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The Management of Graves' Disease in Children, with Special Emphasis on Radioiodine Treatment

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The most common cause of thyrotoxicosis in children and adults is Graves' disease, an autoimmune disorder characterized by diffuse goiter, hyperthyroidism and ophthalmopathy (1–4). Thyrotoxicosis can be also seen in children with T_4 ingestion and acute or subacute thyroiditis, and occasionally in patients with chronic lymphocytic thyroiditis (4). However, the hyperthyroid state is transient in these conditions, whereas thyrotoxicosis is persistent in Graves' disease (4). Toxic adenomas and multinodular goiters may also cause long-standing hyperthyroidism in children (4). These conditions, however, are uncommon causes of thyrotoxicosis in children and may be distinguished from Graves' disease by palpation of the thyroid gland and/or diagnostic imaging (4).

In Graves' disease, the spontaneous development of antibodies (TSAbs) that mimic TSH action leads to the excessive production and release of thyroid hormone, resulting in thyrotoxicosis. Untreated, thyrotoxicosis can have pernicious physical and behavioral effects on growing children and adolescents (1–4) and is commonly associated with weight loss, polyuria and polydipsia, palpitations, impaired skeletal mineralization, behavioral disturbances, and poor academic performance (1–4). Because Graves' disease is a protracted disorder that only rarely spontaneously resolves (1–4), treatment of hyperthyroidism is essential for the well-being of the child and adolescent.

Few subjects raise greater controversy than the treatment of Graves' disease in children. There is no specific cure for the illness, and potential complications are associated with each therapeutic option. Antithyroid drug therapy with thioamides is associated with side-effects and a high relapse rate even after prolonged therapy (2, 5–8). Thyroidectomy achieves high rates of remission, yet is a complex surgical procedure that can result in hypoparathyroidism or dysphonia due to damage to the recurrent laryngeal nerves (9). Radioiodine therapy achieves high rates of remission (8, 10–16), yet the long term safety of iodine-131 in children and adolescents has been evaluated in fewer than 1000 individuals (6, 15, 17–23). Concerns also linger about the oncogenic potential of radioiodine and the potential risks of genetic damage to any offspring after iodine-131 treatment (24–28).

In this report, we review information about the risks and benefits of current treatments for hyperthyroidism in adult and childhood Graves' disease with special emphasis on children and the safety of iodine-131 therapy in the pediatric population.

Antithyroid Drug Therapy

Drug therapy of Graves' disease was introduced in the early 1940s by Astwood (10). Current mainstays of antithyroid therapy include the thioamide derivatives propylthiouracil (PTU), methimazole (MMI), and carbimazole that reduce thyroid hormone synthesis by inhibiting the oxidation and organic binding of thyroid iodide (7, 29, 30). PTU has a short-half life (4–6 h) and requires administration several times each day (7, 29, 30). In contrast, MMI is 10-fold more potent on a weight basis than PTU and has a longer half-life (12–16 h) (7, 29, 30). To control the hyperthyroid state, PTU is typically given every 8 h, whereas MMI can be administered once or twice daily after thyrotoxicosis is controlled (31). Recommended doses for initial therapy are about 5–10 mg/kg·day for PTU and 0.5–1.0 mg/kg·day for MMI (32). However, even lower doses of PTU or MMI may be effective for induction or maintenance therapy.

Maximal clinical responses to medications occur after about 4–6 weeks of therapy. Before that time the signs and symptoms of hyperthyroidism may be controlled with β-blockers such as atenolol or propranolol (7). Biochemical thyrotoxicosis can be controlled more rapidly using solutions of saturated potassium iodide (or Lugol's solution) (7). Iodides block the release of thyroid hormones and reduce the vascularity of the thyroid gland, making them particularly useful for preparing a thyrotoxic patient for surgery (7).

Long term remission rates

Previous studies of adult patients reported remission rates of 40–50% after prolonged therapy (7). However, rates of remission after drug therapy have fallen considerably over the past few decades (33), possibly due to the well documented increase in mean dietary iodine intake (34). Remis-

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sion rates also appear to be similar whether patients are treated with or without levo-T_4 during antithyroid drug therapy (35).

In children, long term remission rates are at best 50–60% after several years of drug therapy (2, 5) and are usually less than 30–40% (2, 6, 8, 36–39). Furthermore, when responses to medical therapy among prepubertal and pubertal children are compared, 1-yr remission rates are considerably less in prepubertal (17%) than in pubertal children (30%) (39).

Increasing evidence shows that the efficacy of the antithyroid drugs is inversely related to serum levels of TSAb (40, 41). After several years of antithyroid therapy, remission rates in adults range from 15% in individuals with high levels of TSAb at the time of diagnosis to 50% in individuals with low pretreatment TSAb levels (40). It has also been suggested that the long term remission rate can be predicted from the response to short term (~4–6 months) antithyroid drug therapy (42, 43). Long term remission is less likely if high levels of TSAb are present or if hyperthyroidism persists after short term drug treatment (40, 42, 43).

Complications of drug therapy

Side-effects of antithyroid drugs are more common in children than adults (32, 44) and may be either idiosyncratic or dose related. Rarely, side-effects may be very serious and even fatal (4, 6) (Table 1). To date, 36 serious complications and 2 deaths in children caused by antithyroid drug therapy have been reported to the FDA MedWatch Program, which is prone to underreporting of drug side-effects (Malozowski, S., personal communication). Published studies including children (2, 6, 8, 36–38), show that 20–30% of patients will develop complications of drug therapy (Table 1). In one third to one fourth of these patients, complications require discontinuation of all thioamide drugs. In the remaining patients, complications may resolve after switching to an alternative thioamide drug.

Mild leukopenia (white blood cell count $<4000/mm^3$) is a common complication of hyperthyroidism and may be exacerbated by treatment with thioamide drugs (45, 46). In most cases, the leukopenia is transient and is not associated with an increased risk of infection (46). Severe leukopenia (total white blood cell count $<2500/mm^3$) or granulocytopenia ($<1000/mm^3$) can be associated with serious opportunistic infections (46) and should prompt discontinuation of thioamide therapy.

Mild increases in liver enzyme levels may accompany hyperthyroidism (7, 47, 48). However, 28% of patients with normal liver function tests at therapy onset will have mild and transient elevations of liver enzymes during therapy with PTU (45, 47, 49). Patients may also develop overt drug-induced hepatitis, which is accompanied by marked elevations in liver enzymes and hepatic necrosis and may be fatal (6, 47, 49, 50). Hepatitis may develop anytime during therapy, but usually occurs within the first 2–3 months (47, 49, 50). MMI characteristically causes cholestatic hepatitis, whereas PTU usually induces cytotoxic hepatitis (47, 49, 50). In such cases, thioamide therapy must be abandoned, and glucocorticoids may hasten recovery.

Cutaneous reactions to thioamides may include generalized macular, papular, and pruritic eruptions; urticaria; and angioedema (46, 51). Depigmentation of the hair may also occur (46, 51). The pruritic rash sometimes resolves if another thioamide drug is substituted for the offending agent and can be treated with antihistamines (46, 51).

Fever, lymphadenopathy, arthralgias, and arthritis may also occur during treatment with thioamides (52). Rarely, patients may develop systemic vasculitis with splenomegaly and positive antinuclear antibodies (52). In such cases glucocorticoids may prove beneficial (52). Other rare and serious adverse effects of thioamide drugs include nephrotic syndrome, hypothrombinemia, and aplastic anemia (45). The development of any of these complications requires discontinuation of drug therapy.

TABLE 1. Complications of antithyroid drug therapy in more than 500 children (2, 4–6, 37, 38)

Complication	Incidence (%)
Mild increases in liver enzymes	28
Mild leucopenia	25
Skin rash[a]	9
Granulocytopenia[b]	4.5
Arthritis[b]	2.4
Nausea[a]	1.1
Agranulocytosis[b]	0.4
Hepatitis[b]	0.4
Loss of taste	Rare
Hypothrombinemia[b]	Rare
Thrombocytopenia[b]	Rare
Aplastic anemia[b]	Rare
Nephrotic syndrome[b]	Rare
Death	Rare

[a] May respond favorably to substitution of an alternative thioamide drug.

[b] Necessitate discontinuation of all thioamide drugs.

Risks of cancer

The incidence of developing thyroid cancer in one's lifetime is 1 in 400 for males and 1 in 300 for females (53). Several reports show that patients with Graves' disease have a higher incidence of thyroid cancer than normal subjects or patients with other forms of thyroid disease (54, 55). Thyroid malignancies developing in patients with Graves' disease may also be more aggressive than cancers occurring in individuals without Graves' disease (54, 55).

The Collaborative Thyrotoxicosis Study Group (CTSG) revealed that the incidence of thyroid carcinomas over 10–20 yr of follow-up (not lifetime incidences) is 5-fold higher in adults with Graves' disease treated with thioamide drugs (follow-up period incidence rate, 1 case/332 individuals) than in patients treated with iodine-131 (1 in 1783) and 8-fold higher than in patients treated surgically (1 in 2820) (56). Rates of thyroid adenomas were also 10 and 20 times higher among the adults treated with antithyroid drugs (1 in 76) than in patients treated with iodine-131 (1 in 802) or surgery (1 in 1692), respectively (56). Rather than reflecting a causative role for medical therapy in the pathogenesis of thyroid neoplasia, these observations may reflect the persistence of more thyroid tissue in patients treated with drugs than in individuals treated with radioiodine or surgery.

Surgery

Subtotal thyroidectomy is the oldest form of therapy for Graves' disease, with the Nobel prize awarded to Kocker in 1909 for innovations in this area (7). Whereas subtotal thyroidectomy was advocated in previous years for children and adults (38, 57), total thyroidectomy is recommended increasingly to reduce the risk of recurrent hyperthyroidism (58–60). Both subtotal and total thyroidectomy are complicated surgical procedures, and the incidence of complications and the rates of recurrence of hyperthyroidism depend in large part on the skill and experience of the surgeon. Referral to surgeons with expertise in thyroid surgery is therefore highly recommended (4, 8).

Long term cure rates

After subtotal thyroidectomy, relief of hyperthyroidism is achieved in about 80% of children and adults, and hypothyroidism develops in about 60% of individuals (38, 57). Hyperthyroidism recurs in about 10–15% of patients after subtotal thyroidectomy (38, 59). In comparison, hyperthyroidism recurs in less than 3% of children and adults who undergo total thyroidectomy, and hypothyroidism is nearly universal (57–61).

Complication rates

Complication rates are comparable following subtotal or total thyroidectomy (59). The most comprehensive survey of the complications of thyroid surgery was based on results of 24,108 thyroid operations on adults and children performed in 1970 (9). These cases were estimated to represent one third of the thyroidectomies performed that year in the United States (9). In-hospital mortality rates were 0.5% for adults and 0.08% (1 death in about 1,000 operations) for children (9). The most frequent nonlethal complications included pain and transient hypocalcemia (9). Hypocalcemia may reflect disruption of the blood supply to the parathyroid glands and/or rapid uptake of calcium by demineralized bones. Less common problems (1–4%) include hemorrhage, permanent hypoparathyroidism, and vocal cord paralysis (9). Other studies describing complications of thyroid surgery in children involved far fewer subjects (38, 58, 62), but showed similar rates of complications (38, 58, 62) (Table 2).

We are unaware of a more recent large follow-up study describing the incidence of complications and deaths after thyroid surgery. Yet, with advances in anesthesia, surgery, and postoperative care, it is possible that complication rates have decreased. However, with increasing use of radioiodine, less thyroid surgery is now performed, and fewer surgeons are able to develop and maintain their skills than in the past (63).

TABLE 2. Complications of thyroidectomy in more than 2,000 children (9, 38, 57, 59, 60, 62)

Complication	Incidence (%)
Pain	100
Transient hypocalcemia (1–7 days)	10
Keloid	2.8
Permanent hypoparathyroidism	2
Vocal cord paralysis	2
Transient hoarseness	1
Temporary tracheostomy	0.7
Hemorrhage/hematoma	0.2
Death	0.08

Radioiodine

Radioiodine therapy for Graves' disease was introduced at Massachusetts General Hospital nearly 60 yr ago (64, 65). We estimate that more than 2 million individuals have received iodine-131 for Graves' disease, making this therapy one of the most widespread therapeutic uses of a systemically administered radionuclide. After oral administration of iodine-131 to patients with Graves' disease, the vast majority of radiation exposure is localized in the thyroid gland (66, 67). Iodine-131 emits both β- and γ-radiation, and destruction of follicular cells is the result of β-particle radiation (66, 67). β-Particles from iodine-131 have a path length of 1–2 mm and will kill cells trapping iodine-131 and those cells in the immediate area (66, 67). Histologic findings after radioiodine treatment include epithelial swelling and necrosis, edema, and leukocyte infiltration (66, 67). The acute inflammation is followed by fibrosis of the gland (66, 67).

The amount of iodine-131 uptake by the thyroid gland reflects the size of the thyroid gland and the activity of the disease. Doses of radioiodine administered to the patient are thus based upon gland size and iodine uptake using standard formulas [dose (mCi) = (μCi of ^{131}I/g of thyroid $\times$ estimated thyroid weight)/24-h radioiodine uptake] (7, 68–70). Thus, if a dose of 200 μCi/g thyroid tissue is desired for a patient with a 40-g thyroid gland and a 50% radioiodine uptake at 24 h, the administered dose will be 16 mCi.

Thyroid size can be assessed clinically relative to the size of a normal thyroid gland size (0.5–1 g/yr of age; 15–20 g for adults) or more precisely by ultrasound (71–73). However, even when accurate gland size, uptake, and effective iodine-131 half-times are measured and a fairly high degree of accuracy of delivered dose is obtained, the outcome is still imprecise due to individual variation in the sensitivity of the thyroid to radioiodine (74). Thus, clinical estimation of thyroid size is usually sufficient when determining the radioiodine dose.

It has been suggested that doses (administered activities) delivering 30,000–40,000 cGy (rads) to the thyroid are required to ablate the thyroid gland (75, 76). However, doses delivering 10,000–20,000 cGy to the thyroid are more commonly used and may result in complete or partial destruction of the thyroid (66, 67, 76). Administered thyroid doses of 150 μCi/g [5.5 megabecquerels (MBq)/g] yield radiation doses of 12,000 cGy to the thyroid (67, 77). Exposures to the stomach, marrow, liver, and gonads will be about 14, 6.8, 4.8, and 2.5 cGy/organ, respectively. The total body exposure will be about 4.0 cGy (67, 77). The effective half-life of iodine-131 is 7 days (67). Thus, at 5 weeks after treatment, less than 1% of the administered activity remains in the thyroid (67).

Within 4–10 days after iodine-131 administration, circulating levels of thyroid hormones may rise as thyroid hormone is released from degenerating follicular cells (78). Symptoms of hyperthyroidism during this time can be controlled using β-blockers (79, 80). Saturated potassium iodide or Lugol's solution will attenuate biochemical hyperthyroid-

ism during this period and not adversely affect the outcome of radioiodine therapy (80). Six to 8 weeks after treatment, the thyroid gland shrinks, and biochemical hypothyroidism, which can be transient, often develops (7, 81). In up to 20% of patients, hyperthyroidism will persist beyond 2 months of therapy; a second dose of radioiodine is recommended for these patients (7, 10). In many centers, a second dose of radioiodine is not given until 6 months after the initial therapy.

The details of iodine-131 therapy for childhood Graves' disease have been reported in several studies (6, 15, 17–23). Patients as young as 1 yr of age have been treated with iodine-131 (22). The reported iodine-131 doses in children and adolescents have ranged from 100–250 μCi/g thyroid tissue (6, 15, 17–23).

Long term cure rates

Long term cure rates are higher in patients treated with larger amounts than in those given smaller amounts of radioiodine (7). There is considerable variability in rates of hyper- and hypothyroidism among different centers using the same administered activity (78).

In adult patients treated with low doses of iodine-131 (50–75 μCi/g), hyperthyroidism persists in 30–50% 1 yr after therapy (82–85). The incidence of hyperthyroidism declines progressively thereafter (86). The incidence of hypothyroidism in patients treated with lower doses ranges from 7–20% at 1 yr and increases with time (84, 86). In comparison, after treatment with higher iodine-131 doses (150–250 μCi/g), only 5–10% of patients are hyperthyroid at 1 yr, and 40–80% become hypothyroid (7, 56, 77, 87).

In children treated with 50–100 μCi/g thyroid tissue, 25–40% of patients are hyperthyroid several years after therapy (88). In comparison, in children treated with a single dose of 150–200 μCi/g thyroid, hyperthyroidism persists in 5–20% of patients, and 60–90% of patients become hypothyroid (10, 21, 22, 89).

The success of radioiodine therapy is influenced by the size of the thyroid gland and possibly by circulating levels of TSAb (90). Responses to iodine-131 therapy are lower in patients with very large glands (>80 g) and high TSAb levels than in patients with smaller glands (90–93). Thus, total surgical thyroidectomy may be associated with higher cure rates than radioiodine therapy for persistently large glands. There is also some evidence that responses to radioiodine are less favorable after treatment with antithyroid drugs (93–95).

Complication rates

Acute complications of iodine-131 therapy have been reported, but the incidence is low and not well defined (7, 78) (Table 3). In children, very few acute adverse responses to iodine-131 therapy of Graves' disease have been described (6, 15, 17–23).

In adults, transient nausea has been reported after radioiodine administration, and mild pain over the thyroid gland, reflecting radiation thyroiditis, may develop 1–3 days after a therapeutic dose (7, 78). These side-effects are self-limited and respond to treatment with nonsteroidal antiinflammatory agents (7, 78). Severe neck swelling and tracheal compression have been reported rarely in patients with very large goiters after iodine-131 administration and can be controlled with large doses of corticosteroids (78). Neck swelling after radioiodine treatment typically occurs with doses greater than 50,000 cGy; such doses are above those needed for ablative therapy (96). Vocal cord paresis occurs very rarely (89, 97).

TABLE 3. Complications of 131-iodine therapy in adults (15, 108)

Complication	Incidence (%)
Worsening of eye disease	3–5
Transient thyroid pain	5%
Nausea	Rare
Thyroid storm	Rare
Transient hypocalcemia	Rare
Hyperparathyroidism	Rare

Thyroid storm has been reported to develop between 1–14 days after iodine-131 treatment in a very small number of patients (98–100). This complication is rare, and no cases were reported among 7000 patients treated with iodine-131 at one center (10). Patients with severe thyrotoxicosis and very large goiters may be at higher risk for thyroid storm. In this setting, antithyroid drugs can be administered for several weeks before radioiodine therapy to ensure that the thyroid has been depleted of stored hormones before radioiodine therapy (7, 100). Thioamides are withdrawn 5–7 days before the administration of radioiodine (7, 100).

Exacerbation of ophthalmopathy

Recent discussions have focused on the association of iodine-131 therapy of Graves' disease with the development or progression of ophthalmopathy (101, 102). Several large retrospective studies have found no effects of iodine-131 therapy on the clinical course of eye disease (86, 103–106), whereas other investigators observed worsening of eye disease after therapy (107). A recent prospective study of adults (ages 15–85 yr) showed worsening of ophthalmopathy in 15% of patients with Graves' disease 2–6 months after treatment with iodine-131 (108). In 70% of these patients, changes in eye findings were modest and transient, and at 1 yr after treatment, eye disease was worse in 5% of patients (108). In comparison, eye disease worsened in 3% of patients treated with methimazole alone (108). Orbital radiotherapy and high dose glucocorticoids were required for 5% of patients treated with radioiodine and 1% of patients treated with methimazole (108).

Several factors may predispose to the development or progression of ophthalmopathy after radioiodine therapy, including preexisting ophthalmopathy, smoking, high pretreatment levels of T_3, and high posttreatment serum concentrations of TSH (109). Thus, some investigators refrain from using radioiodine in patients with severe ophthalmopathy, particularly if they smoke (109). Because high pretreatment levels of T_3 are a risk factor for worsening eye disease after iodine-131 treatment, pretreatment with antithyroid drugs may help reduce the risk of an exacerbation of ophthalmopathy (109, 110). After radioiodine therapy, thyroid hormone and TSH levels should be monitored closely, and T_4 replacement started at early stages to reduce the risk of ophthalmopathy (109).

Data presented in one recent report suggested that the development and progression of ophthalmopathy are prevented by treatment with prednisone for 3 months after radioiodine therapy (108). However, adjunctive prednisone therapy is not recommended for most children because long term progression of ophthalmopathy occurs infrequently and unpredictably after radioiodine treatment (108). Prolonged prednisone administration is also associated with weight gain, immune suppression, and growth failure in children. On the other hand, prednisone may be useful after radioiodine therapy for patients with severe eye disease.

In contrast to adults, children rarely develop severe ophthalmopathy (1, 32, 103). Proptosis is generally mild, nonprogressive, and reversible (1, 103). Of 87 children treated with iodine-131 for Graves' disease, eye signs improved in 90% of children, did not change in 7.5%, and worsened in 3% after treatment (22). In 45 children with ophthalmopathy at the onset of treatment, eye disease improved in 73% and worsened in 2% after 1 yr or more of drug therapy (2). After subtotal thyroidectomy in 80 children, eye disease worsened in 9% (59). In contrast, eye disease was stable in 60 (75%) children after total surgical thyroidectomy (59). Thus, eye disease worsens in only a small percentage of children after medical, radioiodine, or surgical therapy of Graves' disease.

Changes in parathyroid function

During iodine-131 treatment of Graves' disease, the parathyroid glands are exposed to 140–750 cGy (111). Radioiodine therapy has been associated with the development of transient hypoparathyroidism in a few individuals (112, 113). This complication is rare and is typically transient (114). Conversely, parathyroid radiation exposure may predispose to the development of hyperparathyroidism, as observed in atomic bomb survivors (115, 116). Hyperparathyroidism has also been reported in several patients treated with iodine-131 for thyroid carcinoma or Graves' disease (111, 117). Thus, measurement of serum calcium levels every 5 yr has been recommended for patients treated with iodine-131 for Graves' disease (117). The only study of iodine-131-treated patients with Graves' disease involving age- and gender-matched controls, however, did not detect an increased incidence of hyperparathyroidism (118).

Thyroid cancer risks

The increased risk of thyroid cancer after thyroid irradiation in childhood has been recognized for nearly 50 yr (119). Thus, a major concern of iodine-131 therapy relates to the risks of thyroid and nonthyroid cancers. Not surprisingly, this issue has been the focus of several long term follow-up studies involving more than 60,000 patients (56, 120–123). Studies of the effects of external radiation, diagnostic iodine-131 use, and environmental radioiodine and γ-ray exposure have also provided important insights regarding the risks of radiation exposure and thyroid carcinomas (26, 28, 124–128). These studies show that the risk of thyroid cancer is increased with exposure to low or moderate levels of external radiation. In contrast, thyroid cancer risks are much lower after high level irradiation that results in thyroid cell death or reduced capacity of cells to divide (128, 129).

When used diagnostically, a dose of 60 μCi iodine-131 results in the estimated delivery of 6.5 cGy to the thyroid gland in adults (130). There is no evidence of an increased risk of thyroid or nonthyroid cancers after this exposure to iodine-131 (130–133). Also, no risk of thyroid cancer or nodules has been observed among women who lived their entire lives in areas of high natural background radiation in China (134).

In contrast, when the thyroid gland is exposed to 20–2000 cGy of external irradiation, there is an increased risk of thyroid neoplasia (26–28). No excess risk of thyroid cancer has been reported within 5 yr of exposure to external x- or γ-rays (28). The mean latency time for development of malignancy in radiation-exposed patients is between 10–20 yr, with the minimum time to appearance being between 5–9 yr (26–28). More than 85% of tumors are papillary carcinoma (28), 10% of tumors are follicular carcinoma, and 5% of tumors are medullary or undifferentiated carcinomas (28).

Survivors of the atomic bomb explosions in Japan had an increased incidence of thyroid cancer after acute exposures from external x- and γ-rays from air detonations (127). Exposure to fallout containing iodine-131 and other shorter-lived radioiodines in the Marshall islands after nuclear weapons testing resulted in thyroid gland irradiation estimated at 150 cGy for adults and 700-1400 cGy for children (26, 135). These exposures were associated with 3- to 10-fold increases in the rates of both benign and malignant thyroid neoplasms (135). However, the contribution of iodine-131 to thyroid cancer risk could not be determined and was probably very small (128, 135) (Boice, Jr., J. D., personal communication).

The Chernobyl disaster also resulted in an increased rate of thyroid carcinomas (136–138), especially in children less than 10 yr of age (124, 139, 140). In contrast to the long latency periods reported in other studies after thyroid irradiation (26, 27), thyroid cancers were seen as early as 4 yr after the Chernobyl accident (139). These unusual observations may reflect irradiation in a large region of iodine deficiency, intense screening of the population resulting in the early detection of malignancies, and influences of iodine-131 and short-lived radioiodines associated with the Chernobyl fallout (128). The predominant malignancy type in these individuals was papillary carcinoma (139, 140).

The large scale epidemiological surveys of the CTSG involving 36,050 patients in the United States (56) and the Swedish cohort studies (16, 121, 141) have provided considerable information about the relative cancer risks after iodine-131 therapy. After treatment of Graves' disease in adults with iodine-131, which exposes the thyroid gland to high levels of radiation, rates of thyroid cancer and thyroid cancer mortality were not increased (56, 121, 141, 160).

Follow-up data involving children in the CTSG showed that thyroid adenomas developed in 30% of the patients treated in one center with low doses of iodine-131 (50 μCi/g) estimated to result in thyroid exposure of 2500 cGy (56, 88). Yet, in the other centers where children were treated with higher doses of iodine-131 (100–200 μCi/g), the incidence of thyroid neoplasms was not increased (56).

Outcomes after iodine-131 treatment of children and adolescents with hyperthyroidism have been reported for approximately 1000 individuals in other reports (6, 15, 17–23).

The duration of follow-up in these studies ranged from less than 5 yr to 15 yr, with only some subjects followed for more than 20 yr. These studies have not revealed an increased risk of thyroid malignancy.

Nonthyroid malignancies

There are several reports of the influence of radioiodine on nonthyroid malignancies in adults. After iodine-131 treatment for hyperthyroidism, the risk of leukemia does not differ from control populations (16, 121, 123, 141–143). Although slight increases in the relative risk of breast cancer after iodine-131 therapy have been reported, these increases are not statistically significant, and the findings have not been consistently reported (125, 144, 145). When rates of stomach cancer were examined, the Swedish cohort study noted a small (1.14 relative risk), but significant, increase in incidence in adults (121). Importantly, recent CTSG follow-up studies have not found significantly elevated nonthyroid cancer mortality after iodine-131 therapy (160).

Among iodine-131-treated children, a comprehensive follow-up study of nonthyroid cancer risks has yet to be performed.

Is the developing child at higher risk for developing cancer after iodine-131 therapy?

The risk of thyroid malignancy after thyroid irradiation is higher in younger children than in older children or adults (26–28, 146). After the nuclear disaster at Chernobyl, the greatest number of cases of thyroid cancer occurred in infants less than 1 yr of age at the time of the accident (139). When patients were between 0–5 yr of age at the time of exposure, thyroid malignancies predominated (139). After 6 yr of age, thyroid adenomas occurred more frequently than carcinomas (139), and the number of cases of thyroid cancer decreased progressively through 12 yr of age (139). However, it is not clear whether iodine-131 exposure alone had a major contribution to the possible radiation effect (128, 146).

Studies of external thyroid irradiation show that when exposure occurs after 20 yr of age, the risk of thyroid malignancy is not significantly increased (27, 28). Yet when exposure occurs before 20 yr of age, thyroid cancer rates are higher at progressively younger ages (26–28). Atomic bomb survivor data show that thyroid cancer relative risks per Gy are 9.4, 3.0, 0.34, and −0.23 for ages 0–9, 10–19, 20–39, and more than 40 yr, respectively, at the time of exposure (Ron, E., personal communication). For individuals exposed to head and neck irradiation, thyroid cancer relative risks per Gy were 9.0, 5.4, and 1.8 when exposure occurred between 0–5, 5–10, and 10–15 yr of age, respectively (27) (Ron, E., personal communication). However, even after external radiation exposure between 1–15 yr of age, thyroid malignancies occur quite infrequently (1–4 cases/10,000 person-yr) (27).

Whereas young children are more susceptible to cancer risks after external thyroid irradiation, we do not know if children exposed to the higher doses of iodine-131 for treatment of Graves' disease are at increased risk for thyroid carcinomas (26, 56). Radioiodine therapy will destroy most of the thyroid gland, which will decrease or eliminate tumor risk. Recent ultrasound studies have shown that 1 yr after iodine-131 therapy, thyroid size is reduced up to 90% in most patients (90). With progressive fibrosis and cell death after radioiodine, the amount of residual thyroid tissue will progressively decline (67). We are currently unaware of long term follow-up studies that have accurately assessed the amount of thyroid tissue that remains after iodine-131 therapy in children.

In the event that thyroid tissue remains after iodine-131 treatment, there is a theoretical risk that some remaining cells may undergo neoplastic degeneration. However, as cell-killing radiation doses are used and marked reductions in thyroid tissue are achieved (66, 76), thyroid cancer risks will be considerably less after radioiodine therapy than after external radiation. Given the predilection of young children to thyroid cancer after external radiation, we surmise that there is a theoretical risk of a small increase in the rate of thyroid cancer after iodine-131 therapy during childhood. This potential risk will be greatest in children treated before 5 yr of age and progressively lower in children treated between 5–10 and 10–20 yr of age.

Supporting the idea that childhood radioiodine therapy is not associated with moderate or large increases in thyroid cancer risks, we are aware of only four reported cases of thyroid malignancy in children previously treated with iodine-131 (5 yr of age at treatment with 50 μCi/g, 9 yr of age at treatment with 5.4 mCi, 11 yr of age at treatment with 1.25 mCi, and 16 yr of age at treatment with 3.2 mCi) (19, 88, 147–149). Three of these individuals were treated with low doses of iodine-131, and one patient was treated with a moderate dose of iodine-131. As discussed above, low doses of iodine-131 are associated with an increased incidence of thyroid nodules and neoplasms (56).

Regarding the risk of nonthyroid malignancies, iodine-131 therapy is associated with a whole body exposure rate of about 0.45 cGy/mCi (67, 150). Thus, it is estimated that the average child treated with iodine-131 will receive about 4 cGy whole body irradiation (67, 150). Radiation exposure will be slightly higher in the nonthyroidal tissues that accumulate iodine, including the salivary glands, stomach, and bladder (67, 150). However, detecting increases in cancer risk associated with such low doses will be very difficult even if very large populations of children are studied, and any increases in the incidence of nonthyroid cancers are likely to be very small (151).

Health of offspring

Radiation exposure of the gonads during iodine-131 therapy approximates 2.5 cGy, which is comparable to the gonadal exposure from a barium enema or an iv pyelogram (152). The literature contains data on 500 offspring born to approximately 370 subjects treated with iodine-131 for hyperthyroidism during childhood and adolescence (6, 15, 17, 18, 20–22). The incidence of congenital anomalies reported among the offspring of patients treated with radioiodine does not differ from the incidence in the general population. In addition, there was no increased risk of congenital anomalies in the offspring of 77 patients treated in childhood with 80–700 mCi iodine-131 (153). Furthermore, there was no evidence of an increased rate of birth defects in survivors of

the Hiroshima and Nagasaki atomic bomb blasts who were exposed to higher levels of external irradiation of the gonads than are associated with radioiodine therapy (154).

Long term follow-up for iodine-131-treated children

Experimental studies show that increased secretion of TSH predisposes the irradiated thyroid gland to neoplasia (8, 10, 77). Thus, it has been suggested that replacement doses of levo-T_4 be administered to iodine-131-treated patients to prevent elevations in TSH secretion and hypothyroidism (77). Although attractive, we do not know the long term efficacy of this strategy in humans.

Reports show that patients with Graves' disease have a higher incidence of thyroid neoplasia than patients with other forms of thyroid disease or the normal population (54, 55). Rates of thyroid cancer may be higher in patients with Graves' disease treated with drugs than in those treated with radioiodine or surgery (26). Regular examination of the thyroid is thus essential for all patients with a history of Graves' disease. Prompt biopsy or surgical excision of palpable nodules is recommended to determine whether a malignancy exists. Because radiation-related thyroid tumors more typically appear 10–20 yr after exposure (26, 56), long term follow-up beyond the pediatric years is essential.

In adults, thyroid cancer developed in about 1 in 2000 patients during a 10- to 20-yr follow-up period after radioiodine therapy in the CTSG (56). The most common tumor type after thyroid irradiation is papillary carcinoma (90%) (56, 155–158), which is a slow growing tumor treated by thyroidectomy and adjunctive iodine-131 therapy (156–158). The prognosis of papillary carcinoma in children is excellent, and fatalities from papillary carcinoma occur rarely (156–158). Thus, in the unlikely event that thyroid carcinoma develops after childhood radioiodine therapy, the prognosis should be excellent.

Synopsis

When considering simplicity of treatment, complication rates, cancer risk, and long term remission rates, each treatment option for Graves' disease differs. Medical therapy in children is associated with disappointing long term remission rates of less than 30–40% and a 20–30% incidence of adverse reactions that may rarely be serious or fatal (2, 5, 6, 8, 37). Drug therapy is a first line therapy in many centers (32) and is especially useful when TSAb levels are low and the thyroid gland is small (40, 41). Thioamide treatment is also useful for controlling hyperthyroidism while more definitive forms of therapy are being considered or until the child is considered old enough for radioiodine treatment. Thioamide drugs may also be preferable to radioiodine in those rare children with profound ophthalmopathy.

In contrast to drug therapy, surgery has more favorable cure rates (90%) and reverses the hyperthyroid state rapidly. Total thyroidectomy is a complex surgical procedure with definite surgical risks, including death in about 1 in 1000 operations in children (9). Of concern is the fact that the number of skilled thyroid surgeons has declined over the past several decades (63). When radioiodine therapy is not desired, surgery is useful for the patient who develops drug-related complications or does not achieve lasting remission with drug treatment. Surgery may be preferable when the thyroid gland is very large (>80 g). Surgery should also be considered when there is profound ophthalmopathy and lasting remission cannot be achieved with thioamides (109).

Radioiodine is associated with high cure rates that are typically greater than 90%. Iodine-131 therapy is the simplest and least expensive treatment option for Graves' disease (159) and rarely is accompanied by acute side-effects (124). Possible complications include an exacerbation of ophthalmopathy in a small proportion of patients, particularly those who smoke (108). Studies of children with Graves' disease treated with ablative doses of iodine-131 have not revealed an increased risk of thyroid neoplasia (6, 15, 17–23). However, as only several thousand children have been treated with iodine-131 and not all have been followed long term, it is only possible to conclude that radioiodine is not associated with moderate or large increases in the incidence of thyroid cancer. A long term study of larger populations is needed to define the true incidence of thyroid neoplasia in children treated with radioiodine.

Children as young as 1 yr of age have been treated with iodine-131 for Graves' disease (22). Yet, we do not know whether there is an age below which high dose iodine-131 therapy should be avoided. Risks of thyroid cancer after external irradiation are highest in children less than 5 yr of age and progressively decline with advancing age (27, 28). Thus, if there is residual thyroid tissue after radioiodine treatment, there may be a small increase in the incidence of thyroid cancer in young children treated with iodine-131. Therefore, it may be prudent to avoid radioiodine therapy in children less than 5 yr of age. Fortunately, in the unlikely event that thyroid cancer develops after childhood iodine-131 therapy, it should be associated with an excellent prognosis. The use of higher doses of iodine-131 (150–200 μCi/g thyroid tissue; 5.5–7.4 MBq/g; 12,000–16,000 cGy/g) to ablate the thyroid gland will also decrease the risks of radioiodine-induced tumors and is clearly preferable to lower dose therapy in children.

Selection of a treatment modality for the child with Graves' disease is often a difficult and highly personal decision. The small risk of an increase in the rate of thyroid cancer after radioiodine therapy needs to be balanced against the known complications of drug therapy or surgery. Discussion of the advantages and risks of each therapeutic option by the physician is therefore essential to help the patient and family select a treatment option. Finally, the lesson that Graves' disease is a serious illness with unavoidable risks of therapy should not be lost.

Summary

1) Radioiodine is a convenient and effective therapy for childhood Graves' disease.

2) The efficacy of iodine-131 therapy is dose related. After administered activity of 150–200 μCi/g tissue, long term cure rates of hyperthyroidism are 90% or greater. In 85–90% of patients, a single dose of iodine-131 is sufficient to cure hyperthyroidism.

3) Patients with Graves' disease are at higher risk for developing thyroid cancer than the normal population. Thy-

roid cancer risk may be higher in patients treated with antithyroid drugs than in those treated with radioiodine or surgery. This may reflect the presence of more residual thyroid tissue after drug therapy than after iodine-131 treatment or thyroidectomy.

4) The risk of thyroid cancer in children treated with iodine-131 is unknown. Given the considerable increase in the risk of thyroid cancer in young children exposed to external radiation, we hypothesize that there may be a small increase in the risk of thyroid cancer in young children treated with radioactive iodine. This theoretical risk is probably highest in those children treated with radioactive iodine before the age of 5 yr and progressively lower in those treated at 5–10 and 10–20 yr.

5) Children should receive higher doses of iodine-131 (150–200 μCi/g; 5.5–7.4 MBq/g; 12,000–16,000 cGy/g) to minimize residual thyroid tissue and decrease tumor risk. After radioiodine therapy, levo-T_4 therapy should be used to treat hypothyroidism and prevent elevations of serum TSH.

6) There is no evidence of an increased rate of birth defects in offspring of patients treated with radioiodine or exposed to comparable levels of external gonadal radiation.

7) Thioamide therapy of childhood Graves' disease is typically associated with long term remission rates less than 30–40% after prolonged therapy and a 20–30% incidence of adverse side-effects, a small fraction of which may be serious or fatal. Favorable long term responses to drug therapy are seen in those patients with low levels of circulating TSAbs and remission after short term therapy.

8) The preferred form of surgical therapy is total thyroidectomy by an experienced thyroid surgeon. Total thyroidectomy in childhood is associated with 90% cure rates, a 1–5% incidence of adverse side-effects, and a mortality rate approximating 0.08%. For patients with very large thyroid glands (>80 g), cure rates may be higher after thyroidectomy than after drug or radioiodine therapy.

9) Careful follow-up is needed for all patients treated for Graves' disease and should include regular examination of the thyroid gland once a year. All newly appearing thyroid nodules should be biopsied or excised. Thyroid cancer developing after radiation exposure is most commonly papillary carcinoma, which is readily detected on exam and has an excellent prognosis.

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