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CONTROVERSY IN CLINICAL ENDOCRINOLOGY

The Optimal Treatment for Pediatric Graves' Disease Is Surgery

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THE TREATMENT OF pediatric Graves' disease remains one of the great controversies in pediatric endocrinology. Whereas most patients undergo a trial of antithyroid drug therapy, there is a high failure rate with this treatment and alternative therapies become important (1). The debate between radioactive iodine (RAI) ablation *vs.* surgery as definitive management of pediatric Graves' disease is centered on the potential adverse consequences of RAI *vs.* the complications of thyroidectomy. Without long-term, prospective, randomized-control trials, practitioners are left to base treatment decisions on individual expertise. Our practice has been to recommend surgery in children and young adults, and not RAI, for a number of reasons.

Much of the controversy surrounding RAI therapy for pediatric Graves' disease concerns its potential teratogenic effects, especially on the thyroid. We know from the literature that thyroid cancers after radiation exposure usually present after several decades, with a third of cancers presenting after more than 20 yr (2, 3). Furthermore, from the aftermath of Chernobyl, Hiroshima, and Nagasaki, we know that children (especially those younger than 5 yr at the time of exposure) are at increased risk for developing thyroid cancer after radiation exposure (4–7). These cancers may present as early as 4 yr after exposure or up to many decades later. Given these considerations, even ardent supporters of RAI in children suggest that it should be avoided in those younger than 5 yr old (8). Although a few studies suggest that there is no increased risk of thyroid cancer with RAI for pediatric Graves' disease, until recently there had been no studies looking at long term follow-up (9–11).

As such, Read *et al.* (12) undertook the daunting task of collecting 26- to 36-yr follow-up data for children who received RAI for Graves' disease. Their data confirmed a number of findings. First, they documented that remission of hyperthyroidism is directly correlated with dose of RAI and that the risk of genetic defects in offspring was not increased. Whereas their efforts represent a tour de force in the era of Health Insurance Portability and Accountability Act (HIPAA), their data did not settle the crucial question of long-term malignancy risk to the thyroid with modern RAI regimens because most of their patients received low-dose RAI, and only a small percentage of these patients received high-dose RAI equivalent to that used in today's treatments. Indeed, the bulk of these data is moot because few physicians today treat patients with low-dose RAI. Whereas one expects that higher ablative doses would decrease the chance of malignancy, there are reported cases of thyroid malignancy, even after high-dose RAI therapy (3). Worse, these malignancies tend to be more aggressive (3, 13). Without long-term follow-up in patients receiving high-dose RAI, we cannot know its true carcinogenic effect on the thyroid.

In addition to concerns about potential thyroid malignancy, we do not know the full malignant potential for the rest of the body with higher doses of RAI. This notion of increased total body cancer risk with high-dose RAI is supported by a Swedish investigation that found a statistically significant increased risk of brain, kidney, and stomach cancers (with the latter increasing over time and with increased dose) in 10,000 patients who received RAI (14). Indeed, the authors conclude that "if anything, risks at low doses might be lower than predicted from high-dose therapy." Without long-term follow-up of a significant number of patients receiving high-dose RAI, we cannot know its full malignant potential.

Another pitfall of RAI therapy is the potential for inducing hyperparathyroidism. From decades of experience, we know that both internal and external radiation exposure predispose one to developing primary hyperparathyroidism in a dose-related manner (15, 16). Gorman and Robertson (17) demonstrated that tissue immediately adjacent to hot thyroid nodules received carcinogenic doses of radiation in patients treated with RAI. This concept has been borne out in many studies that have found instances of hyperparathyroidism many years after RAI (18–20). Indeed, Esselstyn *et al.* (21) found an incidence of hyperparathyroidism after RAI that was "several times normal." Similarly, Triggs and Williams (16) reported that 10 of 159 patients developed hyperparathyroidism after RAI therapy for Graves' disease as children or adolescents, a rate that is higher than expected from the general population. In addition, Ito and colleagues (18, 20) found that patients treated with RAI were more likely to

Abbreviation: RAI, Radioactive iodine.

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develop hyperparathyroidism than those treated with antithyroid drugs. Clearly, close screening is required for patients undergoing RAI therapy to prevent the possible adverse effects of hyperparathyroidism. We are not aware of any increased risk of developing hyperparathyroidism after antithyroid drug therapy or thyroidectomy. In addition to the metabolic problems of hyperparathyroidism itself, these patients may require a subsequent cervical exploration. Although it has not been our experience, Waldhausen (22) warns that "subsequent surgery is more difficult because of tissue scarring and distortion" due to RAI-induced damage.

Finally, patients receiving RAI therapy have slightly higher mortality rates than those not receiving RAI. This small but statistically significant increase in cardiovascular and overall mortality when compared with the population at large has been documented in a number of studies (2, 13, 23, 24). In the study by Read *et al.* (12), two of the 116 original patients died soon after RAI therapy. Whereas one patient's lethal hepatic necrosis likely resulted from antithyroid medications, the second patient death 10 d after treatment seems directly related to RAI therapy. In contrast, the mortality rate after thyroidectomy is less than 0.1% and in some large series is 0% in patients with Graves' disease (16, 25, 26).

Unlike RAI therapy, the risks and outcomes for surgery have been known since Kocher's first successful series of thyroidectomies in 1883 (27). In the hands of experienced surgeons, thyroidectomy yields cure rates in excess of 97% with low complication rates equivalent to that of high-dose RAI (1, 8, 11, 28). Multiple series report surgical complication rates of less than 1–2% (29). Furthermore, research has demonstrated the intuitive concept that surgeons who perform higher volumes of thyroidectomy have better outcomes (30). Clearly, patients should be referred to a surgeon with extensive experience with pediatric thyroidectomy, even if this means traveling outside the local area. The choice of operation depends primarily on the desired end point. If control of hyperthyroidism is the most important factor, most surgeons recommend total or near-total thyroidectomy because complication rates are comparable with subtotal resection, there is less chance of worsening ophthalmopathy (although few children have significant eye disease to begin with), less tissue left at risk for undergoing malignant transformation, and a lower recurrence rate than with subtotal resection (22). Unfortunately, partially due to the variability in judging remnant size, recurrence can occur in 1.2–16.2% of patients undergoing subtotal thyroidectomy (31). However, if achieving euthyroidism is paramount, then we recommend leaving a thyroid remnant of 2–4 g because children are more prone to recurrence than adults (32). For patients with recurrent hyperthyroidism, we typically recommend RAI ablation because of the increased risk of complications associated with a second operation.

Clear indications for thyroidectomy include patient preference, noncompliance with medical or RAI regimens, suspicious nodules or known cancer, pregnancy, large glands (>80 g), inadequate uptake on RAI scan, requirement for immediate control of disease, obstructive or compressive symptoms, necessity for euthyroidism as an end point, and age younger than 5 yr. Although the remission rates are similar for high-dose RAI and surgery with virtually all patients requiring thyroid hormone supplementation, the small but increased risk of death, nonthyroid neoplasms, hyperparathyroidism, and potential increase in thyroid malignancy make surgery a more appealing option than high-dose RAI, especially in children. Clearly, this issue calls for a large randomized-control study with long-term follow-up to settle this issue definitively. In the interim, surgical management by an experienced surgeon appears to be the safest, most effective treatment for children with Graves' disease.

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