment (clinical N0).

concentration (UIC) was 133 $\mu\text{g/L}$ (95% CI, 128–141) (Herrick *et al.* 2018). The lowest median UIC was in the 40- to 49-year-old age group at 107 $\mu\text{g/L}$ and the highest adult median UIC was in the 70+ age group at 169 $\mu\text{g/L}$. The ATA recommends a 1- to 2-week LID (<50 $\mu\text{g/day}$) (Haugen *et al.* 2016). A systematic review showed that this LID target appeared to be associated with a reduction in urinary iodine secretion as well as an increase in ^{131}I uptake, compared with no LID (Sawka *et al.* 2010). When assessing compliance with LID, one can measure 24 urine iodine levels (gold standard, cumbersome) or spot urinary iodine to creatinine ratio (easier, potentially less accurate). A study directly comparing 24 h urine ($\mu\text{g/day}$) vs spot urine iodine levels ($\mu\text{g/L}$) showed a poor correlation in patients on a LID (Kim *et al.* 2010). The correlation was significantly improved when using the spot urine iodine to creatinine ratio ($\mu\text{g/g Cr}$). If urine iodine is measured after LID, it is reasonable to aim for a 24 h UIC of < 100 $\mu\text{g/L}$ or a spot ratio of <100 $\mu\text{g/g Cr}$ (Li *et al.* 2016). If these values exceed 200 $\mu\text{g/L}$ or $\mu\text{g/g Cr}$, postponement of the RAI should be considered. Measurement of UIC is generally reserved for patients at high risk for recurrence or known metastatic disease. We generally use a 1-week LID for patients receiving adjuvant therapy for intermediate-risk disease and do not routinely measure urine iodine. For patients with a metastatic disease requiring RAI therapy, we generally use a 2-week LID and measure urine iodine, especially if a negative scan will render the patient RAI-refractory. The iodine contribution of levothyroxine, continued when patients are prepared with recombinant human TSH (rhTSH), is considered to be fairly small (Fujimoto *et al.* 2021).

In order to drive RAI into remnant thyroid cells and RAI-avid thyroid cancer cells, serum TSH must be temporarily elevated. The ATA thyroid nodules and cancer guidelines recommend that rhTSH is an ‘acceptable alternative’ to thyroid hormone withdrawal (THW) in patients where the intent is remnant ablation (Haugen *et al.* 2016). In patients with a higher risk of recurrence, where RAI is being used as adjuvant therapy, rhTSH may be ‘considered as an alternative to THW’. At our institution, as is similar at many institutions with large thyroid tumor programs, we almost exclusively use rhTSH preparation for patients being treated as adjuvant therapy and remnant ablation, based on multiple short-term follow-up studies (Mallick *et al.* 2012b, Schlumberger *et al.* 2012, Pak *et al.* 2014, Tu *et al.* 2014, Leenhardt *et al.* 2019). Patients who are at high risk for recurrence need individualized decision-making about using rhTSH or THW since the evidence is more limited in this subgroup (Tala *et al.* 2011, Klubo-Gwiedzinska *et al.* 2012, Iizuka *et al.* 2020).

Hyponatremia with LID was more frequent after THW compared with rhTSH, which is another advantage of using rhTSH to prepare for RAI treatment (Li *et al.* 2016). High-risk individuals should have serum sodium measured weekly after starting LID until a week after RAI treatment. It is important to encourage low iodine salt intake, especially in higher-risk individuals. Administered activities will be discussed in more detail below.

Goals of radioactive iodine therapy

Thyroid remnant ablation

The term ‘remnant ablation’ refers to the administration of RAI to ablate the postsurgical thyroid remnant in order to facilitate staging and monitoring for disease recurrence. The ATA guidelines recommend choosing a lower administered RAI activity over higher activities when RAI is used for remnant ablation in patients with low-risk DTC (Haugen *et al.* 2016).

Lower RAI activities have been shown to be just as effective as higher activities in achieving ablation of the postoperative thyroid remnant following thyroidectomy. Two large multicenter randomized trials from France (ESTIMABL1) and the UK (HiLo) simultaneously evaluated the method of TSH stimulation (rhTSH vs THW) and compared two different RAI activities, 30 mCi (1.1 GBq) and 100 mCi (3.7 GBq). Both studies found that ablation success was independent of method and dose (Mallick *et al.* 2012b, Schlumberger *et al.* 2012). A recent systematic review and meta-analysis of 3,821 patients with DTC (90.3% PTC; 4% FTC; 5.7% unspecified) assessed ablation success and clinical outcomes with RAI activities above or below 81 mCi (3 GBq) (James *et al.* 2021). All patients were at low or intermediate risk for structural recurrence. A subgroup analysis demonstrated no significant difference in the frequency of successful ablation between the low and high dose groups, confirming the noninferiority of lower RAI activities for this purpose.

When postoperative RAI is selected for patients determined to have low-risk DTC as defined by the ATA guidelines, the primary therapeutic intent is for remnant ablation and not adjuvant therapy. Therefore, low RAI activities (i.e. 30 mCi) should be preferentially used. One factor that may influence the decision to recommend RAI remnant ablation to patients with low-risk DTC is the presence of anti-thyroglobulin antibodies. However, these have been shown to progressively decline in most patients with DTC who do not receive RAI after thyroidectomy,

and thus their presence should not be considered a strong indication for RAI in an otherwise low-risk individual (Matrone *et al.* 2018).

The administration of RAI to ablate the contralateral thyroid lobe is not recommended as a standard management approach following lobectomy but has been described in the literature. An unblinded study from Italy randomized 136 consecutive patients with DTC to receive RAI activities of 30 mCi (1.1 GBq) or 100 mCi (3.7 GBq) after lobectomy (Giovannella *et al.* 2013). All patients had AJCC T1b-T2 tumors and would have been considered low risk for recurrence according to the ATA guidelines (Haugen *et al.* 2016). Successful thyroid ablation, which was defined as a negative diagnostic RAI WBS and stimulated thyroglobulin level <2 ng/mL in the absence of anti-thyroglobulin antibodies at 12 months, was significantly higher with 100 mCi than 30 mCi (74% vs 54%). Half of the patients in the low dose group and 66% in the high dose group experienced painful thyroiditis, and one-third of patients in the high dose group required moderate dosages of prednisone for symptom relief. The frequency of structural recurrence was not assessed in this study (Giovannella *et al.* 2013). A recent systematic review and meta-analysis of 695 patients demonstrated successful ablation achieved in 69%. Although structural incomplete responses were uncommon, 8–24% of patients experienced a biochemical incomplete response, and this occurred more frequently with lower RAI activities (~30 mCi). Painful thyroiditis was reported in ~18% of patients (Piccardo *et al.* 2020).

In conclusion, the use of RAI to ablate the contralateral lobe can be considered in cases with clear indications for postoperative RAI when there are also contraindications to completion thyroidectomy (e.g. recurrent laryngeal nerve injury on the previously operated side) or if patient preference dictates. Higher administered activities should be considered in such cases, given the higher failure rates with lower doses.

Adjuvant therapy

The term ‘adjuvant therapy’ refers to the administration of postoperative RAI for the purpose of targeting and treating persistent (often microscopic) thyroid cancer that has yet to be identified. When the primary objective of RAI treatment is for adjuvant therapy, doses above those used for remnant ablation up to 150 mCi (5.55 GBq) are recommended (Haugen *et al.* 2016). Adjuvant therapy is indicated for patients who have an increased risk for structural recurrence and/or thyroid cancer-related death. Contributing factors include patient age, postoperative

disease status, and tumor-specific factors, including the histological subtype, the existence of extrathyroidal extension (ETE), and the presence of metastasis.

An individual’s clinical, histologic, and postoperative data is used to determine their risk of recurrence classification in the ATA system (i.e. low, intermediate, or high risk). This can be used to help inform clinical management decisions, including whether adjuvant RAI should be considered. Postoperative disease status can be assessed through a number of means, including measurement of serum thyroglobulin (performed 3–4 weeks postoperatively), neck ultrasonography, and diagnostic RAI WBS, the utility of which was discussed earlier (Haugen *et al.* 2016). One study of low-risk PTC found that 98.5% of patients with stimulated thyroglobulin levels < 1 ng/dL had no evidence of persistent/recurrent disease after a median follow-up of 44 months (Rosario *et al.* 2012). A subsequent study by the same authors demonstrated that the combination of low unstimulated serum thyroglobulin, negative anti-thyroglobulin antibodies and non-suspicious neck ultrasonography was sufficient to rule out persistent disease in low-risk patients (Rosario *et al.* 2015). Conversely, low postoperative thyroglobulin alone cannot rule out persistent disease in patients with intermediate or high-risk DTC (Robenshtok *et al.* 2013). In our experience, we have found this more often to be the case when the preoperative thyroglobulin level is lower than expected. Lastly, an inappropriately elevated postoperative thyroglobulin level after thyroidectomy in an otherwise low-risk patient should prompt further evaluation for persistent disease.

Low-risk thyroid cancer

Patients with ATA low-risk thyroid cancer are expected to have very low disease-specific mortality and a low (<5–10%) risk of persistent or recurrent disease. There is no evidence that RAI confers a survival advantage, and it is also unlikely to have a meaningful impact on the risk of recurrence because recurrence rates are low at baseline. Since total thyroidectomy is not required if RAI is not needed, the ATA guidelines endorse thyroid lobectomy as an acceptable operative strategy for patients with T1–2 PTC and FTC in the absence of gross ETE or metastatic disease (Haugen *et al.* 2016).

As previously mentioned, RAI is not associated with improved survival in patients with low-risk DTC. A retrospective study of 1298 patients with AJCC pT1–2 disease and no nodal or distant metastases demonstrated no difference in overall or disease-free survival between patients who did or did not receive RAI after 10.3 years

follow-up (Schvartz *et al.* 2012). Similar findings were reported for another cohort of patients 45 years and older (Nixon *et al.* 2012a). A study of 199,371 patients with DTC in the National Cancer Database (NCDB) and 77,187 in the Surveillance, Epidemiology and End Results (SEER) database not only demonstrated a lack of benefit but also found that disease-specific mortality was higher in patients with T1a disease who received RAI (Orosco *et al.* 2019).

High-quality prospective data indicate that longer-term recurrence rates are similar in patients with low-risk DTC treated with low or high RAI activities. After a median follow-up of 5.4 years in ESTIMABL1 and 6.5 years in HiLo, cumulative recurrence rates were no different for patients treated with 30 mCi (1.1 GBq) or 100 mCi (3.7 GBq) (Schlumberger *et al.* 2018, Dehbi *et al.* 2019). Prospective clinical trials designed to evaluate the outcomes of patients with low-risk DTC managed with or without RAI, including the Iodine or Not (ION) trial (UK) and ESTIMABL2 (France), are underway (Mallick *et al.* 2012a). The current body of published literature, which includes prospective and retrospective cohort studies and meta-analyses, provides reassurance that outcomes remain excellent in patients with low-risk DTC managed without RAI. Rosario *et al.* demonstrated that the combination of a low unstimulated postoperative serum thyroglobulin and negative neck ultrasonography in patients with low-risk PTC >1 cm could accurately rule out persistent disease and the need for postoperative RAI (Rosario *et al.* 2015). A prospective study of 57 patients with ATA low-risk disease (tumor size <4 cm and no ETE or aggressive histology) managed without RAI showed had no cases with persistent/recurrent disease after 3–8 years follow-up. An excellent response to therapy could be accurately confirmed by the combination of neck ultrasonography and the temporal thyroglobulin trend (Janovsky *et al.* 2016). A recent meta-analysis that included 17,699 patients with low-risk thyroid cancer (T1–2 N0 PTC and FTC) demonstrated no difference in recurrence rates or 20-year survival following lobectomy or total thyroidectomy with or without RAI, while complications were higher in the group treated with thyroidectomy plus RAI (Rodriguez Schaap *et al.* 2020).

In conclusion, there is a sufficient body of evidence that adjuvant RAI can be safely deferred in patients with low-risk DTC based on substantial observational data that RAI does not meaningfully affect recurrence risk or improve survival in this population. Unfortunately, a recent study showed that patients with low-risk DTC continue to be overtreated with RAI (Moten *et al.* 2019).

Intermediate-risk thyroid cancer

The ATA intermediate-risk group encompasses a heterogeneous population with a risk for structural recurrence ranging from >5–10% to ~20%. The ATA guidelines suggest that postoperative RAI should be considered in such patients (Haugen *et al.* 2016). However, the published literature exhibits a substantial lack of clarity regarding the need for and optimal dosing of adjuvant RAI.

The impact of RAI on the survival of patients with intermediate-risk thyroid cancer remains uncertain, although observational studies suggest a greater likelihood of benefit in older individuals. A study from the SEER database found that RAI was associated with improved overall survival for patients with tumor size >4 cm, microscopic ETE, or lymph node metastasis regardless of age, but the absolute risk reduction in those <45 years was small with high survival rates observed with or without RAI (99% vs 98%) (Ruel *et al.* 2015). Similarly, a meta-analysis of 79 studies published between 1966 and 2008 found that RAI was associated with improved disease-specific survival in patients >45 years with what would mostly be considered intermediate-risk disease according to the ATA guidelines, while benefit was uncertain in younger patients (Sacks *et al.* 2010).

Several studies have sought to evaluate the impact of different RAI activities on recurrence rates in patients with intermediate-risk DTC. A few have analyzed specific subpopulations within this group, including patients with T3 disease and those with lymph node metastases, while other intermediate-risk subgroups have yet to be explicitly studied (e.g. PTC with vascular invasion). A study with 204 intermediate-risk patients (97% PTC) treated with RAI compared the clinical outcomes of those who received 30 mCi (1.11 GBq) to those treated with 100 or 150 mCi (3.7 or 5.55 GBq). After a median follow-up of 10 years, 25% of those who received 30 mCi had a biochemical/structural incomplete response to therapy vs 10% in the higher dose group. However, there were differences in the baseline characteristics of the two groups, including a significantly higher proportion of patients with minimal ETE in the low dose group (Jeong *et al.* 2017). Another study documented more early recurrences in patients who had the combined findings of T3/4 (including minimal ETE) and lymph node disease if they were treated with RAI activities <50 mCi (1.85 GBq) (Chu *et al.* 2018). As previously described, a recent meta-analysis of patients with DTC who were considered either low or intermediate risk (T3 and/or lymph node disease) compared the outcomes of those treated with lower RAI activities, ranging from 30 to 81 mCi (1.1 to 3 GBq), to those who received >81 to 150 mCi (>3 to 5.5 GBq)

(James *et al.* 2021). There was no difference in recurrence rates; however, when compared to the studies described earlier, the low dose group included patients treated with relatively higher RAI activities (up to 81 mCi). James *et al.* also documented no dose-related differences in a subgroup analysis that was limited to patients with 5+ years follow-up or another subgroup analysis of just the intermediate-risk group (James *et al.* 2021).

There is some evidence that adjuvant RAI activities above 100 mCi do not confer additional benefit to patients with intermediate-risk DTC. A retrospective cohort study of 436 patients with PTC and N1b disease demonstrated no significant difference in response to therapy or recurrence-free survival between patients who received 100 mCi (3.7 GBq) or 150 mCi (5.55 GBq) (Jin *et al.* 2020). An earlier study by Sabra *et al.* also found that adjuvant RAI doses >100 mCi were unlikely to improve the initial response to therapy of patients with N1b disease, especially younger individuals (Sabra *et al.* 2014).

Ongoing clinical trials, including the ION trial (UK) and a non-randomized prospective cohort study from China, will help to clarify the role of postoperative RAI in intermediate-risk DTC, specifically in the setting of tumor size >4 cm, minimal ETE and/or central neck lymph node metastases (Mallick *et al.* 2012a, Qu *et al.* 2017). Future prospective studies that specifically evaluate different RAI activities in patients with intermediate-risk thyroid cancer with higher-risk features are also needed. Individualized treatment decisions should be emphasized, generally favoring the use of adjuvant RAI for patients whose estimated risk of structural recurrence falls in the higher intermediate risk range. Adjuvant RAI activities between 50 and 100 mCi are likely preferred in such patients, but current data are limited. Conversely, low RAI activities (i.e. 30 mCi) should be preferentially used in patients with intermediate-risk thyroid cancer with lower risk features if postoperative RAI is chosen.

High-risk thyroid cancer

The ATA guidelines consider patients to be at high risk for structural recurrence if they have known or suspected (based on the serum thyroglobulin) distant metastases, FTC with extensive vascular invasion, or tumors that demonstrate gross ETE, lymph node metastases >3 cm, or an incomplete surgical resection (Table 3). The ATA guidelines recommend the routine use of adjuvant RAI after thyroidectomy in patients who are at high risk for structural recurrence (Haugen *et al.* 2016).

RAI therapy is associated with improved survival in patients with high-risk DTC. A retrospective study of

199,371 patients with DTC from the NCDB database and 77,187 from the SEER database demonstrated improved survival related to RAI in patients with M1, stage IV, T4, and/or N1 disease (Orosco *et al.* 2019). An earlier meta-analysis of 79 studies compared patient outcomes with and without RAI and found that RAI was associated with improved disease-specific survival in patients with AJCC stage IV thyroid cancer. There was also evidence of benefit in patients <45 years with gross ETE or distant metastases (Sacks *et al.* 2010).

A few studies have assessed clinical outcomes in patients with high-risk DTC after treatment with different doses of RAI. A retrospective study of 253 patients with ATA intermediate- and high-risk disease (T4 and/or N1b) compared adjuvant RAI with rhTSH plus 100 mCi (3.7 GBq) to THW plus 150 mCi (5.55 GBq). The primary outcome was ablation success, and secondary outcomes were a response to therapy and recurrence-free survival. Although there was no significant difference in ablation success based on TSH-stimulated serum thyroglobulin levels or neck ultrasonography, 26.5% of patients had thyroid bed uptake on diagnostic RAI WBS in the group treated with rhTSH plus 100 mCi vs 5.6% in the THW plus 150 mCi group. Despite this observation, there was no difference in the secondary outcomes of response to therapy or recurrence-free survival after a median follow-up of 3.6 years (Jeong *et al.* 2019). Another retrospective cohort study with 183 patients from France and the US. demonstrated different results. After a median follow-up of 4.5 years, the observed recurrence rate was significantly higher among those who received a median RAI dose of 100 mCi as compared to those treated with ≥ 150 mCi (36% vs 20%) (Gray *et al.* 2019). However, the study population was different in that it was limited to patients with high-risk disease, some of whom had distant metastases.

In conclusion, observational studies indicate that the routine use of postoperative RAI is associated with improved clinical outcomes in patients with high-risk DTC. Prospective studies are needed to clarify the optimal dosing of adjuvant RAI for patients with ATA high-risk thyroid cancer.

Therapy

RAI can be administered with the intention of treating persistent/recurrent thyroid cancer (i.e. therapy). The most common location of disease recurrence is in the neck. Surgical resection alone or in combination with RAI is preferred over RAI alone in most cases of persistent/recurrent DTC involving cervical lymph nodes, especially

for bulky disease or when recurrence occurs in a previously unoperated compartment. Active surveillance is an option for patients with smaller volume lymph node metastases, especially if a complete surgical dissection of the involved compartment has previously been completed. Distant metastases are found in ~3% of patients with DTC at initial presentation (Nixon *et al.* 2012b). The most common sites of distant metastasis in order of decreasing frequency are lungs, bone, brain, and liver. The goals of RAI therapy in the setting of distant metastasis are variable and may include complete remission, stabilization and/or palliation of disease.

Either an empiric ^{131}I dose may be chosen, or whole-body dosimetry can be utilized when RAI therapy is administered for the treatment of distant metastatic disease. The purpose of dosimetry is to estimate an effective dose that maximizes uptake by tumor cells but limits potential toxicity to other tissues (e.g. bone marrow). Dosimetry should be considered if the administered ^{131}I activity exceeds 200 mCi or 150 mCi in older adults (over 70) (Haugen *et al.* 2016). One study showed that empiric dose determination exceeded the maximum tolerated radiation dose in up to 22% of individuals who underwent dosimetry, and older patients were disproportionately affected (Tuttle *et al.* 2006). We review the use of dosimetry as it relates to RAI side effects further in a later section.

The lungs are the most common site of distant metastasis in patients with DTC. Pulmonary metastases can lead to respiratory failure and are associated with 10-year disease-specific survival ranging from 50 to 73% (Kitamura *et al.* 1999, Song *et al.* 2015, Sohn *et al.* 2018). The ATA guidelines recommend empiric activities of 100 to 200 mCi or dosing determined by dosimetry (goal whole-body retention <80 mCi at 48 h) for the treatment of RAI-avid pulmonary metastases. RAI therapy can be repeated every 6–12 months as long as the disease remains RAI-avid (Haugen *et al.* 2016). Bone marrow suppression and pulmonary fibrosis are possible therapy-limiting complications. The highest rates of complete remission are reported in patients with pulmonary micrometastases. In contrast, pulmonary macronodular disease (≥ 1 cm) is associated with decreased progression-free survival and infrequent complete remission of disease with RAI therapy (Sabra *et al.* 2016, Kim *et al.* 2017). RAI therapy should be considered in patients with pulmonary macronodular disease and may be repeated in the setting of objective clinical response (i.e. substantial reduction in serum thyroglobulin and/or decrease in the size or rate of progression of metastases), but overall survival is low

(Haugen *et al.* 2016). A large retrospective study from China evaluated the impact of RAI in 372 patients with DTC and pulmonary metastasis. Among the 69% of patients in this study with RAI-avid disease, 68% demonstrated a significant decrease in serum thyroglobulin levels, and 61% had a reduction in metastases on follow-up CT imaging, but only 24% experienced a complete remission of the disease. Ten-year survival was 91% for patients with RAI uptake on nuclear imaging, but no structural correlate on chest CT, but decreased to 69 and 31%, respectively, for patients with micronodular and macronodular metastases. Older age, multiple sites of distant metastasis, and increasing size of pulmonary metastases were independent predictors of lower survival (Song *et al.* 2015).

The skeleton is the second most common site of distant metastasis in patients with DTC and is more often affected in FTC than PTC. RAI therapy can benefit selected patients with bone metastasis but is rarely curative. The ATA guidelines recommend the use of RAI therapy for the treatment of bone metastasis with empiric activities of 100 to 200 mCi or dosing determined by dosimetry (Haugen *et al.* 2016). The MOSCATI (Metastases of the Skeleton from Carcinoma of the Thyroid) study was a multicenter retrospective observational study from Italy that included 143 patients with DTC and bone metastases. RAI was administered to 131 patients and was the only treatment that was associated with decreased overall mortality (Mazziotti *et al.* 2018). A study of 77 patients from the US found that the combination of RAI and one or more directed or systemic therapies were associated with significantly higher overall survival than RAI therapy alone (Wu *et al.* 2019). Another study found that patients with solitary bone metastasis had a better prognosis and response to therapy than those with multifocal metastases (Qiu *et al.* 2011). Lastly, bone metastases detected on RAI WBS without a structural correlate on cross-sectional imaging appear to represent a unique clinical finding. A retrospective study of 288 patients with bone metastases included 14 patients with RAI-avid bone lesions in the absence of a structural correlate on CT or MRI. After a median follow-up of 5 years (range 2–14 years), all 14 patients were alive and none had experienced structural bone metastasis or skeletal-related adverse events (Robenshtok *et al.* 2014).

Special situations

Chronic kidney disease

The presence of chronic kidney disease (CKD) adds further complexity to the process of administering RAI.

Although iodine is eliminated to some degree through saliva, sweat, and stool, it is primarily cleared by the kidneys. Patients with renal failure thus have substantially higher serum concentrations of inorganic and protein-bound iodine than those with normal kidney function. The serum concentration of ^{131}I increases by 3.5 times in patients with CKD and as much as nine times in end-stage renal disease (ESRD). Only 11% of the administered dose of RAI is eliminated by 24 h in patients with ESRD (Saracyn *et al.* 2014). This means that patients with ESRD who are treated with standard doses of RAI for thyroid cancer may experience a higher risk of excessive total body radiation and bone marrow toxicity. The ATA guidelines thus recommend caution in administering empiric ^{131}I activities above 100–150 mCi in patients with CKD and that dosimetry be considered in this setting (Haugen *et al.* 2016).

There are conflicting recommendations regarding how to approach the use of RAI in patients with DTC and ESRD with respect to both the administered dose and timing of dialysis sessions. Unfortunately, the published literature evaluating the use of RAI in such patients is limited to case reports and small case series. Two different approaches to the administration of RAI in patients with ESRD have been proposed. The first approach is to use a standard dose of RAI followed by more frequent dialysis sessions (Murcutt *et al.* 2008) since 30–68% of the administered dose can be removed per hemodialysis session (Yeyin *et al.* 2016, Vermandel *et al.* 2020). The second approach is to substantially lower the administered activity of RAI and maintain the patient's usual dialysis schedule (Kaptein *et al.* 2000, Holst *et al.* 2005, Vermandel *et al.* 2020). RAI dose reductions ranging from 20 to 50% have been recommended if this approach is used. A retrospective study of six patients with ESRD on hemodialysis found that administering 30% of the standard RAI dose preserved therapeutic efficacy, with successful thyroid ablation achieved in most patients while avoiding significant hematologic toxicity (Vermandel *et al.* 2020). Another study evaluated the use of RAI in patients receiving continuous ambulatory peritoneal dialysis (CAPD). Ten patients with DTC (two with ESRD on CAPD and eight with normal renal function) and eight patients with intact thyroid glands and ESRD on CAPD were included. The observed ^{131}I clearance rate through urine plus dialysate in patients on CAPD was only 20% that of patients with preserved renal function. The authors concluded that five-fold reductions in the administered RAI activity would be needed to prevent excessive total body radiation doses and bone marrow toxicity (Kaptein *et al.* 2000).

Pregnancy and lactation

Thyroid cancer is the second most common malignancy diagnosed during pregnancy after breast cancer. RAI is strictly contraindicated during pregnancy and would be highly destructive to the fetal thyroid gland if administered within 40 days of when the fetal thyroid begins to concentrate iodine at ~10–12 weeks. On the other hand, a history of treatment with RAI at least 6 months prior to pregnancy is not associated with worse fetal or neonatal outcomes; specifically, there is no increased risk of miscarriage, preterm delivery, or congenital malformations (Kim *et al.* 2019). In addition, higher rates of thyroid disease or non-thyroid malignancy have not been observed in the children of mothers previously treated with RAI (Schlumberger *et al.* 1996).

Iodide is actively transported into the lactating mammary gland. If administered during lactation, ^{131}I would concentrate in the breast, and 13–48% of the radioactivity would be transferred into breastmilk, posing a significant risk to the infant (Rubow & Kloppe 1988, Leide-Svegborn *et al.* 2016). The very long half-life of ^{131}I (~8 days) and active transport of ^{131}I into breastmilk necessitate the termination of breastfeeding prior to the administration of RAI. In addition, cessation of lactation should occur a minimum of 4–6 weeks prior to the administration of RAI to reduce radiation exposure to breast tissue (Khaled *et al.* 2016). In order to confirm the absence of breast uptake 4–6 weeks after the cessation of lactation, we recommend obtaining a diagnostic RAI WBS prior to administering therapeutic doses of ^{131}I . If significant breast uptake is identified then RAI treatment should be postponed.

Children

Treatment goals for RAI in children include eliminating iodine-avid residual disease as well as reducing the risk of thyroid cancer recurrence. Historically, RAI therapy following surgery was considered the standard approach in all pediatric patients with DTC. However, we are moving away from this approach given increasing awareness of possible long-term adverse effects of RAI and moving toward an individualized approach that identifies children who would be more likely to benefit from therapy.

The ATA guidelines for the management of DTC in children recommend RAI in children who have unresectable locoregional/nodal disease or distant metastases known or presumed to be iodine avid (Francis *et al.* 2015). Pulmonary metastases in children typically demonstrate excellent RAI uptake, and although many children may not achieve a complete response, the majority will have stable disease and low disease-specific morbidity

and mortality (Pawelczak *et al.* 2010, Zhang *et al.* 2018, Nies *et al.* 2021). It also generally agreed upon that patients with invasive histology, extrathyroidal/extranodal extension, or extensive lymph node involvement should receive RAI (Rivkees *et al.* 2011, Bauer 2020). Pediatric patients with low-risk disease (defined as disease grossly confined to the thyroid with N0/Nx or incidental N1a disease) likely do not require RAI. Postoperative staging with TSH-stimulated thyroglobulin level and diagnostic RAI WBS can help further guide RAI in children with intermediate or high-risk disease.

The determination of ^{131}I dosing activity may be determined empirically or via whole-body dosimetry. Empiric dosing is typically calculated either based strictly on body weight (1–1.5 mCi/kg) or body surface area or by adjusting typical adult dosing by a fraction based on the child's weight in kg/70 kg (Francis *et al.* 2015). Reynolds calculated relative doses (defined as mCi administered that yields equivalent exposure as 1 mCi administered to an adult) for children by age: 15 years, 0.83; 10 years, 0.54; 5 years 0.35 (Reynolds 1993). Some suggest a fixed-dose based on institutional experience and the extent of disease. Others suggest weight adjusting risk-stratified adult activities: 30–100 mCi for tumor limited to the thyroid, 150–175 mCi for tumor extending beyond the thyroid capsule and/or with locoregional metastases, 175–200 mCi for high-risk patients and distant metastases (Parisi & Mankoff 2007, Lazar *et al.* 2009). Whole-body dosimetry may be considered in patients who are requiring multiple doses of RAI, who have diffuse pulmonary metastases, or in whom there is a concern for limited bone marrow reserve, but it is not available at all referral centers. To date, there are no studies comparing outcomes using these different methods in pediatric patients.

In order to encourage uptake of ^{131}I , preparation in pediatric patients typically involves THW for a period of 2–3 weeks (with goal TSH > 30 mU/L) as well as adherence to a LID for 10–14 days preceding therapy. The use of rhTSH in the pediatric population is considered off-label as it is not currently approved for use in patients < 18 years of age. Data regarding the safety and efficacy of rhTSH in children are limited. Studies have reported appropriate TSH elevation and well-tolerated use of rhTSH at typical adult dosing (Iorcansky *et al.* 2005, Luster *et al.* 2009, Schumm *et al.* 2021). In one recent study comparing preparation with rhTSH and THW, time to progression ($P=0.13$) and disease persistence/recurrence rates ($P=0.14$) were similar in both groups (Schumm *et al.* 2021). Patients may be admitted to the hospital or discharged home for isolation following their RAI dose. Factors that may impact whether

or not children can safely isolate at home include age and ability to adhere to radiation safety instructions, travel means/time home after receiving RAI, living arrangements (e.g. sharing a bedroom, other young children in the home), contamination management (e.g. bathroom/toileting management, medical devices).

In summary, understanding treatment goals as well as risks and benefits of RAI as part of the treatment of DTC in the pediatric population is critical in determining which children will benefit optimally. In the next section, we will review the potential adverse effects of RAI in both children and adults.

Adverse effects of radioactive iodine

Overall, RAI is a fairly safe and effective ‘targeted therapy’ in selected patients. A list of potential adverse effects of RAI treatment that should be discussed with patients are listed in Table 4.

Xerostomia is one of the most common adverse effects of RAI therapy and is directly correlated with administered activity and cumulative dose. A recent combination of questionnaire-based studies assessed consecutive patients receiving 100 mCi ^{131}I (3.7 GBq) over a 2-year period (Moreddu *et al.* 2017, Le Roux *et al.* 2020). Questionnaires were sent to 800 patients 1 year after treatment (early) and again approximately 7 years (late) after RAI. Twenty-seven percent of patients had salivary gland discomfort or swelling at the early time point, which persisted in 14% of patients at the late time point. Xerostomia was seen in 39% of patients at the early time point and persisted in 32% of patients at the late time point. Responses were limited (52% response at early time point, and 42% of those who responded early responded to the late questionnaire), and it is likely that many patients with no symptoms did not respond. Nevertheless, at least 6–7% of the 800 patients treated noted persistent long-term symptoms of xerostomia. Also, all patients were treated starting at 4 h

Table 4 Potential adverse effects of RAI treatment that should be discussed with patients.

Loss of taste/altered taste
Xerostomia/dental caries
Sialoadenitis
Epiphora
Reduced sperm counts (discuss sperm banking in those receiving ≥ 400 mCi cumulative dose)
Marrow suppression (low CBC)
Secondary malignancy

after RAI therapy with lemon juice three times daily. The ATA guidelines found evidence lacking to recommend for or against the use of routine agents like lemon juice to prevent salivary gland damage after RAI therapy (Haugen *et al.* 2016). Limiting the administered activity of RAI and hydration are likely the best measures to prevent salivary gland damage.

One of the first descriptions of epiphora (excessive tearing) was described by Kloos *et al.* (2002). Of 390 patients receiving RAI therapy, 10 (2.6%) had epiphora and evidence of nasolacrimal drainage system obstruction. The lowest cumulative dose of ^{131}I associated with obstruction was 150 mCi (5.5 GBq). A later report showed a prevalence of 4.6% epiphora among 563 patients treated with ^{131}I (Burns *et al.* 2004).

Radiation from ^{131}I can affect the gonads. Fortunately, there is no clear evidence of RAI treatment being associated with female infertility, miscarriage, or fetal malformations. It is recommended that women of childbearing age have a negative screening evaluation for pregnancy before administration of ^{131}I , and they avoid pregnancy for 6–12 months after receiving RAI (Haugen *et al.* 2016). Men have temporary reduction in sperm counts and elevated follicle-stimulating hormone after RAI treatment for DTC (Wichers *et al.* 2000, Hyer *et al.* 2002, Bourcigaux *et al.* 2018). One group suggested that younger men who receive cumulative ^{131}I activities ≥ 400 mCi consider sperm banking if future conception is an option (Hyer *et al.* 2002). Some specialists also recommend that men wait approximately 3 months after RAI therapy (one full sperm cycle) to avoid potential transient chromosomal abnormalities (Haugen *et al.* 2016).

Higher administered activities of ^{131}I can cause transient marrow suppression. An early report showed that keeping radiation doses below 200 cGy to the bone marrow resulted in minimal transient effects on the complete blood count (CBC) (Benua *et al.* 1962). In order to keep marrow exposure below 200 cGy, this measurement requires whole-body dosimetry. The ATA has recommended considering whole-body dosimetry for any patients where single-dose administered activity is >200 mCi or in older patients (>70 years old) receiving >150 mCi (Haugen *et al.* 2016). Atkins and colleagues recommended a simplified dosimetry approach based on the patient's body surface area and percent retention value at 48 h (Sisson *et al.* 2003, Atkins *et al.* 2015). Durski *et al.* recently showed, in a single case report, that this simplified dosimetry may be possible using ^{123}I (Durski *et al.* 2021). Finally, in response to the ATA guidelines, Duskin-Bitan performed a retrospective

analysis on patients > 70 years of age and found only transient mild marrow suppression, even in those who received 150–200 mCi as a single dose (Duskin-Bitan *et al.* 2019).

A secondary malignancy is the least common but most concerning adverse effect of RAI. A meta-analysis of two large multicenter studies showed that the relative risk of second primary malignancies (SPM) in patients treated with RAI for DTC was 1.19 (95% CI, 1.04–1.36) compared with DTC patients not treated with RAI (Sawka *et al.* 2009). The Rubino study quoted in this meta-analysis also showed a linear dose relationship between cumulative RAI activity and SPM (Rubino *et al.* 2003). Based on the overall risk of SPM in patients with DTC (7–8%), the estimated excess risk of SPM in patients treated with RAI would be approximately 1% (Sawka *et al.* 2009). While this absolute increased risk is quite small, it is likely due to the RAI therapy and is likely dose-related. Therefore, RAI treatment should only be considered for patients where there is a high likelihood of benefit, and the administered activity should be the lowest to achieve therapeutic goals. We also recommend additional caution when considering RAI treatment in patients with a personal or strong family history of multiple other malignancies.

Acute and long-term adverse effects of RAI have been well described in adults, but there are limited studies focusing solely on outcomes in patients treated with RAI in childhood. Children and young adults treated with RAI for DTC are at increased risk for developing SPM, in particular salivary gland cancer (Adly *et al.* 2018, Marti *et al.* 2015). Albano *et al.* analyzed 105 pediatric patients (≤ 18 years of age) who received a total of 302 RAI treatments. Early adverse events occurred in 35% of patients (nausea/vomiting 29%, sialoadenitis 22%, thyroiditis 19%, dry mouth 14%, BM suppression 6%) (Albano *et al.* 2017). Late events occurred in 11% of patients (permanent salivary gland dysfunction 2%, permanent BM suppression 4%, pulmonary fibrosis 5%, SPM 4%, fertility changes in females 7%) and except for fertility changes, correlated with number of treatments and cumulative administered ^{131}I dose (Albano *et al.* 2017). Another study evaluating salivary gland function in adult survivors of pediatric DTC found that moderate to severe xerostomia was present in 35.5% of patients and was related to cumulative ^{131}I dose (Selvakumar *et al.* 2019). Due to concerns regarding pulmonary fibrosis, children with significant pulmonary uptake on diagnostic whole-body scan may benefit from consideration of reduced dosing or utilization of dosimetry for dose calculation.

Radioactive iodine refractory disease

The ATA defines RAI-refractory DTC in patients with structural evident disease after appropriate iodine preparation and TSH stimulation in one of four ways: (1) no uptake outside the thyroid bed at the first therapeutic RAI treatment, (2) the tumor tissue loses the ability to concentrate RAI after previous evidence of RAI-avid disease, (3) RAI is concentrated in some lesions, but not others, and (4) metastatic disease progresses despite significant concentration of RAI (Haugen *et al.* 2016). A joint statement between Endocrinology and Nuclear Medicine experts supports these basic definitions and applies this to common clinical scenarios (Tuttle *et al.* 2019). Others consider significant ^{18}F FDG uptake on PET/CT imaging as a criterion for RAI-refractory disease.

Kinase signaling pathways have emerged as a promising target for redifferentiation therapy in patients with RAI-refractory DTC. Preclinical studies have shown that expression of the *BRAFV600E* or *RET-PTC* oncogenes impairs expression of thyroid function genes, which is reversible by suppression with *BRAF* or *MEK* inhibitors (Knauf *et al.* 2003, Chakravarty *et al.* 2011). Based on these data, a number of small studies have explored the use of selective kinase inhibitors to improve RAI uptake and therapeutic benefit in patients with RAI-refractory disease. A nice review of this area was recently published (Lamartina *et al.* 2021). One of the earliest studies by Ho and colleagues was tumor mutation agnostic (Ho *et al.* 2013). Twenty patients were treated with selumetinib (*MEK* inhibitor) for 4 weeks and assessed for restoration of RAI uptake. Twelve out of 20 (60%) had restoration of RAI uptake. Eight patients were treated with ^{131}I (most had *RAS* mutation), and at 6 months, five patients achieved a partial response while three had stable disease. Four subsequent studies (ranging from 1 to 10 patients each), showed that 4–8 weeks of *BRAF* inhibitor (vemurafenib or dabrafenib) increased RAI uptake in most patient with *BRAFV600E* mutation and led to a partial response in approximately 35–40% of patients (Rothenberg *et al.* 2015, Huillard *et al.* 2017, Dunn *et al.* 2019, Lebouilleux *et al.* 2019). There was also a recent report of a patient with an *NTRK* fusion having significant RAI uptake after 3 weeks of treatment with the *NTRK* inhibitor larotrectinib (Groussin *et al.* 2020). The potential appeal of these redifferentiation therapies is that patients only need to be treated for 3–8 weeks rather than indefinitely. These targeted therapies, however, are not without potentially significant side effects. Many institutions have been exploring the use of these redifferentiation agents, and mutation-directed

clinical trials are being developed for patients with genetic alterations in *BRAF*, *RAS*, *NTRK*, and *RET*. Watch this space.

Conclusions

We recommend an individualized approach to RAI treatment in patients with DTC in order to optimally balance risks, benefits, and patient preferences. This requires an awareness of the therapeutic intent of RAI in each individual to confirm that treatment is warranted and inform dosing decisions. Although progress has been made, there are many ongoing areas of uncertainty related to the use of RAI in DTC, highlighting the need for continued high-quality research in this area.

Declaration of interest

Dr Haugen: Serves on the advisory board of Eisai. Dr Mayson and Dr Chan: Declare no conflicts of interest that could be perceived as prejudicing the impartiality of this review.

Funding

This work did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

References

- Adly MH, Sobhy M, Rezk MA, Ishak M, Afifi MA, Shafie AE, Ali MA, Zekri W, Alfaar AS & Rashed WM 2018 Risk of second malignancies among survivors of pediatric thyroid cancer. *International Journal of Clinical Oncology* **23** 625–633. (<https://doi.org/10.1007/s10147-018-1256-9>)
- Albano D, Bertagna F, Panarotto MB & Giubbini R 2017 Early and late adverse effects of radioiodine for pediatric differentiated thyroid cancer. *Pediatric Blood and Cancer* **64** e26595. (<https://doi.org/10.1002/pbc.26595>)
- Atkins F, Van Nostrand D, Moreau S, Burman K & Wartofsky L 2015 Validation of a simple thyroid cancer dosimetry model based on the fractional whole-body retention at 48 hours post-administration of $(^{131}\text{I})\text{I}$. *Thyroid* **25** 1347–1350. (<https://doi.org/10.1089/thy.2014.0616>)
- Bauer AJ 2020 Pediatric thyroid cancer: genetics, therapeutics and outcome. *Endocrinology and Metabolism Clinics of North America* **49** 589–611. (<https://doi.org/10.1016/j.ecl.2020.08.001>)
- Benua RS, Cicale NR, Sonenberg M & Rawson RW 1962 The relation of radioiodine dosimetry to results and complications in the treatment of metastatic thyroid cancer. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* **87** 171–182.
- Borges de Souza P & McCabe C 2021 Radioiodine treatment: an historical and future perspective. *Endocrine-Related Cancer* **28** T121–T124. (<https://doi.org/10.1530/ERC-21-0037>)
- Bourcigaux N, Rubino C, Berthaud I, Toubert ME, Donadille B, Leenhardt L, Petrot-Keller I, Brailly-Tabard S, Fromiguet J, De Vathaire F, *et al.* 2018 Impact on testicular function of a single ablative activity of 3.7 GBq radioactive iodine for differentiated thyroid carcinoma.

- Human Reproduction* **33** 1408–1416. (<https://doi.org/10.1093/humrep/dey222>)
- Burns JA, Morgenstern KE, Cahill KV, Foster JA, Jhiang SM & Kloos RT 2004 Nasolacrimal obstruction secondary to I(131) therapy. *Ophthalmic Plastic and Reconstructive Surgery* **20** 126–129. (<https://doi.org/10.1097/01.iop.0000117340.41849.81>)
- Chakravarty D, Santos E, Ryder M, Knauf JA, Liao XH, West BL, Bollag G, Kolesnick R, Thin TH, Rosen N, *et al.* 2011 Small-molecule MAPK inhibitors restore radioiodine incorporation in mouse thyroid cancers with conditional BRAF activation. *Journal of Clinical Investigation* **121** 4700–4711. (<https://doi.org/10.1172/JCI46382>)
- Chu KP, Baker S, Zenke J, Morad A, Ghosh S, Morrish DW, Mcewan AJBS, Williams DC, Severin D & McMullen TPW 2018 Low-activity radioactive iodine therapy for thyroid carcinomas exhibiting nodal metastases and extrathyroidal extension may lead to early disease recurrence. *Thyroid* **28** 902–912. (<https://doi.org/10.1089/thy.2017.0136>)
- Dehbi HM, Mallick U, Wadsley J, Newbold K, Harmer C & Hackshaw A 2019 Recurrence after low-dose radioiodine ablation and recombinant human thyroid-stimulating hormone for differentiated thyroid cancer (HiLo): long-term results of an open-label, non-inferiority randomised controlled trial. *Lancet: Diabetes and Endocrinology* **7** 44–51. ([https://doi.org/10.1016/S2213-8587\(18\)30306-1](https://doi.org/10.1016/S2213-8587(18)30306-1))
- Dunn LA, Sherman EJ, Baxi SS, Tchekmedyian V, Grewal RK, Larson SM, Pentlow KS, Haque S, Tuttle RM, Sabra MM, *et al.* 2019 Vemurafenib redifferentiation of BRAF Mutant, RAI-refractory thyroid cancers. *Journal of Clinical Endocrinology and Metabolism* **104** 1417–1428. (<https://doi.org/10.1210/jc.2018-01478>)
- Durski JM, Hruska CB, Bogsrud TV, Ryder M & Johnson GB 2021 123I scan with whole-body retention measurement at 48 hours for simplified dosimetry before 131I treatment of metastatic thyroid cancer. *Clinical Nuclear Medicine* **46** e151–e153. (<https://doi.org/10.1097/RLU.00000000000003464>)
- Duskin-Bitan H, Leibner A, Amitai O, Diker-Cohen T, Hirsch D, Benbassat C, Shimon I & Robenshtok E 2019 Bone-marrow suppression in elderly patients following empiric radioiodine therapy: real-life data. *Thyroid* **29** 683–691. (<https://doi.org/10.1089/thy.2018.0423>)
- Francis GL, Waguespack SG, Bauer AJ, Angelos P, Benvenga S, Cerutti JM, Dinauer CA, Hamilton J, Hay ID, Luster M, *et al.* 2015 Management guidelines for children with thyroid nodules and differentiated thyroid cancer. *Thyroid* **25** 716–759. (<https://doi.org/10.1089/thy.2014.0460>)
- Fujimoto K, Hataya Y, Okubo M & Matsuoka N 2021 Influence of levothyroxine with recombinant human TSH on urine iodine excretion before radioactive iodine administration. *Endocrine Practice* [epub]. (<https://doi.org/10.1016/j.eprac.2021.03.012>)
- Giovannella L, Piccardo A, Paone G, Foppiani L, Treglia G & Ceriani L 2013 Thyroid lobe ablation with iodine-(1)(3)(1)I in patients with differentiated thyroid carcinoma: a randomized comparison between 1.1 and 3.7 GBq activities. *Nuclear Medicine Communications* **34** 767–770. (<https://doi.org/10.1097/MNM.0b013e3283622f3d>)
- Gray KD, Bannani S, Caillard C, Amanat S, Ullmann TM, Romanov P, Brunaud L, Beninato T, Fahey 3rd TJ, Mirallie E, *et al.* 2019 High-dose radioactive iodine therapy is associated with decreased risk of recurrence in high-risk papillary thyroid cancer. *Surgery* **165** 37–43. (<https://doi.org/10.1016/j.surg.2018.04.059>)
- Groussin L, Clerc J & Huillard O 2020 Larotrectinib-enhanced radioactive iodine uptake in advanced thyroid cancer. *New England Journal of Medicine* **383** 1686–1687. (<https://doi.org/10.1056/NEJMc2023094>)
- Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, *et al.* 2016 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid* **26** 1–133. (<https://doi.org/10.1089/thy.2015.0020>)
- Haynie TP, Nofal MM, Beierwaltes WH 1963 Treatment of thyroid carcinoma with I131: results at fourteen years. *JAMA* **183** 303–306. (<https://doi.org/10.1001/jama.1963.03700050035008>)
- Herrick KA, Perrine CG, Aoki Y & Caldwell KL 2018 Iodine status and consumption of key iodine sources in the U.S. population with special attention to reproductive age women. *Nutrients* **10** 874. (<https://doi.org/10.3390/nu10070874>)
- Hertz S, Roberts A & Evans RD 1938 Radioactive iodine as an indicator in the study of thyroid physiology. *Proceedings of the Society for Experimental Biology and Medicine* **38** 510–513.
- Ho AL, Grewal RK, Leboeuf R, Sherman EJ, Pfister DG, Deandreis D, Pentlow KS, Zanzonico PB, Haque S, Gavane S, *et al.* 2013 Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. *New England Journal of Medicine* **368** 623–632. (<https://doi.org/10.1056/NEJMoa1209288>)
- Holst JP, Burman KD, Atkins F, Umans JG & Jonklaas J 2005 Radioiodine therapy for thyroid cancer and hyperthyroidism in patients with end-stage renal disease on hemodialysis. *Thyroid* **15** 1321–1331. (<https://doi.org/10.1089/thy.2005.15.1321>)
- Hu YH, Wang PW, Wang ST, Lee CH, Chen HY, Chou FF, Huang YE & Huang HH 2004 Influence of 131I diagnostic dose on subsequent ablation in patients with differentiated thyroid carcinoma: discrepancy between the presence of visually apparent stunning and the impairment of successful ablation. *Nuclear Medicine Communications* **25** 793–797. (<https://doi.org/10.1097/01.mnm.0000126626.17166.ed>)
- Huillard O, Tenenbaum F, Clerc J, Goldwasser F & Groussin L 2017 Restoring radioiodine uptake in BRAF V600E-mutated papillary thyroid cancer. *Journal of the Endocrine Society* **1** 285–287. (<https://doi.org/10.1210/js.2016-1114>)
- Hyer S, Vini L, O'connell M, Pratt B & Harmer C 2002 Testicular dose and fertility in men following I(131) therapy for thyroid cancer. *Clinical Endocrinology* **56** 755–758. (<https://doi.org/10.1046/j.1365-2265.2002.t01-1-01545.x>)
- Iizuka Y, Katagiri T, Ogura K, Inoue M, Nakamura K & Mizowaki T 2020 Comparison of thyroid hormone withdrawal and recombinant human thyroid-stimulating hormone administration for adjuvant therapy in patients with intermediate- to high-risk differentiated thyroid cancer. *Annals of Nuclear Medicine* **34** 736–741. (<https://doi.org/10.1007/s12149-020-01497-0>)
- Iorcansky S, Herzovich V, Qualey RR & Tuttle RM 2005 Serum thyrotropin (TSH) levels after recombinant human TSH injections in children and teenagers with papillary thyroid cancer. *Journal of Clinical Endocrinology and Metabolism* **90** 6553–6555. (<https://doi.org/10.1210/jc.2005-1550>)
- James DL, Ryan EJ, Davey MG, Quinn AJ, Heath DP, Garry SJ, Boland MR, Young O, Lowery AJ & Kerin MJ 2021 Radioiodine remnant ablation for differentiated thyroid cancer: a systematic review and meta-analysis. *JAMA Otolaryngology: Head and Neck Surgery* **147** 544–552. (<https://doi.org/10.1001/jamaoto.2021.0288>)
- Janovsky CC, Maciel RM, Camacho CP, Padovani RP, Nakabashi CC, Yang JH, Malouf EZ, Ikejiri ES, Mamone MC, Wagner J, *et al.* 2016 A prospective study showing an excellent response of patients with low-risk differentiated thyroid cancer who did not undergo radioiodine remnant ablation after total thyroidectomy. *European Thyroid Journal* **5** 44–49. (<https://doi.org/10.1159/000442048>)
- Jeong JH, Kong EJ, Jeong SY, Lee SW, Cho IH, Ah Chun K, Lee J & Ahn BC 2017 Clinical outcomes of low-dose and high-dose postoperative radioiodine therapy in patients with intermediate-risk differentiated thyroid cancer. *Nuclear Medicine Communications* **38** 228–233. (<https://doi.org/10.1097/MNM.0000000000000636>)
- Jeong SY, Lee SW, Kim WW, Jung JH, Lee WK, Ahn BC & Lee J 2019 Clinical outcomes of patients with T4 or N1b well-differentiated thyroid cancer after different strategies of adjuvant radioiodine

- therapy. *Scientific Reports* **9** 5570. (<https://doi.org/10.1038/s41598-019-42083-3>)
- Jin M, Ahn J, Lee YM, Sung TY, Kim WG, Kim TY, Ryu JS, Kim WB, Shong YK & Jeon MJ 2020 Clinical outcomes of N1b papillary thyroid cancer patients treated with two different doses of radioiodine ablation therapy. *Endocrinology and Metabolism* **35** 602–609. (<https://doi.org/10.3803/EnM.2020.741>)
- Kaptein EM, Levenson H, Siegel ME, Gadallah M & Akmal M 2000 Radioiodine dosimetry in patients with end-stage renal disease receiving continuous ambulatory peritoneal dialysis therapy. *Journal of Clinical Endocrinology and Metabolism* **85** 3058–3064. (<https://doi.org/10.1210/jcem.85.9.6813>)
- Khaled H, Al Lahloubi N & Rashad N 2016 A review on thyroid cancer during pregnancy: multitasking is required. *Journal of Advanced Research* **7** 565–570. (<https://doi.org/10.1016/j.jare.2016.02.007>)
- Kim HK, Lee SY, Lee JI, Jang HW, Kim SK, Chung HS, Tan AH, Hur KY, Kim JH, Chung JH, *et al.* 2010 Usefulness of iodine/creatinine ratio from spot-urine samples to evaluate the effectiveness of low-iodine diet preparation for radioiodine therapy. *Clinical Endocrinology* **73** 114–118. (<https://doi.org/10.1111/j.1365-2265.2009.03774.x>)
- Kim M, Kim WG, Park S, Kwon H, Jeon MJ, Lee JJ, Ryu JS, Kim TY, Shong YK & Kim WB 2017 Initial size of metastatic lesions is best prognostic factor in patients with metastatic differentiated thyroid carcinoma confined to the lung. *Thyroid* **27** 49–58. (<https://doi.org/10.1089/thy.2016.0347>)
- Kim HI, Kim K, Park SY, Choe JH, Kim JH, Kim JS, Oh YL, Hahn SY, Shin JH, Ahn HS, *et al.* 2018 Refining the eighth edition AJCC TNM classification and prognostic groups for papillary thyroid cancer with lateral nodal metastasis. *Oral Oncology* **78** 80–86. (<https://doi.org/10.1016/j.oraloncology.2018.01.021>)
- Kim HO, Lee K, Lee SM & Seo GH 2019 Association between pregnancy outcomes and radioactive iodine treatment after thyroidectomy among women with thyroid cancer. *JAMA Internal Medicine* **180** 54–61. (<https://doi.org/10.1001/jamainternmed.2019.4644>)
- Kim H, Park SY, Choe JH, Kim JS, Hahn SY, Kim SW, Chung JH, Jung J & Kim TH 2020 Preoperative serum thyroglobulin and its correlation with the burden and extent of differentiated thyroid cancer. *Cancers* **12** 625. (<https://doi.org/10.3390/cancers12030625>)
- Kitamura Y, Shimizu K, Nagahama M, Sugino K, Ozaki O, Mimura T, Ito K, Ito K & Tanaka S 1999 Immediate causes of death in thyroid carcinoma: clinicopathological analysis of 161 fatal cases. *Journal of Clinical Endocrinology and Metabolism* **84** 4043–4049. (<https://doi.org/10.1210/jcem.84.11.6115>)
- Kloos RT, Duvuuri V, Jhiang SM, Cahill KV, Foster JA & Burns JA 2002 Nasolacrimal drainage system obstruction from radioactive iodine therapy for thyroid carcinoma. *Journal of Clinical Endocrinology and Metabolism* **87** 5817–5820. (<https://doi.org/10.1210/jc.2002-020210>)
- Klubo-Gwiedzinska J, Burman KD, Van Nostrand D, Mete M, Jonklaas J & Wartofsky L 2012 Radioiodine treatment of metastatic thyroid cancer: relative efficacy and side effect profile of preparation by thyroid hormone withdrawal versus recombinant human thyrotropin. *Thyroid* **22** 310–317. (<https://doi.org/10.1089/thy.2011.0235>)
- Knauf JA, Kuroda H, Basu S & Fagin JA 2003 RET/PTC-induced dedifferentiation of thyroid cells is mediated through Y1062 signaling through SHC-RAS-MAP kinase. *Oncogene* **22** 4406–4412. (<https://doi.org/10.1038/sj.onc.1206602>)
- Lamartina L, Anizan N, Dupuy C, Leboulleux S & Schlumberger M 2021 Redifferentiation-facilitated radioiodine therapy in thyroid cancer. *Endocrine-Related Cancer* **28** T179–T191. (<https://doi.org/10.1530/ERC-21-0024>)
- Lazar L, Lebenthal Y, Steinmetz A, Yackobovitch-Gavan M & Phillip M 2009 Differentiated thyroid carcinoma in pediatric patients: comparison of presentation and course between pre-pubertal children and adolescents. *Journal of Pediatrics* **154** 708–714. (<https://doi.org/10.1016/j.jpeds.2008.11.059>)
- Le Roux MK, Graillon N, Guyot L, Taieb D, Galli P, Godio-Raboutet Y, Chossegros C & Foletti JM 2020 Salivary side effects after radioiodine treatment for differentiated papillary thyroid carcinoma: long-term study. *Head and Neck* **42** 3133–3140. (<https://doi.org/10.1002/hed.26359>)
- Leboulleux S, Dupuy C, Lacroix L, Attard M, Grimaldi S, Corre R, Ricard M, Nasr S, Berdelou A, Hadoux J, *et al.* 2019 Redifferentiation of a BRAF(K601E)-mutated poorly differentiated thyroid cancer patient with dabrafenib and trametinib treatment. *Thyroid* **29** 735–742. (<https://doi.org/10.1089/thy.2018.0457>)
- Leenhardt L, Leboulleux S, Bournaud C, Zerdoud S, Schvartz C, Ciappuccini R, Kelly A, Morel O, Dygai-Cochet I, Rusu D, *et al.* 2019 Recombinant thyrotropin vs levothyroxine withdrawal in 131I therapy of N1 thyroid cancer: a large matched cohort study (ThyrNod). *Journal of Clinical Endocrinology and Metabolism* **104** 1020–1028. (<https://doi.org/10.1210/jc.2018-01589>)
- Leide-Svegborn S, Ahlgren L, Johansson L & Mattsson S 2016 Excretion of radionuclides in human breast milk after nuclear medicine examinations. Biokinetic and dosimetric data and recommendations on breastfeeding interruption. *European Journal of Nuclear Medicine and Molecular Imaging* **43** 808–821. (<https://doi.org/10.1007/s00259-015-3286-0>)
- Li JH, He ZH, Bansal V & Hennessey JV 2016 Low iodine diet in differentiated thyroid cancer: a review. *Clinical Endocrinology* **84** 3–12. (<https://doi.org/10.1111/cen.12846>)
- Luster M, Handkiewicz-Junak D, Grossi A, Zacharin M, Taieb D, Cruz O, Hitzel A, Casas JA, Mader U, Dottorini ME, *et al.* 2009 Recombinant thyrotropin use in children and adolescents with differentiated thyroid cancer: a multicenter retrospective study. *Journal of Clinical Endocrinology and Metabolism* **94** 3948–3953. (<https://doi.org/10.1210/jc.2009-0593>)
- Mallick U, Harmer C, Hackshaw A, Moss L & Io NTMG 2012a Iodine or not (IoN) for low-risk differentiated thyroid cancer: the next UK National Cancer Research Network randomised trial following HiLo. *Clinical Oncology* **24** 159–161.
- Mallick U, Harmer C, Yap B, Wadsley J, Clarke S, Moss L, Nicol A, Clark PM, Farnell K, McCreedy R, *et al.* 2012b Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. *New England Journal of Medicine* **366** 1674–1685. (<https://doi.org/10.1056/NEJMoa1109589>)
- Marti JL, Jain KS & Morris LG 2015 Increased risk of second primary malignancy in pediatric and young adult patients treated with radioactive iodine for differentiated thyroid cancer. *Thyroid* **25** 681–687. (<https://doi.org/10.1089/thy.2015.0067>)
- Matrone A, Latrofa F, Torregrossa L, Piaggi P, Gambale C, Faranda A, Ricci D, Agate L, Molinaro E, Basolo F, *et al.* 2018 Changing trend of thyroglobulin antibodies in patients with differentiated thyroid cancer treated with total thyroidectomy without (131)I ablation. *Thyroid* **28** 871–879. (<https://doi.org/10.1089/thy.2018.0080>)
- Mazzotti G, Formenti AM, Panarotto MB, Arvat E, Chiti A, Cuocolo A, Dottorini ME, Durante C, Agate L, Filetti S, *et al.* 2018 Real-life management and outcome of thyroid carcinoma-related bone metastases: results from a nationwide multicenter experience. *Endocrine* **59** 90–101. (<https://doi.org/10.1007/s12020-017-1455-6>)
- Moreddu E, Baumstarck-Barrau K, Gabriel S, Fakhry N, Sebag F, Mundler O, Chossegros C & Taieb D 2017 Incidence of salivary side effects after radioiodine treatment using a new specifically-designed questionnaire. *British Journal of Oral and Maxillofacial Surgery* **55** 609–612. (<https://doi.org/10.1016/j.bjoms.2017.03.019>)
- Moten AS, Zhao H & Willis AI 2019 The overuse of radioactive iodine in low-risk papillary thyroid cancer patients. *Surgical Oncology* **29** 184–189. (<https://doi.org/10.1016/j.suronc.2019.05.011>)
- Mumtaz M, Lin LS, Hui KC & Mohd Khir AS 2009 Radioiodine I-131 for the therapy of Graves' disease. *Malaysian Journal of Medical Sciences* **16** 25–33.
- Murcutt G, Edwards J, Boakye J & Davenport A 2008 Hemodialysis of chronic kidney failure patients requiring ablative radioiodine therapy. *Kidney International* **73** 1316–1319. (<https://doi.org/10.1038/ki.2008.95>)

- Nies M, Vassilopoulou-Sellin R, Bassett RL, Yedururi S, Zafereo ME, Cabanillas ME, Sherman SI, Links TP & Waguespack SG 2021 Distant metastases from childhood differentiated thyroid carcinoma: clinical course and mutational landscape. *Journal of Clinical Endocrinology and Metabolism* **106** e1683–e1697. (<https://doi.org/10.1210/clinem.dgaa935>)
- Nixon IJ, Patel SG, Palmer FL, Dilorenzo MM, Tuttle RM, Shaha A, Shah JP & GANLY I 2012a Selective use of radioactive iodine in intermediate-risk papillary thyroid cancer. *Archives of Otolaryngology: Head and Neck Surgery* **138** 1141–1146. (<https://doi.org/10.1001/jamaoto.2013.760>)
- Nixon IJ, Whitcher MM, Palmer FL, Tuttle RM, Shaha AR, Shah JP, Patel SG & Ganly I 2012b The impact of distant metastases at presentation on prognosis in patients with differentiated carcinoma of the thyroid gland. *Thyroid* **22** 884–889. (<https://doi.org/10.1089/thy.2011.0535>)
- Orosco RK, Hussain T, Noel JE, Chang DC, Dosiou C, Mittra E, Divi V & Orloff LA 2019 Radioactive iodine in differentiated thyroid cancer: a national database perspective. *Endocrine-Related Cancer* **26** 795–802. (<https://doi.org/10.1530/ERC-19-0292>)
- Pacini F, Capezzone M, Elisei R, Ceccarelli C, Taddei D & Pinchera A 2002 Diagnostic 131-iodine whole-body scan may be avoided in thyroid cancer patients who have undetectable stimulated serum Tg levels after initial treatment. *Journal of Clinical Endocrinology and Metabolism* **87** 1499–1501. (<https://doi.org/10.1210/jcem.87.4.8274>)
- Pak K, Cheon GJ, Kang KW, Kim SJ, Kim IJ, Kim EE, Lee DS & Chung JK 2014 The effectiveness of recombinant human thyroid-stimulating hormone versus thyroid hormone withdrawal prior to radioiodine remnant ablation in thyroid cancer: a meta-analysis of randomized controlled trials. *Journal of Korean Medical Science* **29** 811–817. (<https://doi.org/10.3346/jkms.2014.29.6.811>)
- Parisi MT & Mankoff D 2007 Differentiated pediatric thyroid cancer: correlates with adult disease, controversies in treatment. *Seminars in Nuclear Medicine* **37** 340–356. (<https://doi.org/10.1053/j.semnuclmed.2007.05.001>)
- Pawelczak M, David R, Franklin B, Kessler M, Lam L & Shah B 2010 Outcomes of children and adolescents with well-differentiated thyroid carcinoma and pulmonary metastases following (1)(3)(1)I treatment: a systematic review. *Thyroid* **20** 1095–1101. (<https://doi.org/10.1089/thy.2009.0446>)
- Piccardo A, Trimboli P, Bottoni G & Giovanella L 2020 Radioiodine ablation of remaining thyroid lobe in patients with differentiated thyroid cancer treated by lobectomy: a systematic review and metaanalysis. *Journal of Nuclear Medicine* **61** 1730–1735. (<https://doi.org/10.2967/jnumed.120.244384>)
- Pontius LN, Oyekunle TO, Thomas SM, Stang MT, Scheri RP, Roman SA & Sosa JA 2017 Projecting survival in papillary thyroid cancer: a comparison of the seventh and eighth editions of the American Joint Commission on Cancer/Union for International Cancer Control staging systems in two contemporary national patient cohorts. *Thyroid* **27** 1408–1416. (<https://doi.org/10.1089/thy.2017.0306>)
- Qiu ZL, Song HJ, Xu YH & Luo QY 2011 Efficacy and survival analysis of 131I therapy for bone metastases from differentiated thyroid cancer. *Journal of Clinical Endocrinology and Metabolism* **96** 3078–3086. (<https://doi.org/10.1210/jc.2011-0093>)
- Qu Y, Huang R & Li L 2017 Low- and high-dose radioiodine therapy for low-/intermediate-risk differentiated thyroid cancer: a preliminary clinical trial. *Annals of Nuclear Medicine* **31** 71–83. (<https://doi.org/10.1007/s12149-016-1133-4>)
- Reynolds J 1993 Comparison of I-131 absorbed radiation doses in children and adults: a tool for estimating therapeutic I-131 doses in children. In *Treatment of Thyroid Cancer in Children*. Ed J Robbins, pp 127–135. Washington, USA: US Department of Energy and US Department of Commerce, Technology, Administration, National Technical Information.
- Rivkees SA, Mazzaferri EL, Verburg FA, Reiners C, Luster M, Breuer CK, Dinauer CA & Udelsman R 2011 The treatment of differentiated thyroid cancer in children: emphasis on surgical approach and radioactive iodine therapy. *Endocrine Reviews* **32** 798–826. (<https://doi.org/10.1210/er.2011-0011>)
- Robenshtok E, Grewal RK, Fish S, Sabra M & Tuttle RM 2013 A low postoperative nonstimulated serum thyroglobulin level does not exclude the presence of radioactive iodine avid metastatic foci in intermediate-risk differentiated thyroid cancer patients. *Thyroid* **23** 436–442. (<https://doi.org/10.1089/thy.2012.0352>)
- Robenshtok E, Farooki A, Grewal RK & Tuttle RM 2014 Natural history of small radioiodine-avid bone metastases that have no structural correlate on imaging studies. *Endocrine* **47** 266–272. (<https://doi.org/10.1007/s12020-013-0123-8>)
- Rodriguez Schaap PM, Botti M, Otten RHJ, Dreijerink KMA, Nieveen Van Dijkum EJM, Bonjer HJ, Engelsman AF & Dickhoff C 2020 Hemithyroidectomy versus total thyroidectomy for well differentiated T1-2 N0 thyroid cancer: systematic review and meta-analysis. *BJS Open* **4** 987–994. (<https://doi.org/10.1002/bjs5.50359>)
- Rosario PW, Mineiro Filho AF, Prates BS, Silva LC & Calsolari MR 2012 Postoperative stimulated thyroglobulin of less than 1 ng/ml as a criterion to spare low-risk patients with papillary thyroid cancer from radioactive iodine ablation. *Thyroid* **22** 1140–1143. (<https://doi.org/10.1089/thy.2012.0190>)
- Rosario PW, Mourao GF, Siman TL & Calsolari MR 2015 A low postoperative nonstimulated serum thyroglobulin level excludes the presence of persistent disease in low-risk papillary thyroid cancer patients: implication for radioiodine indication. *Clinical Endocrinology* **83** 957–961. (<https://doi.org/10.1111/cen.12668>)
- Rothenberg SM, Mcfadden DG, Palmer EL, Daniels GH & Wirth LJ 2015 Redifferentiation of iodine-refractory BRAF V600E-mutant metastatic papillary thyroid cancer with dabrafenib. *Clinical Cancer Research* **21** 1028–1035. (<https://doi.org/10.1158/1078-0432.CCR-14-2915>)
- Rubino C, de Vathaire F, Dottorini ME, Hall P, Schwartz C, Couette JE, Dondon MG, Abbas MT, Langlois C & Schlumberger M 2003 Second primary malignancies in thyroid cancer patients. *British Journal of Cancer* **89** 1638–1644. (<https://doi.org/10.1038/sj.bjc.6601319>)
- Rubow S & Klopfer J 1988 Excretion of radioiodine in human milk following a therapeutic dose of I-131. *European Journal of Nuclear Medicine* **14** 632–633. (<https://doi.org/10.1007/BF00251790>)
- Ruel E, Thomas S, Dinan M, Perkins JM, Roman SA & Sosa JA 2015 Adjuvant radioactive iodine therapy is associated with improved survival for patients with intermediate-risk papillary thyroid cancer. *Journal of Clinical Endocrinology and Metabolism* **100** 1529–1536. (<https://doi.org/10.1210/jc.2014-4332>)
- Sabra MM, Grewal RK, Ghossein RA & Tuttle RM 2014 Higher administered activities of radioactive iodine are associated with less structural persistent response in older, but not younger, papillary thyroid cancer patients with lateral neck lymph node metastases. *Thyroid* **24** 1088–1095. (<https://doi.org/10.1089/thy.2013.0465>)
- Sabra MM, Ghossein R & Tuttle RM 2016 Time course and predictors of structural disease progression in pulmonary metastases arising from follicular cell-derived thyroid cancer. *Thyroid* **26** 518–524. (<https://doi.org/10.1089/thy.2015.0395>)
- Sacks W, Fung CH, Chang JT, Waxman A & Braunstein GD 2010 The effectiveness of radioactive iodine for treatment of low-risk thyroid cancer: a systematic analysis of the peer-reviewed literature from 1966 to April 2008. *Thyroid* **20** 1235–1245. (<https://doi.org/10.1089/thy.2009.0455>)
- Saracyn M, Bilski M, Kaminski G & Niemczyk S 2014 Can radioiodine be administered effectively and safely to a patient with severe chronic kidney disease? *Clinical Endocrinology* **81** 169–174. (<https://doi.org/10.1111/cen.12480>)
- Sawka AM, Thabane L, Parlea L, Ibrahim-Zada I, Tsang RW, Brierley JD, Straus S, Ezzat S & Goldstein DP 2009 Second primary malignancy risk after radioactive iodine treatment for thyroid cancer: a systematic review and meta-analysis. *Thyroid* **19** 451–457. (<https://doi.org/10.1089/thy.2008.0392>)

- Sawka AM, Ibrahim-Zada I, Galacgac P, Tsang RW, Brierley JD, Ezzat S & Goldstein DP 2010 Dietary iodine restriction in preparation for radioactive iodine treatment or scanning in well-differentiated thyroid cancer: a systematic review. *Thyroid* **20** 1129–1138. (<https://doi.org/10.1089/thy.2010.0055>)
- Schlumberger M, De Vathaire F, Ceccarelli C, Delisle MJ, Francesc C, Couette JE, Pinchera A & Parmentier C 1996 Exposure to radioactive iodine-131 for scintigraphy or therapy does not preclude pregnancy in thyroid cancer patients. *Journal of Nuclear Medicine* **37** 606–612.
- Schlumberger M, Catargi B, Borget I, Deandreis D, Zerdoud S, Bridji B, Bardet S, Leenhardt L, Bastie D, Schwartz C, *et al.* 2012 Strategies of radioiodine ablation in patients with low-risk thyroid cancer. *New England Journal of Medicine* **366** 1663–1673. (<https://doi.org/10.1056/NEJMoa1108586>)
- Schlumberger M, Lebouilleux S, Catargi B, Deandreis D, Zerdoud S, Bardet S, Rusu D, Godbert Y, Buffet C, Schwartz C, *et al.* 2018 Outcome after ablation in patients with low-risk thyroid cancer (ESTIMABL1): 5-year follow-up results of a randomised, phase 3, equivalence trial. *Lancet: Diabetes and Endocrinology* **6** 618–626. ([https://doi.org/10.1016/S2213-8587\(18\)30113-X](https://doi.org/10.1016/S2213-8587(18)30113-X))
- Schumm MA, Pyo HQ, Kim J, Tseng CH, Yeh MW, Leung AM & Chiu HK 2021 Recombinant human thyroid-stimulating hormone versus thyroid hormone withdrawal preparation for radioiodine ablation in differentiated thyroid cancer in children, adolescents and young adults. *Clinical Endocrinology* **95** 344–353. (<https://doi.org/10.1111/cen.14457>)
- Schwartz C, Bonnetain F, Dabakuyo S, Gauthier M, Cuffe A, Fieffe S, Pochart JM, Cochet I, Crevisy E, Dalac A, *et al.* 2012 Impact on overall survival of radioactive iodine in low-risk differentiated thyroid cancer patients. *Journal of Clinical Endocrinology and Metabolism* **97** 1526–1535. (<https://doi.org/10.1210/jc.2011-2512>)
- Seidlin SM, Marinelli LD & Oshry E 1946 Radioactive iodine therapy: effect on functioning metastases of adenocarcinoma of the thyroid. *JAMA* **132** 838–847.
- Selvakumar T, Nies M, Klein Hesselink MS, Brouwers AH, Van Der Horst-Schrivers ANA, Klein Hesselink EN, Tissing WJE, Vissink A, Links TP, Bocca G, *et al.* 2019 Long-term effects of radioiodine treatment on salivary gland function in adult survivors of pediatric differentiated thyroid carcinoma. *Journal of Nuclear Medicine* **60** 172–177. (<https://doi.org/10.2967/jnumed.118.212449>)
- Sisson JC, Shulkin BL & Lawson S 2003 Increasing efficacy and safety of treatments of patients with well-differentiated thyroid carcinoma by measuring body retentions of ¹³¹I. *Journal of Nuclear Medicine* **44** 898–903.
- Sohn SY, Kim HI, Kim YN, Kim TH, Kim SW & Chung JH 2018 Prognostic indicators of outcomes in patients with lung metastases from differentiated thyroid carcinoma during long-term follow-up. *Clinical Endocrinology* **88** 318–326. (<https://doi.org/10.1111/cen.13489>)
- Song HJ, Qiu ZL, Shen CT, Wei WJ & Luo QY 2015 Pulmonary metastases in differentiated thyroid cancer: efficacy of radioiodine therapy and prognostic factors. *European Journal of Endocrinology* **173** 399–408. (<https://doi.org/10.1530/EJE-15-0296>)
- Tala H, Robbins R, Fagin JA, Larson SM & Tuttle RM 2011 Five-year survival is similar in thyroid cancer patients with distant metastases prepared for radioactive iodine therapy with either thyroid hormone withdrawal or recombinant human TSH. *Journal of Clinical Endocrinology and Metabolism* **96** 2105–2111. (<https://doi.org/10.1210/jc.2011-0305>)
- Tam S, Boonsripitayanon M, Amit M, Fellman BM, Li Y, Busaidy NL, Cabanillas ME, Dadu R, Sherman S, Waguespack SG, *et al.* 2018 Survival in differentiated thyroid cancer: comparing the AJCC cancer staging seventh and eighth editions. *Thyroid* **28** 1301–1310. (<https://doi.org/10.1089/thy.2017.0572>)
- Tu J, Wang S, Huo Z, Lin Y, Li X & Wang S 2014 Recombinant human thyrotropin-aided versus thyroid hormone withdrawal-aided radioiodine treatment for differentiated thyroid cancer after total thyroidectomy: a meta-analysis. *Radiotherapy and Oncology* **110** 25–30. (<https://doi.org/10.1016/j.radonc.2013.12.018>)
- Tuttle RM, Leboeuf R, Robbins RJ, Qualey R, Pentlow K, Larson SM & Chan CY 2006 Empiric radioactive iodine dosing regimens frequently exceed maximum tolerated activity levels in elderly patients with thyroid cancer. *Journal of Nuclear Medicine* **47** 1587–1591.
- Tuttle MML, Haugen B, Shah J, Ja S, Rohren E, Subramaniam R, Hunt JI & Perrier Nd 2017a Thyroid-differentiated and anaplastic carcinoma. In *AJCC Cancer Staging Manual*, 8th ed. Eds ES Amin Mb, F Greene, D Byrd, RK Brookland, MK Washington, J Gershenwald, CC Compton, KR Hess, DC Sullivan, JM Jessup, *et al.* New York, NY, USA: Springer International Publishing.
- Tuttle RM, Haugen B & Perrier ND 2017b Updated American Joint Committee on Cancer/tumor-node-metastasis staging system for differentiated and anaplastic thyroid cancer (eighth edition): what changed and why? *Thyroid* **27** 751–756. (<https://doi.org/10.1089/thy.2017.0102>)
- Tuttle RM, Ahuja S, Avram AM, Bernet VJ, Bourguet P, Daniels GH, Dillehay G, Draganescu C, Flux G, Fuhrer D, *et al.* 2019 Controversies, consensus, and collaboration in the use of ¹³¹I therapy in differentiated thyroid cancer: a joint statement from the American Thyroid Association, the European Association of Nuclear Medicine, the Society of Nuclear Medicine and Molecular Imaging, and the European Thyroid Association. *Thyroid* **29** 461–470. (<https://doi.org/10.1089/thy.2018.0597>)
- Van Nostrand D 2017 Selected controversies of radioiodine imaging and therapy in differentiated thyroid cancer. *Endocrinology and Metabolism Clinics of North America* **46** 783–793. (<https://doi.org/10.1016/j.ecl.2017.04.007>)
- van Velsen EFS, Stegenga MT, Van Kemenade FJ, Kam BLR, Van Ginhoven TM, Visser WE & Peeters RP 2018 Comparing the prognostic value of the eighth edition of the American Joint Committee on Cancer/tumor node metastasis staging system between papillary and follicular thyroid cancer. *Thyroid* **28** 976–981. (<https://doi.org/10.1089/thy.2018.0066>)
- Vermandel M, Debruyne P, Beron A, Devos L, Talbot A, Legrand JF, Provot F & Lion G 2020 Management of patients with renal failure undergoing dialysis during (¹³¹I) therapy for thyroid cancer. *Journal of Nuclear Medicine* **61** 1161–1170. (<https://doi.org/10.2967/jnumed.119.232017>)
- Wichers M, Benz E, Palmedo H, Biersack HJ, Grunwald F & Klingmuller D 2000 Testicular function after radioiodine therapy for thyroid carcinoma. *European Journal of Nuclear Medicine* **27** 503–507. (<https://doi.org/10.1007/s002590050535>)
- Wu D, Gomes Lima CJ, Moreau SL, Kulkarni K, Zeymo A, Burman KD, Wartofsky L & Van Nostrand D 2019 Improved survival after multimodal approach with (¹³¹I) treatment in patients with bone metastases secondary to differentiated thyroid cancer. *Thyroid* **29** 971–978. (<https://doi.org/10.1089/thy.2018.0582>)
- Yeyin N, Cavdar I, Uslu L, Abuqbeith M & Demir M 2016 Effects of hemodialysis on iodine-131 biokinetics in thyroid carcinoma patients with end-stage chronic renal failure. *Nuclear Medicine Communications* **37** 283–287. (<https://doi.org/10.1097/MNM.0000000000000439>)
- Zhang XY, Song HJ, Qiu ZL, Shen CT, Chen XY, Sun ZK, Wei WJ, Zhang GQ & Luo QY 2018 Pulmonary metastases in children and adolescents with papillary thyroid cancer in China: prognostic factors and outcomes from treatment with (¹³¹I). *Endocrine* **62** 149–158. (<https://doi.org/10.1007/s12020-018-1678-1>)

Received in final form 21 June 2021

Accepted 7 July 2021

Accepted Manuscript published online 13 July 2021