Chapter 7
Radioiodine Treatment in Patients with Graves' Disease

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History of Radioiodine

Controversy surrounds the discovery and initial use of radioiodine to treat Graves' hyperthyroidism [1]. Two Massachusetts General Hospital (MGH) physicians, Saul Hertz and J. Howard Means, collaborated with two Massachusetts Institute of Technology physicists, Robley Evans and Arthur Roberts, and were the first to study radioiodine (128-I, half-life 25 min) in animal models. Using the Berkeley, California cyclotron in 1939, Joseph Hamilton, Mayo Soley, and Ernest Lawrence made 130-I (half-life 12 h) and 131-I (half-life 8 days) and used these isotopes to study physiology in humans. Hertz and Roberts in Boston during March 1941 and Hamilton and Lawrence in Berkeley during October 1941 both treated hyperthyroid patients with radioiodine, initially with the short-lived isotope, and both reported their preliminary data at a national meeting in 1942. The Second World War interrupted Hertz' studies, and Earl Chapman took over his practice at MGH. Since non-radioactive iodine ameliorates Graves' hyperthyroidism, Hertz had initially treated his patients with radioiodine followed a few days later by supersaturated potassium iodine (SSKI). Chapman used radioiodine alone to avoid any ambiguity regarding its beneficial effect [2]. After the war, Hertz was not allowed to return to MGH. In May 1946, the Journal of the American Medical Association published two papers on the use of radioiodine to treat hyperthyroidism, one authored by Hertz and Roberts, the second by Chapman and Evans.

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Mechanism of Action

Sodium 131-I can be obtained in capsule form or in solution for administration to patients. The isotope is rapidly absorbed and transported from the blood into thyroid follicular cells, where it is organified to tyrosyl residues on thyroglobulin. Beta emissions from the isotope have a path length of 1–3 mm and result in cell damage and necrosis [3]. After an interval of approximately 8–16 weeks, most thyroid glands have been effectively ablated and can no longer produce normal amounts of thyroid hormone.

Choice of Therapy

In a survey of endocrinologists who are members of the American Thyroid Association, The Endocrine Society, or the American Association of Clinical Endocrinologists, 54 % would recommend antithyroid drugs, 45 % radioiodine, and 1 % thyroidectomy for a typical patient with uncomplicated Graves' hyperthyroidism [4]. Endocrinologists from the United States were more likely to choose radioiodine (60 %), compared to their European colleagues (13 %). Since all three options for treatment are effective, however, the choice of therapy importantly needs to incorporate the values of the patient; e.g., some patients may fear radioiodine, and others may fear surgery or side effects from antithyroid drug. The choice of therapy is discussed in detail in Chap. 5.

Contraindications

Pregnancy and nursing are absolute contraindications to the use of radioiodine. Fetal thyroid tissue is present by 10–12 weeks of gestation and would concentrate and would be destroyed by radioiodine. Cretinism or developmental abnormalities could potentially occur in such infants. Guidelines suggest that all women of childbearing age have a pregnancy test before receiving radioiodine [5]. A survey of the outcome after radioiodine was inadvertently administered to 237 pregnant women (55 of whom had therapeutic abortions) reported 6 hypothyroid infants, of whom 4 had mental deficiencies [6]. In order to limit radiation exposure to breast tissue, radioiodine should be delayed until production of breast milk ceases, usually about 6 weeks after weaning.

Use in Patients with Ophthalmopathy

Many studies including a randomized controlled trial of the three treatment options for Graves' hyperthyroidism [7] suggest that radioiodine is more likely than antithyroid drugs or surgery to be associated with new onset or worsening ophthalmopathy.

The mechanism may be transiently higher levels of thyrotropin receptor antibody following radioiodine [8]. The concurrent use of corticosteroids may prevent worsening ophthalmopathy [9]. There is not uniform agreement among experts regarding the use of radioiodine in patients with moderate or severe ophthalmopathy. Radioiodine alone, as initial therapy in patients with ophthalmopathy, was recommended by only 2 % of endocrinologists, while radioiodine with corticosteroids was recommended by 17 % of specialists [4]. The 2011 American Thyroid Association guidelines for the treatment of hyperthyroidism suggested the concomitant use of corticosteroids in patients with mild ophthalmopathy and in smokers and advised against using radioiodine in patients with moderate or severe ophthalmopathy [5]. This topic is discussed in detail in Chap. 16.

Pretreatment with Antithyroid Drugs

Radioiodine administration as initial therapy for treatment of Graves' hyperthyroidism is generally safe. The concomitant use of beta-adrenergic blocking agents helps to control symptoms and tachycardia.

There are several reasons why pretreatment with antithyroid drugs prior to radioiodine administration may be desirable. Thyroid function becomes normal on average 5.7 weeks after methimazole treatment [10], and 97 % of patients are euthyroid by 12 weeks [11]. In contrast, radioiodine takes on average 8–16 weeks before a euthyroid state is obtained, and 14 % of patients fail to respond to the initial dose and require a second treatment [12]. Therefore, hyperthyroid symptoms and the risk for hyperthyroid complications (e.g., atrial fibrillation) are ameliorated more rapidly when patients are rendered euthyroid with methimazole prior to radioiodine administration.

Additionally, chemical hyperthyroidism and hyperthyroid symptoms may transiently worsen shortly after radioiodine administration, and this can be prevented by pretreatment with antithyroid drugs [13–15]. Rarely, thyroid storm has been reported shortly after radioiodine administration, although reported episodes may be due to prolonged omission of antithyroid drug therapy prior to radioiodine [16].

The 2011 American Thyroid Association guidelines recommended pretreatment with antithyroid drugs only in elderly patients, patients who were poorly tolerating hyperthyroid symptoms, and patients whose free T4 concentrations are two to three times higher than the upper limit of normal [5]. In contrast, most patients in the United Kingdom are pretreated with antithyroid drugs [17].

Resistance to Radioiodine Caused by Antithyroid Drugs

There is controversy regarding whether the use of antithyroid drugs, specifically PTU, prior to radioiodine administration, reduces the effectiveness of radioiodine. Two retrospective studies have concluded that the use of PTU within 55 days [18] or 15 days [19] of radioiodine administration, compared to patients using

methimazole or no antithyroid drug pretreatment, reduced cure rates from 61–66 % to 24 % and from 73–78 % to 32 %, respectively. However, a meta-analysis limited to randomized trials did not include these retrospective reports and concluded that the risk of treatment failure was increased and the risk of hypothyroidism decreased, after antithyroid drug pretreatment, and that there was no difference between PTU and methimazole [20]. Regardless, higher cure rates can be achieved by administering higher doses of radioiodine [20].

Stopping Antithyroid Drugs Before Giving Radioiodine

Since antithyroid drugs prevent organification of iodine (and therefore radioiodine) to proteins in the thyroid follicular cells, they should be stopped prior to radioiodine administration. Surprisingly, radioiodine may still be partially effective even when antithyroid drugs are continued. In one study, treatment was successful in 61 % of patients in whom methimazole was stopped 8 days prior to radioiodine and in 44 % of patients who did not stop the methimazole [21]. For the majority of patients, the optimal time to stop methimazole is 2–3 days before radioiodine administration. An analysis of patients who did not receive pretreatment or who had antithyroid drugs stopped for 1 or 2 days before radioiodine administration demonstrated that uptake, uptake curves, and isotope half-life were restored to normal 2 days after discontinuing methimazole and that 87 % of patients receiving radioiodine 2 days after discontinuing methimazole were cured [22].

Discontinuing antithyroid drugs more than 2–3 days before radioiodine treatment defeats one of the reasons for pretreatment—avoiding the increase in thyroid hormone levels that can occur following radioiodine administration. In one study comparing patients whose antithyroid drug was stopped 7 days or 2 days before radioiodine, free T4 levels were increased during the week off antithyroid drugs, but not after stopping antithyroid drugs for only 2 days, while the 24-h radioiodine uptake and the outcome at 6 months and 2 years were identical in the two groups [23]. In another study, thyroid hormone levels did not increase after radioiodine when antithyroid drugs were held for 3 days prior to treatment [24].

Resuming Antithyroid Drugs After Radioiodine

While some do not resume antithyroid drugs once radioiodine is administered, because of the 6–18-week delay for radioiodine to become effective, it is common to resume antithyroid drugs 3–7 days after radioiodine treatment, to avoid exacerbation of chemical and clinical hyperthyroidism in the few weeks between administering radioiodine and before it becomes effective. In one study, patients who resumed methimazole 7 days after radioiodine treatment had free T4 index values after 3 weeks that were 6 % lower than the values at the time of radioiodine treatment, compared to patients who did not restart methimazole, whose values were 36 % higher than those at the time of radioiodine treatment [25].

Radioiodine Dose and Outcome

Low Versus High

When radioiodine was first used to treat Graves' hyperthyroidism, it was hoped that a dose could be selected that would destroy enough tissue to render the patient euthyroid, but leave enough tissue to avoid hypothyroidism. Despite the use of complex formulas [26], this hope was never realized. Low doses, especially repetitive low doses, will prolong the duration of overt or subclinical hyperthyroidism and increase complications such as reduced bone density or atrial fibrillation. Patients who initially appeared to be euthyroid after radioiodine treatment might subsequently develop recurrent hyperthyroidism or insidiously become hypothyroid. Additionally, especially in children, there is evidence that neoplasia could develop in the remaining irradiated remnant [27]. Therefore, most experts and the American Thyroid Association guidelines recommend the use of a dose of radioiodine, especially in children, that results in near complete ablation of the gland and permanent hypothyroidism [5, 28]. After higher doses of radioiodine, most patients require thyroid hormone replacement within 3 months of treatment.

Fixed Versus Calculated

There are multiple factors that can influence the effectiveness of the ablative dose of radioiodine including gland size, radioiodine uptake, the degree of hyperthyroidism (which is associated with the turnover of thyroid hormone and iodine and therefore the duration of radioiodine retention in the gland), age and renal function, and dietary iodine intake, as well as the prior use of antithyroid drugs. While some models have used elaborate dosimetry to calculate ablative doses, most centers either use a fixed dose or adjust the dose based on only two variables—gland size and the radioiodine uptake.

Calculated dose regimens use 100–200 μCi/g of thyroid tissue adjusted by the radioiodine uptake, for example:

$$150\ \upsilon\text{Ci/g of tissue} \times 45\ \text{g thyroid / uptake of } 55\ \% = 12.3\ \text{mCi}.$$

In one study using 128–155 υCi/g of tissue, 90 % of patients were cured, and 80 % became hypothyroid [12].

Low fixed doses are not as effective as higher fixed doses. Five mCi resulted in only a 67 % cure rate and 41 % permanent hypothyroidism, while 10 mCi cured 85 % and made 61 % hypothyroid [29]. In theory, fixed dose regimens would undertreat patients with low radioiodine uptake or large glands. Studies have demonstrated the dependence of successful treatment on gland size when using fixed dose regimens [30]: ablation was successful in all patients with glands less than 15 g, but success was attained in only 25 % of patients whose glands exceeded 75 g. A variable fixed dose regimen—5 mCi for small glands, 10 mCi for medium glands, and 15 mCi for large glands—compares favorably to a standard calculated dose regimen [31].

Additionally, a randomized controlled trial of a higher fixed dose (15 mCi) versus a calculated dose regimen failed to show superiority of the calculated dose regimen [30].

Radioiodine-Resistant Graves' Hyperthyroidism: High Turnover

Some patients fail repetitive radioiodine treatments because of rapid turnover of iodine and thyroid hormone. In addition to the dose administered and the size of the gland, the duration of the retention of radioiodine within the gland is an important determinate of absorbed radiation dose. The ratio of the 4- to 6-h radioiodine uptake to the 24-h radioiodine uptake has been used as a surrogate marker for radioiodine turnover. In one study, this ratio was the most important determinate of radioiodine efficacy with a 48 % failure rate if the ratio exceeded 1.0 compared to an 11 % failure rate for a ratio less than or equal to 1.0 [32]. In another study, patients with a 5- to 24-h uptake ratio greater than or equal to 0.8 had a 34 % rate of treatment failure, compared to 16 % if the ratio was less than 0.8 [33]. The authors of that study utilized "double doses" of radioiodine (200 υCi/g instead of 100 υCi/g) in patients with high turnover and demonstrated a reduction in the failure rate. Another suggested approach is to use lithium in these patients to reduce turnover [34]. Patients with large isoechoic glands also have higher radioiodine failure rates compared to patients with hypoechoic glands, 22 % versus 7 %, respectively [35].

Dosing in Patients with Renal Failure

Because radioiodine is cleared by the kidneys, the use of high-dose radioiodine in treating patients with thyroid cancer is problematic, since lethal bone marrow exposure could occur with standard dose regimes. Fortunately, the doses used to treat hyperthyroidism do not approach maximal permissible exposures to bone marrow and other organs [36] and do not require adjustment. However, since iodine is concentrated in the dialysate, for patients receiving hemodialysis, radioiodine administration should be administered a minimum of 10 h before a dialysis treatment and is usually given shortly after a dialysis session, 24–48 h prior to the next session.

Treatment Failure: Repeat Treatment with Radioiodine

Failure of the first dose of radioiodine to achieve either a euthyroid or hypothyroid state occurs in 14 % of patients [12]. There is no fixed rule for when a second treatment should be administered. In one study utilizing a fixed dose of 11.8 mCi of radioiodine (not all patients had Graves' disease), hypothyroidism occurred before 8 weeks in 16 % of patients, after 8 and before 16 weeks in 46 % of patients, after 16 and before 24 weeks in 24 % of patients, and after 24 weeks in 14 % of patients

[37]. In addition to assessing thyroid hormone levels, the extent to which the goiter has regressed also correlates with a successful ablation. For example, a patient who remains chemically hyperthyroid 3 months after radioiodine, and whose gland has not regressed, might be retreated early, while a patient who remains mildly hyperthyroid 3 months after radioiodine, but whose gland has reduced to a normal or subnormal size, should be followed for another 4–8 weeks, as the success of the ablation may be delayed. Most of the patients who fail the first dose respond to a second dose of radioiodine, but rare patients may require 3 or more doses. One should question patients regarding iodine ingestion and iodine exposures (if using a fixed dose) and consider the possibility of rapid turnover in patients who fail one or more radioiodine treatments. An occasional patient who remains minimally hyperthyroid following radioiodine may be treated with nonradioactive iodine (e.g., SSKI) to avoid a second radiation exposure (see below).

Adjunctive Use of Beta-Adrenergic Blocking Agents

In patients who are not pretreated with antithyroid drugs, radioiodine may have little effect on thyroid hormone levels for the first 4–8 weeks or longer. During that time, chemical hyperthyroidism and/or hyperthyroid symptoms may transiently worsen before getting better. Unless there are contraindications, the use of beta-adrenergic blocking drugs should be administered to reduce symptoms and prevent complications [38].

Adjunctive Use of Lithium

Lithium prolongs the retention of radioiodine in thyroid tissue and in theory could increase the effectiveness of radioiodine or permit the use of lower doses. Several studies have reported higher cure rates and shorter duration to cure, when lithium at 800–900 mg per day was given with or before radioiodine administration [39, 40]. Additionally, lithium prevents the rise in free T4 when antithyroid drugs are discontinued prior to radioiodine administration [41]. However, a large randomized controlled trial failed to show a benefit of adjunctive lithium [42]. And 10 % of patients treated with lithium may experience adverse side effects including nausea, vomiting, or diarrhea [42].

Adjunctive Use of Iodine

Uptake of iodine into thyroid follicular cells is normally autoregulated: high intracellular levels reduce further transport of iodine uptake into follicular cells. Iodine ameliorates Graves' hyperthyroidism by interfering with its own uptake as well as inhibiting release of thyroid hormone. In selected patients who might have been

good candidates for pretreatment with antithyroid drugs had they not had contraindications, the use of supersaturated potassium iodine (SSKI) commencing 1 week after radioiodine administration shortens the interval before achieving a euthyroid state by several weeks [43].

The inhibitory effect of iodine on thyroid hormone synthesis and release is increased after radioiodine exposure [44]. In patients who remain minimally hyperthyroid following a first dose of radioiodine, the hyperthyroidism may be ameliorated by a drop or two of SSKI daily for as long as several years, and the patient may be able to avoid a second radiation exposure.

Low Iodine Diet

When radioiodine is used to treat patients with thyroid cancer, patients are instructed in a low iodine diet, since remnant radioiodine uptake is usually quite low. In contrast, patients with Graves' hyperthyroidism generally have high radioiodine uptake, and the use of low iodine diets is unnecessary. It is prudent, however, to question patients regarding the use of seaweeds, kelp, or other iodine-containing supplements (which may have been recommended by alternative healthcare practitioners), topical iodophors including iodine-containing douches, or recent iodinated radiocontrast exposures, since these and other high iodine exposures may reduce the radioiodine uptake and result in treatment failure. Similarly, recent radiocontrast may significantly lower the radioiodine uptake for up to several weeks. In such patients, using a calculated dose regimen rather than a fixed dose regimen may be preferable.

Patient Management After Radioiodine

Monitoring After Radioiodine

Patients require close monitoring of thyroid function following radioiodine administration, since they might develop transient exacerbation of hyperthyroidism, they usually develop hypothyroidism over the following 6–18 weeks, they occasionally develop transient euthyroidism or even hypothyroidism followed by recurrent hyperthyroidism, and they may have persistent hyperthyroidism (treatment failure). Patients are usually reassessed at 4–8-week intervals until chemically stable.

Hyperthyroidism results in suppression of the pituitary-thyroid axis, and once suppressed, pituitary TSH production may remain subnormal for up to 2 months or occasionally longer [45, 46]. It is therefore critical to assess patients with serum free T4 measurements in the weeks following radioiodine administration, since the TSH level may well remain subnormal, even though the patient is chemically and symptomatically hypothyroid with low free T4 concentrations [46]. Serum T3 levels may also be useful in a patient with low or normal free T4 and low TSH to distinguish between persistent T3 toxicosis and transient "central hypothyroidism" after

radioiodine. Since these patients are all known to be recently hyperthyroid, once hypothyroidism is diagnosed, treatment with a full replacement dose based on body weight is appropriate, but close monitoring remains essential since a rare patient will develop recurrent hyperthyroidism.

Long-Term Outcomes and Patient Satisfaction

Even patients who receive low-dose radioiodine treatment and achieve euthyroidism subsequently become hypothyroid at a rate of 2–3 % a year [47]. Once patients have achieved a stable TSH level on a stable dose of thyroid hormone, monitoring can be reduced to every 6–12 months. In the randomized trial of radioiodine, surgery, or antithyroid drugs for the treatment of Graves' hyperthyroidism, patients were equally satisfied with their outcomes shortly after treatment, as well as 14–21 years later [48].

Radiation Precautions

Patients who receive radioiodine may expose household and workplace contacts to radiation, as well as the general public, due to radiation in their saliva or urine or emitting directly from their bodies. Recommendations for minimizing harm to contacts have been inconsistent and have varied among states and countries. In 2011, the American Thyroid Association published recommendations based primarily on calculation of exposures and dose limits established by the Nuclear Regulatory Commission [49]. For example, patients are instructed to sleep alone for 3 days after 10 mCi or 6 days after 15 mCi; this is increased to 15 and 18 days, respectively, if sleeping with a pregnant woman or a child. The limit for sitting next to a nonpregnant adult (e.g., on a bus, on an airplane, or in the workplace) is 5.9 and 3.9 h on the day of treatment after 10 or 15 mCi, respectively, and increases to 9.2 and 6.1 h on the first day after treatment and 13.0 and 8.7 h on the second day after treatment with 10 or 15 mCi, respectively.

In Europe, the recommended exposure limits are tenfold lower than in the United States. As a result, precautions are recommended for approximately 1, 2, and 3 weeks after 5, 10, or 15 mCi of radioiodine [50], and some countries require that the patients be admitted to the hospital because of public safety concerns.

Pregnancy After Radioiodine

An arbitrary recommendation to delay pregnancy for 4–6 months after radioiodine is not supported by data, and probably one menstrual cycle is sufficient to allay any concern regarding the radiation exposure to the eggs. However, it usually takes 4–6

months after radioiodine therapy to ascertain that the hyperthyroidism is cured and the hypothyroidism is adequately treated and that serum levels of thyroid hormone are stable and optimal for a pregnancy. The dose to the ovary after radioiodine treatment for hyperthyroidism is about 3 rads, similar to that received from a hysterosalpingogram or a barium enema [51]. Birth defects are not more common in the offspring of children and adolescent who received radioiodine [52]. Theoretical risks of genetic damage suggest a risk of 0.005 %, which compares to the spontaneous risk of 0.8 % [53].

Gonadal Function in Men

Transient reductions in serum testosterone concentrations are seen after radioiodine, but no change in FSH. Sperm motility is impaired in hyperthyroid men and improves after radioiodine; there is no change in sperm concentration or morphology [54]. It is prudent for men to wait at least 3 months after receiving radioiodine before trying to impregnate their partner, thus allowing for complete turnover of the sperm exposed to the radioiodine.

Cost

While the average dose of radioiodine costs approximately $ 400–$ 800, facility charges for a nuclear pharmacy and radiation safety programs add considerably to the total costs. In an analysis that took into account laboratory tests, office visits, imaging, and complications, the cost of treating a patient with radioiodine for Graves' disease based on 2007 Medicare reimbursement rates was 23,610 compared to $33,195 for a thyroidectomy [55]. This does not include the costs of missed work or childcare, which might be necessary to comply with radiation safety requirements.

Adverse Effects

Radiation Thyroiditis and Thyroid Storm

One percent or fewer patients who receive radioiodine develop a radiation thyroiditis. This results in severe thyroid pain, which can be associated with dysphagia, and may last as long as 3 weeks. Transient recurrent laryngeal nerve dysfunction and hypoparathyroidism have also been described after radioiodine [53]. Nonsteroidal anti-inflammatory drugs usually provide adequate pain control, but some patients require corticosteroids.

Radiation thyroiditis might also be associated with exacerbation of thyrotoxicosis, especially if thyroid hormone stores were not first depleted by pretreatment with antithyroid drugs. Treatment with prednisone may limit the exacerbation of chemical hyperthyroidism.

Increase in Thyrotropin Receptor Antibodies

Thyrotropin receptor antibodies (TRAb) may increase after the administration of radioiodine, while they tend to fall after surgery and during the administration of antithyroid drugs [56]. It is likely that this is the mechanism for initiation or exacerbation of ophthalmopathy after radioiodine therapy. While fetal hyperthyroidism from transplacental passage of TRAb is rare, in theory this might occur with increased frequency in women who become pregnant within a few months of radioiodine treatment [57].

Cardiovascular Events and Mortality

Several studies suggest that radioiodine therapy is associated with increased cardiovascular events and mortality; however, it is difficult to ascertain whether the adverse outcomes are attributable to the radioiodine treatment or the underlying hyperthyroidism. Three studies from the same group of investigators have reported excess mortality in patients receiving radioiodine. In their first study, the standardized mortality ratio (SMR) was 1.1 (95 % confidence interval 1.1–1.2), but most of the excess deaths occurred in the first year following treatment [58]. In another study, the increased mortality occurred only in patients who did not become hypothyroid or in patients prior to thyroid hormone therapy [59]. In their third study, the SMR was 1.30 (95 % confidence interval 1.05–1.61) during treatment with antithyroid drugs and 1.24 (1.04–1.46) prior to thyroid hormone replacement therapy, but it was no longer increased once the patient was treated with thyroid hormone replacement [60]. While these data suggest that the excess mortality after radioiodine is related to hyperthyroidism per se, another study found higher rates of hospitalization for atrial fibrillation, cerebrovascular disease, hypertension, and heart failure after radioiodine, and these rates remained elevated for 35 years after radioiodine treatment [61].

Carcinogenesis

In the United States, the Cooperative Thyrotoxicosis Therapy Follow-up Study has followed 35,593 patients from 26 centers with a mean follow-up of 21 years. There has been no increase in overall cancer mortality [62, 63]. A small increase in thyroid

cancer was observed in patients who received radioiodine for toxic nodular goiter. It is uncertain whether this is due to the radioiodine or the known increased risk of thyroid cancer in nodular thyroids.

In the United Kingdom, despite no overall increased cancer mortality among 7,417 patients, there was an increased incidence of thyroid cancer and cancer of the small bowel [64]. A small study from Finland of 2,793 patients found an increased risk of breast, stomach, and kidney cancer [65].

Use in Children and Adolescents

The use of radioiodine in adolescents generally parallels treatment considerations in adults. Children with Graves' disease present additional considerations. It is well established that low levels of radiation exposure predispose to thyroid neoplasia in children through age 20 [66]. However, the risk appears to be greatest for exposures from the thyroid equivalent dose of 30 υCi/g of tissue or less and not the ablative doses used to treat Graves' hyperthyroidism [5, 67]. In the Cooperative Thyrotoxicosis Therapy Follow-up Study, there was no increase in thyroid neoplasia in adults with Graves' disease treated with radioiodine [27]. However, almost 30 % of children who received 50 υCi of radioiodine per gram of thyroid tissue developed thyroid adenomas, but children who received 100–200 υCi/g did not have an increased risk of neoplasia [67]. Thus, it is particularly important in children to use higher ablative doses of radioiodine to prevent thyroid neoplasia.

Whole body radiation exposure is also a concern in children. Using phantom modeling, the estimated whole body radiation exposure was 0.85 rem/mCi for adults, 0.9 rem/mCi for adolescents aged 15, and 1.45 and 2.4 rem/mCi for children aged 10 and 5 years, respectively [5]. The corresponding estimated relative lifetime cancer risk for a 15 mCi dose was 1.02 for adults, 1.04 for adolescents, and 1.08 and 1.16 for children aged 10 and 5 years, respectively. Small long-term studies have failed to show an increased risk in children treated with radioiodine [68]. Nonetheless, based on the above theoretical concerns, radioiodine was not recommended by the American Thyroid Association for children under age 5 and was felt to be an acceptable treatment for children between age 5 and 10 only if the calculated fully ablative dose was under 10 mCi [5]. In the United Kingdom, the use of radioiodine among those under age 21 has increased from 0.2 to 1.5 % of all treatments between 1990 and 2008 [69].

Conclusions

Radioiodine has been used successfully to treat Graves' hyperthyroidism for almost seven decades. Its safety has been well established, but its use in the United States has fallen slightly, likely because of the possibility that it will exacerbate

ophthalmopathy. Radiation precautions and childcare issues also provide obstacles to its use. Until we have an effective treatment that reverses the underlying pathophysiology of Graves' disease, radioiodine will remain one of the three mainstays of treatment, all of which are effective, none of which are ideal.

Checklist for Radioiodine Therapy for Hyperthyroidism

Pretreatment
Beta-blockers for most patients
Antithyroid drugs for patients at increased risk of hyperthyroid complications
Elderly, severe symptoms, free T4 more than 2–3 times upper normal
Stop antithyroid drugs 2–3 days before treatment
Pregnancy test when appropriate
Patient not lactating
Measure radioiodine uptake in a patient with recent or ongoing iodine exposure
Patient can comply with radiation safety precautions
Ask about young children or pregnant women in the home
Ask about proximity to co-workers
Ask about urinary incontinence
Restart antithyroid drugs 3–7 days after treatment in most pretreated patients
Consider prophylactic steroid coverage in patients with ophthalmopathy
Especially smokers
Monitor free T4 and TSH every 4–8 weeks until "cured" and stable
Antithyroid drugs can usually be stopped between 8 and 16 weeks after radioiodine
Levothyroxine is started when free T4 becomes subnormal (TSH may still be low)
Watch for occasional patients who are transiently eu- or hypothyroid, then relapse
Retreat by 12–18 weeks if goiter and moderately severe hyperthyroidism persist
Consider measurement of the 6-h/24-h radioiodine uptake ratio

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