Radioiodine Ablation following Thyroidectomy for Differentiated Thyroid Cancer: Literature Review of Utility, Dose, and Toxicity

Nicholas S. Andresen^a John M. Buatti^a Hamed H. Tewfik^b Nitin A. Pagedar^c
Carryn M. Anderson^a John M. Watkins^a

^aDepartment of Radiation Oncology, University of Iowa, Iowa City, IA, USA; ^bIowa City Cancer Treatment Center, Iowa City, IA, USA; ^cDepartment of Otolaryngology-Head and Neck Surgery, University of Iowa, Iowa City, IA, USA

Keywords

Thyroid cancer · Thyroidectomy · Radioiodine · Risk reduction · Secondary malignancies

Abstract

Management recommendations for differentiated thyroid cancer are evolving. Total thyroidectomy is the backbone of curative-intent therapy, with radioiodine ablation (RAI) of the thyroid remnant routinely performed, in order to facilitate serologic surveillance and reduce recurrence risk. Several single-institution series have identified patient subsets for whom recurrence risk is sufficiently low that RAI may not be indicated. Further, the appropriate dose of RAI specific to variable clinicopathologic presentations remains poorly defined. While recent randomized trials demonstrated equivalent thyroid remnant ablation rates between low- and high-dose RAI, long-term oncologic endpoints remain unreported. While RAI may be employed to facilitate surveillance following total thyroidectomy, cancer recurrence risk reduction is not demonstrated in favorable-risk patients with tumor size ≤ 1 cm without high-risk pathologic features. When RAI is indicated, in patients without macroscopic residual disease or metastasis, the evidence suggests that the rate of

successful remnant ablation following total thyroidectomy is equivalent between doses of 30–50 mCi and doses ≥ 100 mCi, with fewer acute side effects; however, in the setting of subtotal thyroidectomy or when preablation diagnostic scan uptake is $>2\%$, higher doses are associated with improved ablation rates. Historical series demonstrate conflicting findings of long-term cancer control rates between dose levels; long-term results from modern series have yet to be reported. For high-risk patients, including those with positive surgical margins, gross extrathyroidal extension, lymph node involvement, subtotal thyroidectomy, or $>5\%$ uptake, higher-dose RAI therapy appears to provide superior rates of ablation and cancer control.

© 2017 European Thyroid Association
Published by S. Karger AG, Basel

Introduction

Thyroid cancer is the most frequently occurring endocrine cancer, with an increasing incidence noted in the US over the past 15 years [1]. Papillary and follicular histologic subtypes, known as “differentiated thyroid cancers”, account for the majority of these cases, and are generally associated with an excellent prognosis ($>95\%$ 10-year sur-

vival) [2, 3]. Total thyroidectomy, removing both lobes and the isthmus (plus the pyramidal lobe, if present), is considered the mainstay of curative-intent therapy, though in selected lower-risk cases, subtotal thyroidectomy or ultrasound-based surveillance may be considered [4–6].

When total thyroidectomy is performed, many patients with differentiated thyroid cancer are treated with postoperative radioiodine therapy (RAI) to ablate residual thyroid tissue and, in intermediate- to high-risk cases, to postoperatively (adjuvantly) treat occult foci of cancer in the surgical bed and elsewhere (for the purposes of this review, we will employ the term “ablation” in relation to any postthyroidectomy use of RAI, with remnant ablation and cancer control objectives discussed in separate sections). Following an iodine restriction period of 1–2 weeks, during which a patient’s dietary and other exogenous iodine exposure is minimized, ^{131}I (RAI) is administered orally. RAI treatment is performed 1–6 months following thyroidectomy while patients are significantly hypothyroid (optimal thyroid-stimulating hormone, TSH, >30 mIU/L) or iatrogenically stimulated (with recombinant human TSH, rhTSH), in order to deliver a targeted ablative dose to any remnant thyroid tissue within the thyroid bed and/or elsewhere (e.g., thyroglossal duct tract and/or metastatic foci). The objectives of RAI ablation are 2-fold:

1. to reduce the probability of cancer recurrence in at-risk patients, and
2. to facilitate serologic surveillance via thyroglobulin (Tg).

However, as with any form of ionizing radiation, RAI has potential short-term morbidity and late adverse effects, for which risk minimization should be adopted when safe and feasible.

At present, there is a lack of consensus regarding which specific patient subsets benefit from the recurrence risk reduction goal of RAI. Further, there is uncertainty regarding which dose of RAI therapy is appropriate for specific clinicopathologic presentations. While several single-institution series have identified patient subsets for whom the recurrence risk is sufficiently low that RAI may not be indicated [7, 8], and recent phase III trials have demonstrated equivalent rates of thyroid remnant ablation with 30 versus 100 mCi doses of RAI [9, 10], practice patterns remain highly variable by individual practitioner [11]. The present review critically appraises the current evidence concerning RAI utilization and, in particular, the dose for thyroid remnant ablation following total thyroidectomy.

Discussion

Radioiodine Ablation versus Surveillance Only

Following surgical therapy for differentiated thyroid cancer, clinicians and patients must determine whether RAI remnant ablation is indicated. This decision is difficult for several reasons. First, recurrence rates and cause-specific mortality for differentiated thyroid cancer are very low, at 14 and 5% over 25 years, respectively [3]. Second, most patients present with small, localized disease, with approximately 80% presenting with intrathyroid, node-negative disease, three-quarters of whom have tumor size of 2 cm or smaller [3]. Third, the short- and long-term effects of RAI therapy are being increasingly recognized, the importance of which is magnified by the increasing number of younger age patients with small tumors (and associated low risk of recurrence).

Presently, there are no randomized trials evaluating the efficacy of surgery followed by RAI therapy compared with surgery alone. However, this question has been evaluated through surveillance series, including several large multi-institutional series and many single-institution experiences [7, 12–18] (Table 1). A large combination registry series from the US Air Force Registry and the Ohio State University demonstrated reductions in both 15-year recurrence (38 vs. 16%) and mortality (8 vs. 3%) with postoperative RAI compared with surveillance [14]. However, as noted by subsequent investigators [19], these rates were felt to be higher than those reported elsewhere, possibly due to the extent of surgical resection [20, 21]. Supporting this, a large case series from the Mayo Clinic found no survival or recurrence-free survival benefit with RAI therapy [3], but noted a much lower recurrence rate for patients managed with thyroidectomy alone (8–13% at 20 years) than that observed in the Air Force Registry series. Certainly, institutional and selection biases for RAI treatment in these retrospectively evaluated populations explain some of the differences, but this comparison accurately characterizes the challenges clinicians face in interpreting the available mature outcomes data.

As summarized in Table 1, the large historical series demonstrate a variable impact of RAI on cancer recurrence and mortality. The differences are largely explained by variations in patient demographics, preoperative imaging work-up, evolution in surgical techniques and extent of resection, tumor-specific factors (e.g., stage), variable timing and dose of RAI, and use of posttreatment thyrotropin suppression. This is supported by outcomes reported from the National Thyroid Cancer Treatment

Table 1. Ablation versus surveillance only: observational series studying the effect of RAI ablation versus surveillance

Study (first author, year)	Patients, <i>n</i>	Years	Extent of surgery	RAI dose, mCi	RAI timing	Follow-up	Outcome comparison	
							recurrence	mortality
Illinois (Cunningham, 1990) [12]	2,282	1970–1984	TT, NTT, or STT	NR	NR	Mdn 6.5 years	NS	RR = 1.54 ^a <i>p</i> = 0.05
UCSF (Loh, 1997) [13]	700 ^b	1970–1995	79% TT/NTT 19% STT 2% “other”	30–50 or 75–200	≤12months postop.	Mean 11.3 years	RR = 2.1 <i>p</i> = 0.0001	RR = 1.1 <i>p</i> = 0.76
Ohio State/Air Force Registry (Mazzaferrri, 1997) [14]	1,005	1962–1996(?)	90% TT or NTT	29–200	NR	Mdn 18.7 years	<i>p</i> < 0.001	<i>p</i> = 0.001 (for patients older than 40 and tumor ≥1.5 cm)
New Mexico (Morris, 1998) [15]	1,075	1969–1993	NR	NR	NR	Mdn 99 months (survivors)	NR	HR = 0.96 <i>p</i> = 0.151
NTCTCSR (Taylor, 1998) [16]	1,607	1987–1997(?)	82% TT or NTT	<30 (17%) 30–75 (9%) >75 (74%)	NR	Mean 3.1 years	RR = 0.30 <i>p</i> = 0.01	<i>p</i> = 0.04 ^c
NTCTCSR (Jonklaas, 2006) [7]	2,936	1987–2001	85% TT or NTT 15% other	None (32%) <30 (12%) 31–75 (6%) >75 (50%)	NR	Mdn 3 years	Stage I: NS Stages II–IV: Sig	Stage I: NS Stages II–IV: Sig
Mayo Clinic (Hay, 2002) [17]	2,512	1940–2000	87% TT or NTT	N/A	≤6 months postop.	Mdn 14 years	NS (MACIS <6)	NS (MACIS <6)
SEER (Podnos, 2005) [18]	19,918	NR	NR	NR	NR	NR	NR	RR = 1.128 <i>p</i> < 0.05

RAI, radioactive iodine (¹³¹I); TT, total thyroidectomy; NTT, near total thyroidectomy; STT, subtotal thyroidectomy; NR, not reported; Mdn, median; NS, nonsignificant difference; HR, hazard Ratio, for no RAI vs. RAI; RR, risk ratio, for no RAI vs. RAI; NTCTCSR, National Thyroid Cancer Treatment Cooperative Study Registry.

^a By ANOVA at multivariable analysis. ^b Subset of 492 patients with >pT1N0 disease, as patients without thyroid uptake at diagnostic ¹²³I scan or with unifocal papillary tumors ≤1 cm were selectively not treated with RAI. ^c Cancer-specific mortality.

Cooperative Study Registry (NTCTCSR), which demonstrated significant improvements in cancer control and mortality between postthyroidectomy RAI and thyroidectomy alone for stage II–IV patients, but not for stage I patients (defined by registry-specific classification as age <45 and tumor ≤4 cm) [7].

In the most comprehensive report to date, a meta-analysis of 9 postthyroidectomy RAI versus observation studies published through 2002 was performed [2]. The findings were mixed, with 4 large series demonstrating a lower recurrence rate for RAI-treated patients, while 6 others showed no difference in recurrence. The authors felt that this might be attributable to variations in study design between trials (e.g., endpoint assessment) and patient demographics (i.e., baseline recurrence risk). Thus, no definitive recommendation regarding the routine use of postsurgical RAI was made.

Two recent literature reviews have analyzed the conflicting data and provided limited guidance for the prudent use of postthyroidectomy RAI therapy [22, 23]. The authors of the 2 reviews agree that:

- RAI is not indicated for cancer recurrence risk reduction in the case of tumors of <1 cm maximal dimension with the absence of extrathyroidal extension (<T3) without high-risk clinicopathologic features (e.g., lymphovascular invasion, positive margin), and
- RAI is indicated in the case of distant metastasis or gross extrathyroidal extension (T4).

However, the guidelines differ in the assessment of completeness of tumor resection and the definition of patient risk stratification. Further illustrating the limitations of the available data in recommending RAI (and dose selection), Pacini et al. [22] identified an intermediate risk subset as candidates for “probable” RAI therapy,

suggesting dose options of 30 or 100 mCi. While a randomized trial of postthyroidectomy RAI versus observation in low-risk thyroid cancer is presently underway in the UK ("IoN"; NCT01398085), long-term (>10 years) follow-up will be required before any difference in cancer recurrence rate and/or survival can be expected (or equivalence declared).

Dose Selection: Dosimetric Calculation versus Fixed Dose (Empiric)

The American Thyroid Association (ATA) guidelines state the minimum RAI activity necessary to achieve successful remnant ablation should be utilized, particularly for low-risk patients [4]. There are 2 approaches to RAI dose prescription: dosimetrically calculated and fixed dose (empiric). In common practice, dosimetric methods are typically reserved for complex clinical situations, such as patients with renal insufficiency [24], children [25], the elderly [26], and patients with extensive pulmonary metastasis [4]. While small series have suggested favorable outcomes for dosimetrically determined RAI administration in the context of metastatic disease [27, 28], this has not been demonstrated in the nonmetastatic postthyroidectomy setting most representative of the vast majority of contemporary thyroid cancer presentations. Further, fixed-dose RAI regimens are easier and safer to implement clinically, and are more commonly employed, with nearly all prospective RAI remnant ablation series employing this approach. Thus, the remainder of this review will focus on comparisons of fixed-dose regimens of RAI.

Dose Efficacy: Remnant Ablation

Once the decision has been made to proceed with RAI for thyroid remnant ablation, the appropriate dose of therapy must be chosen. Nearly all contemporary comparison prospective randomized trials in the nonmetastatic setting have employed doses between 30 mCi (1.1 GBq) and 100 mCi (3.7 GBq) (Table 2). Two large multi-institutional randomized trials have been recently reported, enrolling patients with stage T1 to T3 primary tumors, with or without regional lymph node involvement, and without distant metastasis [9, 10]. The patient populations in these trials were generally low-risk, with high proportions of females, young patients, and smaller tumors. Both studies found that 30 and 100 mCi produced equivalent ablation rates (85–90%, employing Tg <1–2 ng/mL and either negative ultrasound or total body scan uptake <0.1%, measured at 6–10 months post-RAI). A recent 5-year outcome update of one of these trials (the French ESTIMABL-1) demonstrated no difference in

long-term ablation rates or retreatment rates [29]. Further, in the 631 patients with complete ablation at 8 months, only 17 had abnormalities during subsequent follow-up, of whom 2 had lymph node recurrence (the remaining 15 were without evidence of disease, without intervention).

A smaller Finnish trial compared the same doses and also demonstrated equivalent ablation rates, albeit much lower (52–56%) than those described in the above trials [30]. In contrast to this, a large Polish randomized trial comparing 30 versus 60 mCi for low-risk and 60 versus 100 mCi for high-risk patients demonstrated a significantly higher retreatment rate for the group taking 30 mCi (22%) compared with the others (13 and 11%, respectively; $p < 0.001$) [31, 32]. Similar inferior outcomes for lower-dose groups were reported in Middle Eastern and Asian trials as well [33–36]. Differences in surgical technique (and thus residual thyroid remnant volume) and adherence to a low-iodine diet were potential factors contributing to inconsistent results. Relating to the former, a Brazilian randomized trial compared 30 versus 100 mCi, and in reporting outcomes by residual neck uptake, the rate of successful ablation was 90 versus 92% ($p = 0.95$), respectively, for uptake <2% [37]. The differences were more apparent at higher levels of uptake (65 vs. 87% for 2–5% uptake, and 47 vs. 70% for >5% uptake), though these did not reach statistical significance. Other investigators have reported similar findings [33].

While several observational series have also been reported [14, 38–43], these have been generally less likely to detect a difference between groups. In at least 1 case, the lower dose demonstrated superior ablation rates [39]; however, this is almost certainly due to selection bias, with higher-risk cases more likely to receive higher-dose RAI. When appropriately matched by risk level, the ablation rates appear similar [41], with 1 study favoring higher-dose RAI [43]. Thus, it would seem that a higher burden of residual thyroid tissue is sufficient to warrant the higher dose of RAI for successful remnant ablation.

Dose Efficacy: Cancer Control

While the 2 recent large randomized trials have thus far reported only rates of remnant ablation [9,10], preliminary findings from the ESTIMABL-1 trial update suggest low rates of recurrence and no cancer-specific mortality at 5 years, independent of RAI dose (30 vs. 100 mCi) [29]. Further, several smaller trials also have sufficient follow-up to report cancer control outcomes. The Finnish trial reported by Maenpaa et al. [30] did not demonstrate a difference in cancer recurrence at a median fol-

Table 2. Thyroid remnant ablation: comparison of RAI doses (series with >100 patients)

Study (first author, year)	Study type	Patients, <i>n</i>	Extent of surgery	Low iodine diet prep.	Thyroid stimulation	RAI doses, mCi	RAI timing (postop.)	Timing of postablation assessment	Criteria for successful ablation	Follow-up		Outcome comparison	
												remnant ablation	cancer recurrence
France (Schlumberger, 2012) [9]	RT	752	TT	Yes	rhTSH or T4 withdrawal (TSH >30)	30 vs. 100	Mdn 7 weeks	6–10 months	Stimulated Tg <1 ng/mL and negative US	6–10 months	91 vs. 93% (<i>p</i> = NS)	NR	NR
UK (Mallick, 2012) [10]	RT	438	TT	Yes	rhTSH or T4 withdrawal	30 vs. 100	Mdn 11 weeks (2–76)	6–9 months	TBS <0.1% uptake (140–185 MBq), and Tg <2 ng/mL	6–9 months	85 vs. 89% ^a (<i>p</i> = 0.24)	NR	NR
Finland (Maenpaa, 2008) [30]	RT	160	TT or NTT	Yes	T4 withdrawal (TSH >30)	30 vs. 100	Mdn 38 days (27–124)	8 months	TBS <0.1% uptake (140–185 MBq), Tg <1 ng/mL, and no palpable LN	Mdn 51 months (18–77)	52% vs. 56% (<i>p</i> = 0.61)	16 vs. 18% (<i>p</i> = NS)	
Poland (Kukulska, 2010) [31, 32]	RT	309	TT	No	T4 withdrawal	30 vs. 60 vs. 100	NR	12 months	Negative TBS and stimulated Tg <10 ng/mL	Mdn 10 years (2–11)	Retreatment: 22/13/11% (<i>p</i> < 0.001 30 mCi inferior)	5 years local failure 2/3/3% (<i>p</i> = NS)	
Brazil (Rosario, 2004) [37]	RT	155	TT	No	T4 withdrawal	30 vs. 100	NR	6–12 months	Negative TBS	6–12 months	By TBS uptake <2%: 90/92% (<i>p</i> = 0.95) 2–5%: 65/87% (<i>p</i> = 0.14) >5%: 47/70% (<i>p</i> = 0.16)	NR	NR
Thailand (Sirisalipoch, 2006) [33]	RT	138	TT, NTT, STT	No	T4 withdrawal	50 vs. 100	Mean 61 days	6–9 months	Negative TBS (<0.2% uptake) and stimulated Tg <10 ng/mL	NR	65 vs. 87% (RR = 4.04; <i>p</i> = 0.003)	NR	NR
Iran (Fallahi, 2012) [34]	RT	341	TT or NTT	No	T4 withdrawal	30 vs. 100	4–6 weeks	6 and 12 months	Negative US and stimulated Tg <2 ng/mL	12 months	39 vs. 64% (<i>p</i> < 0.0001)	1 vs. 2% (<i>p</i> = NS)	
India (Bal, 1996) [35]	RT	149	NTT (87%), STT (13%)	No	T4 withdrawal	25–34 vs. 35–64 vs. 65–119 vs. 120–200	NR	6–12 months	Negative TBS, or <0.2% uptake and stimulated Tg <10 ng/mL	Mdn 3.8 years (1.5–6)	Dose 25–34 inferior; all other doses equal	NR	NR
India (Bal, 2004) [36]	RT	509	TT, NTT, STT	Yes	T4 withdrawal (TSH >30)	15–>50, in 5-mCi increments	Mdn 2 months (1–108)	6 months	Negative TBS, or <0.2% uptake and stimulated Tg <10 ng/mL	6 months	Dose <25 inferior (<i>p</i> = 0.006); all other doses equal	NR	NR
Ohio State (Mazzaferrri, 1997) [14]	Obs	151	TT, NTT, STT	No	NR	29–50 vs. 51–200	NR	Variable	Clinical exam or TBS	Mdn 14.7 years	NR	3 vs. 5% (NS)	

Table 2 (continued)

Study (first author, year)	Study type	Patients, n	Extent of surgery	Low iodine diet prep.	Thyroid stimulation	RAI doses, mCi	RAI timing (postop.)	Timing of postablation assessment	Criteria for successful ablation	Follow-up	Outcome comparison	
											remnant ablation	cancer recurrence
Michigan (Beierwaltes, 1984) [38]	Obs	511	STT, NTT, or TT	No	T4 withdrawal	100–149 vs. 150–174 vs. 179–199 vs. >200	6 weeks	12 months	Negative TBS	15 years	86/86/90/94% (p = NS)	NR
Australia (Kruijff, 2013) [39]	Obs	970	TT	No	rhTSH or T4 withdrawal	<75 vs. >75	NR	6–12 months	2 consecutive negative TBS and stimulated Tg <0.9 ng/mL	Mdn 52 months (6–276)	85 vs. 77% (p = 0.051) ^b	HR = 1.57 (p = 0.34) ^b
Italy (Castagna, 2013) [40]	Obs	225	NTT	No	rhTSH or T4 withdrawal	30–50 vs. 100	NR	Mdn 9 months (6–18)	Negative TBS and stimulated Tg <1 ng/ mL	6.9 vs. 4.2 years (p < 0.0001)	60 vs. 60% (p = 0.56)	76 vs. 72% (p = 0.043) ^c
MSKCC (Sabra, 2014) [41]	Obs	181 (all pN1b)	TT	Yes	rhTSH or T4 withdrawal	100 vs. 150 vs. >200	NR	6–12 months	Negative US and unstimulated Tg <0.6 ng/mL	Mean 5.7 years (6.3/4.4/8.9)	By Tg: 36/39/45% By imaging: 21/32/23% (p = NS)	NR
Korea (Han, 2014) [42]	Obs	176	TT	No	T4 withdrawal (TSH >30)	30 vs. 150	5–6 weeks	12 months	Negative US and stimulated Tg <1 ng /mL	Mdn 7.2 years (3.3–9.4)	97 vs. 91% (p = 0.24)	3 vs. 10% ^d
Germany (Verburg, 2014) [43]	Obs	1,298	TT, NTT, STT	No	T4 withdrawal	<54 vs. 54–81 vs. >81	NR	6–12 months	Negative TBS and stimulated Tg <1 ng/ mL	Mdn 6–17 years ^e (1–27)	LR, age <45 years 14/34/66% (p < 0.001) LR, age >45 years 30/27/65% (p < 0.001) LR, age >45 years ^f HR, no DM 30/27/45% (p = 0.92) HR, no DM ^f (p = 0.043) 0/2/0% (p = 0.56)	LR, age <45 years ^g 0/1/2% (p = 0.62) LR, age >45 years ^h 4/6/5% (p = 0.92) HR, no DM ^f (p = 0.043) 0/2/0% (p = 0.56)

RAI, radioactive iodine (¹³¹I); TT, total thyroidectomy; NTT, near total thyroidectomy; STT, subtotal thyroidectomy; NR, not reported; Mdn, median; NS, nonsignificant difference Tg, thyroglobulin; RT, randomized trial; Obs, observational series; T4, levothyroxine; rhTSH, recombinant human thyroid-stimulating hormone; TSH, thyroid-stimulating hormone, measured in mIU/L; US, ultrasound; TBS, total body scan; LN, lymph node; RR, risk ratio; HR, hazard ratio; MSKCC, Memorial Sloan-Kettering Cancer Center; LR, low-risk; HR, high-risk; DM, distant metastasis.

^a Based upon both TBS and Tg. ^b Both ablation and recurrence rates favor low dose, primarily owing to higher-stage tumors (pT3 and pN1–2) in the high-dose group. For recurrence, rates were 2.6 vs. 7.5% for low- vs. high-dose; however, this was not statistically significantly associated with recurrence upon multivariable analysis, following corrections for stage. ^c Reported as clinical remission at time of last follow-up, favoring low-dose; differences not apparent when assessed in stage-matched format. ^d Reported as crude rate, favoring low-dose, not corrected for differences in follow-up or stage. ^e Reported by various risk-based subgroups, not reported for population as a whole. ^f Expressed as 10-year estimates for disease control, only for patients able to achieve ablation (82–85% of LR, age <45 years; 78–81% of LR, age ≥45 years; 62–72% of HR, no DM).

Table 3. Radioiodine adverse effect comparison by dose level

Toxicity	Latency	30–50 mCi	100 mCi	>100 mCi
Nausea	Acute	4%	13%	
Neck pain	Acute	7%	17%	
Lacrimal dysfunction	Acute	8–20%	10–24%	
Salivary dysfunction	Acute	6–13%	5–16%	
Altered taste	Acute	0%	6%	
Altered smell	Acute	0%	2%	
Infertility (male)	Subacute			Transient decrease in FSH and reduced sperm motility
Infertility (female)	Late			Lower birth rate in women 35–39 years
Sialoadenitis	Late			2–67%
Nasolacrimal duct obstruction	Late			3.4%
Second primary malignancy	Late			Increased risk of solid tumors and leukemia

Summarized from Schlumberger et al. [9]; Mallick et al. [10]; Maenpaa et al. [30]; Brown et al. [51]; Rubino et al. [52]; Teng et al. [53]; van Nostrand et al. [58]; Burns et al. [59]; Wu et al. [60]; Pacini et al. [61]; Wichers et al. [62]; Handelsman et al. [63]; and Hyer et al. [64].

low-up of 51 months (16% for 30 mCi vs. 18% for 100 mCi; p = nonsignificant). Similarly, the Polish randomized trial reported by Kukulska et al. [31, 32] did not identify differences in local recurrence at a median follow-up of 10 years (2, 3, and 3% for 30, 60, and 100 mCi, respectively; p = nonsignificant). The observational series, while suffering from the aforementioned treatment group imbalances, do provide the opportunity for long-term outcome reporting; however, no differences in outcome have been recognized [14, 39, 42, 43], excepting 1 study demonstrating superior cancer control for the low-dose group [40].

The remaining data rely upon the predictive value of Tg measurements 6–12 months after remnant ablation as a correlate for subsequent cancer control, for which there is some supportive evidence [44–48]. Pacini et al. [48] found that rhTSH-stimulated Tg values alone have a sensitivity of 85% for disease recurrence detection at 2 years (median population follow-up of 21.5 months), rising to 96.3% when combined with neck ultrasound, with a combined negative predictive value of 99.5%. For long-term outcomes, there are limited data linking the success of initial remnant ablation. Further, when retreatment of residual post-RAI remnant is required, cancer control rates still appear favorable [31]. One cohort study of 208 patients found that an initial postablative stimulated Tg of <10 ng/mL performed at 6–12 months post-RAI was associated with disease-free survival of 97% at 4 years [49]. While this threshold is more liberal than the ATA Guide-

lines' concern for a postablative stimulated Tg level >2 ng/mL [4], the principle holds that lower residual Tg levels are associated with superior disease control outcomes. Overall, these data suggest that short-term indicators of successful remnant ablation may be indicative of subsequent cancer control, though more robust datasets with longer follow-up are necessary to validate this.

Dose Toxicity: Adverse Effects

The most reliable data concerning acute effects of RAI originate from the major, multi-institutional randomized trials [9, 10], which systematically collected acute toxicity data as a secondary endpoint, employing an internationally accepted, standardized quality-of-life scale [50]. Higher rates of nausea, neck pain, lacrimal gland dysfunction, salivary gland dysfunction, and altered taste were described for 100 mCi compared with 30 mCi (Table 3). Further, patients treated with 100 mCi also had a longer average hospital stay than patients treated with 30 mCi, though variable institutional regulations regarding post-RAI discharge is a probable confounding variable.

The long-term toxicities of RAI include secondary primary malignancy (SPM) [51–57], sialoadenitis [58], nasolacrimal duct obstruction [59], and infertility [60]. The increased risk of primary malignancy in thyroid cancer survivors compared to the general population is well documented [51–57]. While potential genetic predisposition and environmental factors associated with the development of primary thyroid cancer are confounders,

some evidence suggests that there may be a differential increase in risk of SPM observed in RAI-treated versus RAI-untreated thyroid cancer patients [51–53]. Illustrative of this, 3 studies have demonstrated an increased risk of hematologic malignancies for thyroid cancer patients treated with RAI versus no RAI [51–53], while 1 study did not [54]. The investigations which found an increased risk of SPM for RAI included patients who received RAI exceeding 100 mCi, if the dose was specifically recorded at all. How these data may be applied to lower-risk postthyroidectomy patients receiving low- to moderate-dose RAI remains to be determined. Long-term follow-up of cohorts treated with 30 and 100 mCi doses of RAI will be necessary to determine absolute and differential risk. However, for doses greater than 100 mCi the risk of SPM should be considered carefully in treatment decisions.

RAI therapy also increases the risk of long-term sialoadenitis and nasolacrimal duct obstruction [58, 59]. This evidence is based upon the administration of high single or cumulative doses (>100 mCi) of RAI therapy in retrospective cohort studies, and high-quality evidence regarding this risk in the context of lower doses (30–100 mCi) is lacking at this time.

Infertility and reproductive complications are another potential late consequence of RAI. An age-specific (35–39 years) subset of women who receive RAI therapy have a decreased birth rate compared with women who do not receive RAI therapy [60]. Further, RAI-treated women of all ages demonstrated a delay to first live birth (compared with non-RAI-treated female thyroid cancer patients); however, whether these findings are the result of physician recommendation to delay pregnancy, an impact of RAI therapy on reproductive choice, or an actual biologic mechanism is not clear.

Reproductive toxicities in males include a transient increase in serum FSH and a reduction in sperm motility [61, 62]. Temporary azoospermia has also been documented during the course of remnant ablation with doses of 100 and 150 mCi of RAI therapy [63]. However, the evidence suggests that the effects of RAI-induced azoospermia may not be irreversible. One study of 78 men who had received cumulative RAI doses of 81–1,359 mCi found no evidence of long-term infertility at a median follow-up of 21 years [64]. The same study also found no evidence of increased risk for birth defects. Thus, for males, there is no compelling evidence to suggest long-term reproductive effects, even at high RAI doses.

Conclusions

The management of differentiated thyroid cancer is rapidly evolving as new data become available. Several single-institution studies suggest that certain low-risk patients may not benefit from RAI therapy. The IoN trial, presently underway in the UK, should improve our understanding regarding which patient subsets may be safely managed with thyrotropin suppression alone (without RAI). When RAI is indicated for low- to moderate-risk patients, 2 recent large multi-institutional randomized trials demonstrated that 30 mCi yields similar high rates of thyroid remnant ablation at 6–9 months as 100 mCi, but with fewer acute side effects. In patients with subtotal thyroidectomy or uptake >2%, higher doses appear to achieve superior ablation rates after initial RAI. As long-term cancer control rates between dose levels remain uncertain, clinicians should discuss the risks and benefits of different doses with each patient, individualizing therapy based upon clinicopathologic features and patient concerns. For high-risk patients, including those with positive surgical margins, gross extrathyroidal extension, lymph node involvement, subtotal thyroidectomy, or >5% uptake, higher-dose RAI therapy appears to provide superior rates of ablation and cancer control.

Acknowledgments

The authors would like to thank Drs. Christina Ogrin and Gregory Doelle for their review of the manuscript and suggested references.

Disclosure Statement

None of the authors report potential or actual commercial conflicts of interest with respect to the present review.

References

- 1 Tuttle RM, Ball DW, Byrd D, Dilawari RA, Doherty GM, Duh QY, Ehya H, Farrar WB, Haddad RI, Kandeel F, Kloos RT, Kopp P, Lammonica DM, Loree TR, Lydiatt WM, McCaffrey JC, Olson JA, Parks L, Ridge JA, Shah JP, Sherman SI, Sturgeon C, Waguespack SG, Wang TN, Wirth LJ: Thyroid carcinoma. *J Nat Comp Cancer Netw* 2010;8:228–1274.
- 2 Sawka AM, Thephamongkhon K, Brouwers M, Thabane L, Browman G, Gerstein HC: A systematic review and meta-analysis of radioactive iodine remnant ablation for well-differentiated thyroid cancer: *J Clin Endocrinol Metab* 2002;89:3668–3676.

- 3 Hay ID, Thompson GB, Grant CS, Bergstralh EJ, Dvorak CE, Gorman CA, Maurer MS, McIver B, Mullan BP, Oberg AL, Powell CC, van Heerden JA, Goellner JR: Papillary thyroid carcinoma managed at the Mayo Clinic during six decades (1940–1999): temporal trends in initial therapy and long-term outcome in 2,444 consecutively treated patients. *World J Surg* 2002;26:879–885.
- 4 Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L: 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2016;26:1–136.
- 5 Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W: European Thyroid Cancer Taskforce: European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. *Eur J Endocrinol* 2006;154:787–803.
- 6 Pitoia F, Ward L, Wohlik N, Friguglietti C, Tomimori E, Gauna A, Camargo R, Vaisman M, Harach R, Munizaga F, Corigliano S, Pretell E, Niepomnische H: Recommendations of the Latin American Thyroid Society on the diagnosis and management of differentiated thyroid cancer. *Arq Bras Endocrinol Metabol* 2009;53:884–897.
- 7 Jonklaas J, Sarlis NJ, Litofsky D, Ain KB, Bigos ST, Brierley JD, Cooper DS, Haugen BR, Ladenson BR, Ladenson PW, Magner J, Robbins J, Ross DS, Skarulis M, Maxon HR, Sherman SI: Outcomes of patients with differentiated thyroid carcinoma following initial therapy. *Thyroid* 2006;16:1229–1242.
- 8 Jonklaas J, Cooper DS, Ain KB, Bigos T, Brierley JD, Haugen BR, Ladenson PW, Magner J, Ross DS, Skarulis MC, Steward DL, Maxon HR, Sherman SI: Radioiodine therapy in patients with stage I differentiated thyroid cancer. *Thyroid* 2010;20:1423–1424.
- 9 Schlumberger M, Catargi B, Borget I, Deandreis D, Zerdoud S, Bridgi B, Bardet S, Leenhardt L, Astie D, Schwartz C, Vera P, Morel O, Benisvy D, Bournaud C, Bonichon F, Dejax C, Toubert ME, Leboulleux S, Ricard M, Benhamou E: Strategies of radioiodine ablation in patients with low-risk thyroid cancer. *N Engl J Med* 2012;366:1663–1673.
- 10 Mallick U, Harmer C, Yap B, Wadsley J, Clarke S, Moss L, Nicol A, Clark PM, Farnell R, McCready R, Smellie J, Franklyn JA, John R, Nutting CM, Newbold K, Lemon C, Gerard G, Abdel-Hamid A, Hardman J, Macias E, Rogues T, Whitaker S, Vijayan R, Alvaraz P, Beare S, Forsyth S, Kadalayil L, Hackshaw A: Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. *N Engl J Med* 2012;366:1674–1685.
- 11 Smallridge RC, Diehl N, Bernet V: Practice trends in patients with persistent detectable thyroglobulin and negative diagnostic radioiodine whole body scans: a survey of American Thyroid Association members. *Thyroid* 2014;24:1501–1508.
- 12 Cunningham MP, Duda RB, Recan W, Chmiel JS, Sylvester J, Fremgen A: Survival discriminants for differentiated thyroid cancer. *Am J Surg* 1990;160:344–347.
- 13 Loh KC, Greenspan FS, Gee L, Miller TR, Yeo PPB: Pathological tumor-node-metastasis (pTNM) staging for papillary and follicular thyroid carcinomas: a retrospective analysis of 700 patients. *J Clin Endocrinol Metab* 1997;82:3553–3562.
- 14 Mazzaferri EL: Thyroid remnant ¹³¹I ablation for papillary and follicular thyroid carcinoma. *Thyroid* 1997;7:265–271.
- 15 Morris DM, Boyle PJ, Stidley CA, Altobelli KK, Parnell T, Key C: Localized well-differentiated thyroid carcinoma: survival analysis of prognostic factors and ¹³¹I therapy. *Ann Surg Oncol* 1998;5:329–337.
- 16 Taylor T, Specker B, Robbins J, Sperling M, Ho M, Ain K, Bigos ST, Brierley J, Cooper D, Haugen B, Hay I, Hertzberg V, Klein I, Klein H, Ladenson P, Nishiyama R, Ross D, Sherman S, Maxon HR: Outcome after treatment of high-risk papillary and non-Hurthle-cell follicular thyroid carcinoma. *Ann Intern Med* 1998;129:622–627.
- 17 Hay ID, McConahey WM, Goellner JR: Managing patients with papillary thyroid carcinoma: insights gained from the Mayo Clinic's experience of treating 2,512 consecutive patients during 1940 through 2000. *Trans Am Clin Climatol Assoc* 2002;113:241–260.
- 18 Podnos YD, Smith D, Wagman LD, Ellenhorn JDI: The implication of lymph node metastasis on survival in patients with well-differentiated thyroid cancer. *Am Surg* 2005;71:731–734.
- 19 Pacini F, Schlumberger M, Harmer C, Berg GG, Cohen O, Duntas L, Jamar F, Jarzab B, Limbert E, Lind P, Reiners C, Sanchez Franco F, Smit J, Wiersinga W: Post-surgical use of radioiodine (¹³¹I) in patients with papillary and follicular thyroid cancer and the issue of remnant ablation: a consensus report. *Eur J Endocrinol* 2005;153:651–659.
- 20 DeGroot LJ: Long-term impact of initial and surgical therapy on papillary and follicular thyroid cancer. *Am J Med* 1994;97:499–500.
- 21 Pacini F, Castagna MG, Brilli L, Pentheroudakis G; ESMO Guidelines Working Group: Thyroid cancer: ESMO clinical practice guidelines for diagnosis, treatment, and follow-up. *Ann Oncol* 2010;21(suppl 5):v214–v219.
- 22 Samaan N, Maheshwari YK, Nader S, Hill CS, Schultz PN, Haynie TP, Hickey RC, Clark RL, Goepfert H, Ibanez ML, Litton CE: Impact of therapy for differentiated carcinoma of the thyroid: an analysis of 706 cases. *J Clin Endocrinol Metab* 1983;56:1131–1138.
- 23 Sacks W, Fung CH, Chang JR, Waxman A, Braunstein GD: 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* 2010;20:1235–1245.
- 24 Holst JP, Burman KD, Atkins F, Umans JG, Jonklaas J: Radioiodine therapy for thyroid cancer and hyperthyroidism in patients with end-stage renal disease on hemodialysis. *Thyroid* 2005;15:1321–1331.
- 25 Samuel AM, Rajashekharrao B, Shah DH: Pulmonary metastases and adolescents with well-differentiated thyroid cancer. *J Nucl Med* 1998;39:1531–1536.
- 26 Tuttle RM, Leboeuf R, Robbins RJ, Qualey R, Pentlow K, Larson SM, Chan CY: Empiric radioactive iodine dosing regimens frequently exceed maximum tolerated activity levels in elderly patients with thyroid cancer. *J Nucl Med* 2006;47:1587–1591.
- 27 Maxon HR, Thomas SR, Hertzberg VS, Kerelakes JG, Chen JW, Sperling MI, Saenger EL: Relation between effective radiation dose and outcome of radioiodine therapy for thyroid cancer. *N Engl J Med* 1983;309:937–941.
- 28 Klubo-Gwiedzdinska J, Van Nostrand D, Atkins F, Burman K, Jonklaas J, Mete M, Wartofsky L: Efficacy of dosimetric versus empiric prescribed activity of ¹³¹I for therapy of differentiated thyroid cancer. *J Clin Endocrinol Metab* 2011;96:3217–3225.
- 29 Schlumberger MJ, Borget I, Catargi B, Deandreis D, Zerdoud S, Bardet S, Rosu D, Godbert Y, Leenhardt L, Schwartz C, Vera P, Morel O, Benisvy D, Bournaud C, Toubert M, Kelly A, Leboulleux S: ESTIMABL1: Long term outcome validates the use of 1.1 GBq/rhTSH for ablation in low risk thyroid cancer patients (short call oral abstract 6). 86th Annual Meeting of the American Thyroid Association (ATA), Denver, September 21–25, 2016.
- 30 Maenpaa HO, Keikkonen J, Vallavirta L, Tenhunen M, Joensuu H: Low vs high radioiodine activity to ablate the thyroid after thyroidectomy for cancer: a randomized study. *PLoS One* 2008;3:e1885.
- 31 Kukulska A, Krajewska J, Gawkowska-Suwiriska M, Puch Z, Paliczka-Cieslik E, Roskosz J, Handkiewicz-Junak D, Jarzab M, Gubala E, Jarzab B: Radioiodine thyroid remnant ablation in patients with differentiated thyroid carcinoma (DTC): prospective comparison of long-term outcomes of treatment with 30, 60, and 100 mCi. *Thyroid Res* 2010;3:9.
- 32 Kukulska A, Krajewska J, Roskosz J, Handkiewicz-Junak D, Jarzab M, Paliczka E, Puch Z, Wygoda Z, Gubala E, Jarzab B: Optimization of ¹³¹I ablation in patients with differentiated thyroid carcinoma: comparison of early outcomes of treatment with 100 mCi versus 60 mCi. *Pol J Endocrinol* 2006;57:374–379.

- 33 Sirisalipoch S, Buachum V, Pasawang P, Tepmongkol S, Boonvisut S: Prospective randomized trial for evaluation of efficacy of low versus high dose I-131 for postoperative remnant ablation in differentiated thyroid cancer. *Chula Med J* 2006;50:695–706.
- 34 Fallahi B, Beiki D, Takavar A, Fard-Esfahani A, Gilani KA, Saghari M, Eftekhari M: Low versus high radioiodine dose in postoperative ablation of residual thyroid tissue in patients with differentiated thyroid carcinoma: a large randomized clinical trial. *Nucl Med Commun* 2012;33:275–282.
- 35 Bal C, Padhy AK, Jana S, Pant GS, Basu AK: Prospective randomized clinical trial to evaluate the optimal dose of ¹³¹I for remnant ablation in patients with differentiated thyroid carcinoma. *Cancer* 1996;77:2574–2580.
- 36 Bal CS, Kumar A, Pant GS: Radioiodine dose for remnant ablation in differentiated thyroid carcinoma: a randomized clinical trial in 509 patients. *J Clin Endocrinol Metab* 2004;89:1666–1673.
- 37 Rosario PW, Reis JS, Barroso AL, Rezende LL, Padrao EL, Fagundes TA: Efficacy of low and high ¹³¹I doses for thyroid remnant ablation in patients with differentiated thyroid carcinoma based on post-operative cervical uptake. *Nucl Med Commun* 2004;25:1077–1081.
- 38 Beierwaltes WH, Rabbani R, Dmichowski C, Lloyd RV, Eyre P, Mallette S: An analysis of “ablation of thyroid remnants” with I-131 in 511 patients from 1947–1984: experience at University of Michigan. *J Nucl Med* 1984;25:1287–1293.
- 39 Kruijff S, Aniss AM, Chen P, Sidhu SB, Delbridge LW, Robinson B, Clifton-Bligh RJ, Roach P, Gill AJ, Learoyd D, Sywak MS: Decreasing the dose of radioiodine for remnant ablation does not increase structural recurrence rates in papillary thyroid carcinoma. *Surgery* 2013;154:1337–1345.
- 40 Castagna MG, Cevenini G, Theodoropoulou A, Maino F, Memmo S, Claudia C, Belardini V, Brianzoni E, Pacini F: Post-surgical thyroid ablation with low or high radioiodine activities results in similar outcomes in intermediate risk differentiated thyroid cancer patients. *Eur J Endocrinol* 2013;169:23–29.
- 41 Sabra MM, Grewal RK, Ghossein RA, Tuttle RM: 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* 2014;24:1088–1095.
- 42 Han JM, Kim WG, Kim TY, Jeon MJ, Ryu JS, Song DE, Hong SJ, Shong YK, Kim WB: Effects of low-dose and high-dose postoperative radioiodine therapy on the clinical outcome in patients with small differentiated thyroid cancer having microscopic extrathyroidal extension. *Thyroid* 2014;24:820–825.
- 43 Verburg FA, Mader U, Reiners C, Hanscheid H: Long-term survival in differentiated thyroid cancer is worse after low-activity initial post-surgical ¹³¹I therapy in both high- and low-risk patients. *J Clin Endocrinol Metab* 2014;99:4487–4496.
- 44 Duren M, Siperstein AE, Shen W, Duh QY, Morita E, Clark OH: Value of stimulated serum thyroglobulin levels for detecting persistent or recurrent differentiated thyroid cancer in high- and low-risk patients. *Surgery* 1999;126:13–19.
- 45 Pacini F, Lippi F, Formica N, Elisei R, Anelli S, Ceccarelli C, Pinchera A: Therapeutic doses of iodine-131 reveal undiagnosed metastases in thyroid cancer patients with detectable serum thyroglobulin levels. *J Nucl Med* 1987;28:1888–1891.
- 46 Pineda JD, Lee T, Ain K, Reynolds JC, Robbins J: Iodine-131 therapy for thyroid cancer patients with elevated thyroglobulin and negative diagnostic scan. *J Clin Endocrinol Metab* 1995;80:1488–1492.
- 47 Roelants V, De Nayer P, Bouckaert A, Beckers C: The predictive value of serum thyroglobulin in the follow-up of differentiated thyroid cancer. *Eur J Nucl Med* 1997;24:722–727.
- 48 Pacini F, Molinaro E, Castagna MG, Agate L, Elisei R, Ceccarelli C, Lippi F, Taddei D, Grasso L, Pinchera A: Recombinant human thyrotropin-stimulated serum thyroglobulin combined with neck ultrasonography has the highest sensitivity in monitoring differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 2003;88:3668–3673.
- 49 Toubeau M, Touzery C, Arveux P, Chaplain G, Vaillant G, Berriolo A, Riedinger JM, Boichot C, Cochet A, Brunotte F: Predictive value for disease progression of serum thyroglobulin levels measured in the postoperative period and after ¹³¹I ablation therapy in patients with differentiated thyroid cancer. *J Nucl Med* 2004;45:988–994.
- 50 Ware JE, Serbourne CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473–483.
- 51 Brown AP, Chen J, Hitchcock YJ, Szabo A, Shrieve DC, Tward JD: The risk of second primary malignancies up to three decades after the treatment of differentiated thyroid cancer. *J Clin Endocrinol Metab* 2008;93:504–515.
- 52 Rubino C, de Vathaire F, Dottorini ME, Hall P, Schwartz C, Couette JE, Dondon MG, Abbas MT, Langlois C, Schlumberger M: Second primary malignancies in thyroid cancer patients. 2003;89:1638–1644.
- 53 Teng CJ, Hu YW, Chen SC, Yeh CM, Chiang HL, Chen TJ, Liu CJ: Use of radioactive iodine for thyroid cancer and risk of second primary malignancy: a nationwide population-based study. *J Natl Cancer Inst* 2016;108:djv314.
- 54 Berthe E, Henry-Amar M, Michels JJ, Rame JP, Berthet P, Babin E, Icard P, Samama G, Galateau-Salle F, Mahoudeau J, Bardet S: Risk of second primary cancer following differentiated thyroid cancer. *Eur J Nucl Med Mol Imaging* 2004;31:685–691.
- 55 Chen AY, Levy L, Goepfert H, Brown BW, Spitz MR, Vassilopoulou-Sellin R: The development of breast carcinoma in women with thyroid cancer. *Cancer* 2001;92:225–231.
- 56 Sandeep TC, Strachan MWJ, Reynolds RM, Brewster DH, Scelo G, Pukkala E, Hemminki K, Anderson A, Tracey E, Friis S, McBride ML, Kee-Seng C, Pompe-Kim V, Klierer EV, Tonita JM, Jonasson JG, Martos C, Beffetta P, Brennan P: Second primary cancers in thyroid cancer patients: a multinational record linkage study. *J Clin Endocrinol Metab* 2006;91:1819–1825.
- 57 Subramanian S, Goldstein DP, Parlea L, Thabane L, Ezzat S, Ibrahim-Zada I, Straus S, Briery JD, Tsang RW, Gafni A, Rotstein L, Sawka AM: Second primary malignancy risk in thyroid cancer survivors: a systematic review and meta-analysis. *Thyroid* 2008;17:1277–1288.
- 58 Van Nostrand D: Sialoadenitis secondary to ¹³¹I therapy for well-differentiated thyroid cancer. *Clin Endocrinol* 2011;74:111–117.
- 59 Burns JA, Morgenstern KE, Cahill KV, Foster JA, Jhiang SM, Kloos RT: Nasolacrimal duct obstruction secondary to I(131) therapy. *Ophthalm Plast Reconstr Surg* 2004;20:126–129.
- 60 Wu JX, Young S, Ro K, Li N, Leung AM, Chiu HK, Harari A, Yeh MW: Reproductive outcomes and nononcologic complications after radioactive iodine ablation for well-differentiated thyroid cancer. *Thyroid* 2015;25:133–138.
- 61 Pacini F, Gasperi M, Fugazzola L, Ceccarelli C, Lippi F, Centoni R, Martino E, Pinchera A: Testicular function in patients with differentiated thyroid carcinoma treated with radioiodine. *J Nucl Med* 1994;35:1418–1422.
- 62 Wichers M, Benz E, Palmedo H, Biersack HJ, Grunwald F, Klimmuller D: Testicular function after radioiodine therapy for thyroid cancer. *Eur J Nucl Med* 2000;27:503–507.
- 63 Handelsman DJ, Conway AJ, Donnelly PE, Turtle JR: Azoospermia after iodine-131 treatment for thyroid carcinoma. *Br Med J* 1980;281:1527.
- 64 Hyer S, Vini L, O’Connell M, Pratt B, Harmer C: Testicular dose and fertility in men following I(131) therapy for thyroid cancer. *Clin Endocrinol* 2002;56:755–758.