Radioiodine Treatment for Nontoxic Multinodular Goiter*

Alan H. Maurer and N. David Charkes

Department of Diagnostic Imaging, Division of Nuclear Medicine, Temple University School of Medicine, Philadelphia, Pennsylvania

Although surgery has traditionally been considered the primary treatment for large nontoxic multinodular goiter (NTMNG), several studies and recent reviews have renewed interest in the use of radioiodine for treatment of NTMNG by showing that radioiodine can be used safely and effectively for treating this disorder (1,2). NTMNG can be defined as nodular thyroid gland enlargement without hyperthyroidism. Goiter usually refers to any enlargement of the thyroid gland, whereas endemic goiter is the occurrence of goiter in more than 10% of the population in a defined geographic area (3). Areas with adequate dietary iodine show a low incidence of MNG. For example, in Framingham, MA, the prevalence of MNG has been reported as 4% (4). The most common cause of goiter in iodine-replete developed countries is autoimmune Hashimoto's thyroiditis.

Interest in the treatment of NTMNG with radioiodine remains high because of the prevalence of NTMNG in many areas of the world. Around the world, iodine deficiency is the most common cause of NTMNG. In 1995, the World Health Organization estimated that the total number of people with goiter was 750 million (5).

Because goiter can be prevented by iodination of salt or the addition of iodine to the drinking water, many nations have undertaken programs to supplement dietary iodine. These efforts however have met with varied success.

In the Swiss Alps, the incidence of large goiter in school children was 53% in 1884 (before prophylaxis), 17% in 1938 (salt with 3.75 ppm iodide) and 0.5% in 1988 (salt with 15 ppm iodide) (6).

The sale of iodized salt is voluntary in most European countries and prohibited in one, Denmark. A Danish study recently found that dietary iodine intake remains low, with an occurrence of NTMNG between 9% and 13% (7). In

addition, although iodized salt is required in some countries, public concern over food additives has led to difficulty in imposing mandatory programs. For example, in The Netherlands two bakers won a court challenge to the compulsory addition of iodine to bread (8).

There is also little control in regulating the amount of KI contained in table salt (9). In one study of domestic manufacturers in Yugoslavia, 70% of salt samples had an iodine content lower than the prescribed 10 mg KI/kg salt (9).

Low dietary iodine may not always account for the presence of endemic NTMNG. Other goitrogenic factors exist and nodular goiter may arise from either intrinsic intrathyroidal growth stimulants or from external goitrogens (10–12).

Patients with NTMNG are usually euthyroid, but they may be hypothyroid or hyperthyroid with autonomous nodules. In one long-term study of patients with untreated NTMNG, 36 patients were followed up for a mean period of 13 y (13). Of these patients, 19 had iodine deficiency and 17 had normal plasma inorganic iodine. In general, the iodine deficient patients had more complications. Twenty-six percent became either hyperthyroid, hypothyroid or required partial thyroidectomy (13). Symptoms of airway, esophageal or superior vena cava obstruction with large NTMNG usually require some therapeutic intervention.

CURRENT TREATMENT OPTIONS

Thyroid Hormone Suppression

Early studies with desiccated thyroid showed success in decreasing the size of NTMNG. Patients with NTMNG caused by Hashimoto's thyroiditis treated for 2 y with thyroxine have also demonstrated a significant decrease in the size of the gland (from 50.4 ± 6.8 mL [mean $\pm$ SEM] to 34.1 ± 5.7 mL [32%]; $P < 0.001$) (14). Liothyronine and thyroxine alone, and with antithyroid drugs, have been shown to reduce the size of NTMNG (15–18). However, if successful, patients must be maintained on suppressive doses indefinitely, because discontinuation of therapy results in regrowth of the goiter to pretreatment levels in as little as 3 mo (19,20).

More recent studies have shown that the value of thyroid hormone suppression to decrease and control the size of NTMNG has become controversial. One double-blind study

showed that levothyroxine was not effective in decreasing goiter size (21). In another study, 6 of 11 patients treated with thyroxine did not have an adequate response and underwent ^{131}I therapy because they refused surgery (22). Levothyroxine has not been shown to be effective in shrinking postsurgical goiters (21) or in preventing recurrence of NTMNG (20,23–28).

Particular care must be taken in initiating a trial of thyroid hormone in the elderly or in patients with cardiac disease, because autonomous tissue will continue to secrete thyroid hormone even when thyroid-stimulating hormone (TSH) is suppressed, precipitating symptoms of thyrotoxicosis.

Surgery

Surgical excision of NTMNG has been considered standard therapy, because it results in rapid decompression in patients with symptoms of mechanical obstruction. Fear of cancer is another possible indication for surgical treatment of NTMNG. In societies in which patients are aware of the potential for malignancy, any lump or growth results in high anxiety (29). Fine-needle aspiration cytology is an accurate diagnostic procedure for evaluating solitary nodules, but its effectiveness is reduced in multinodular glands. In a recent series, fine-needle aspiration identified only 30% of cancers in 256 patients who were found to have thyroid cancer by total thyroidectomy (30).

A review of the data on the incidence of papillary and follicular thyroid cancers from the Swedish Health Care Region registry on endemic goiter found an association between the duration of residence in endemic areas and the prevalence of follicular cancers for individuals aged 21–40 y (31). There was also an increased frequency of cancer in individuals older than 50 y. Low iodine exposure during adolescence was associated with an increased risk of papillary cancer, especially in women. Such data support an association of iodine deficiency with the two most common forms of thyroid cancer.

An Italian study analyzed the frequency of thyroid carcinoma in a series of 539 consecutive thyroidectomies for NTMNG in 539 patients (455 females, 84 males; age range 17–78 y, mean age 46 y) (28). The frequency was 7.6% overall, 8.3% in females and 3.6% in males. Another study from Japan showed an even higher incidence (31%) of thyroid cancer in patients with MNG (30). In that series 54% of the surgically confirmed tumors were occult (<10 mm in size).

For some patients, cosmetic appearance may also be an indication for surgery (32).

The recurrence rate of goiter after surgery for NTMNG has been reported to be 10%–20% in 10 y (24,33) and up to 45% after 30 y (34). When reoperation for NTMNG is required, the complication rates are higher than at the time of initial surgery (35). Of 1318 patients who underwent surgery for NTMNG between 1983 and 1994 in Switzerland, there was a 13% reoperation rate (36). The rate of permanent recurrent laryngeal nerve palsy after primary surgery was 1.7% (1983–1990) and 0.7% (1991–1994). This increased to

3.5% (1983–1990) and 5.6% (1991–1994) with reoperation (36). From that study, the authors concluded that more extensive resection is needed at initial surgery to reduce the recurrence rate and the high frequency of nerve injury associated with reoperation.

Newer surgical techniques, including capsular dissection, may significantly lower complication rates for laryngeal nerve palsy (0.5%) and permanent hypoparathyroidism (0.6%) (37).

Radioiodine

Huysmans et al. (2) summarized the findings from early studies of ^{131}I for the treatment of NTMNG. These studies appeared in the German literature between 1964 and 1989 and reported response rates of 65%–99% (38–40). The results could be called into question, however, because these studies used only simple circumference measurements of neck size or thyroid volume measurements based on palpation and planar scintigraphy.

Efficacy of radioiodine therapy of nodular goiter reflects the distribution of ^{131}I within the thyroid gland, because the radiative energy deposited is almost all (90%) from β particles and is absorbed within 2 mm from the source. Functioning, or "warm," areas shrink and "cold" areas do not. Radiation doses deposited within functioning nodules, as much as seven times the dose to the gland, have been calculated (41). Averaging the deposited radioiodine over the entire gland without knowledge of its distribution makes no sense dosimetrically and is discouraged.

Dosimetry requires an estimate of the volume of the functioning tissue within the gland, the radioiodine uptake and the effective half-life (42). Because the volume of concern is the functional volume and not the overall volume, only radioiodine (or pertechnetate) scans are acceptable for this purpose. Because most scintigraphic images are two dimensional, some mathematical method is required to convert the planar image to three dimensional. Early investigators found a strong correlation between thyroidal area and weight in small- and medium-sized goiters (~160 g or less) using rectilinear imaging with ^{131}I that was less in larger goiters (43–45); results with planar pertechnetate imaging are similar (46,47). Scintigraphy tends to underestimate width (46), an error that can be minimized by using the formula for a prolate ellipsoid and assuming depth equal to width (48) (depth is actually about 35%–40% greater [41]). Including lateral views and 1–2 mm pinhole collimation increases accuracy, yielding an average volumetric error approximately 5% of the volume (41). With very large goiters, there is a loss of accuracy when outlining deep nodules.

A comparison of MRI and scintigraphy for estimating size in large goiters showed that MRI had high precision and that scintigraphic volume estimates were less reproducible and correlated poorly with MRI (r = 0.67) (49). The problem of determining accurate volumes of functioning tissue could be circumvented by measuring the thyroid size with ^{123}I SPECT or [124]I PET (50–52).

An initial concern in using ^{131}I therapy for NTMNG was the fear of acute swelling of the gland, resulting in respiratory compromise. Nygaard et al. (53) showed that there was no significant acute increase in size of either toxic or nontoxic goiters with [131]I. In patients with NTMNG, the maximum increase in the median diameter of the gland occurred on day 7 and was only 4% compared with baseline. Toxic MNG showed a maximum increase of 2%. No symptoms of tracheal compression developed in any of the patients (53).

Studies using either sonography, CT or MRI to measure thyroid size show a reliable decrease in the size of NTMNG, when a dose of radioiodine is given to deliver a concentration of 3.7 MBq (100 μCi)/g of tissue. When studied 1–2 y after treatment, the percentage reduction in the size of the gland for seven studies ranged from 34% to 62% (mean 46%) (2,54–59). In none of these studies were any significant acute complications reported. Mean thyroid volume reduction has been reported to be as high as 60% after 3–5 y (2).

A fractionated dose treatment strategy has also been used with a low dose of 1.85 MBq (50μCi)/g for up to three or more doses. Permanent hypothyroidism did not develop in any of the patients. All patients had complete disappearance of the goiter or a marked reduction in size. Successful gland size reduction was achieved in 48% of patients with one dose, 35% after two doses and the remaining 17% required three or more doses. Total mean activity administered was 292 MBq (7.9 μCi) for small goiters, 507 MBq (14.6 μCi) for moderate size and 1136 MBq (30.7 μCi) for large goiters (38).

Long-term complications of ^{131}I therapy for NTMNG include hypothyroidism, the development of autoimmune hyperthyroidism and the potential risk for induction of thyroidal and extrathyroidal cancers.

It is difficult to determine an exact incidence of ^{131}I-induced hypothyroidism given the various treatment regimens that have been used. Kay et al. (60) reported only a 7% incidence of hypothyroidism after up to 13 y in patients treated with large deposited doses of 740–1480 MBq (200–400 μCi)/g. In another study, after 8 y of follow-up, hypothyroidism had developed in all 15 patients (59). With a dose of 3.7 MBq (100 μCi)/g, the incidence of post-therapy hypothyroidism has ranged from 10% to 30% between 2 and 5 y (2,22,54,58,61). When a larger dose of ^{131}I is used, the average decrease in size is similar to a low dose and no acute side effects occur.

In studies in which serial TSH measurements have been obtained, there appears to be a progressive increase in TSH over time, such that hypothyroidism is likely to occur even at a low dose (3.7 MBq [100 μCi/g]) (61). Subtle decreases in TSH using a sensitive third-generation TSH assay (subclinical hyperthyroidism) were shown in a minority of patients (2 of 18 patients) as early as 3 wk after radioactive iodine treatment, whereas 12 of 18 patients had values between euthyroid and hyperthyroidism after a dose of 5.55

MBq (150μCi)/g) (62). The free T4 and free T3 values were insensitive for detecting changes in thyroid status, but TSH measurements progressively increased up to 24 mo after therapy.

Radiation-induced release of thyroid antigens has been reported as a possible cause of autoimmune hyperthyroidism after ^{131}I treatment of NTMNG. Huymans et al. (63) reported late development of hyperthyroidism as a complication of ^{131}I therapy in 3 of 80 patients with initial doses ranging from 740 to 3182 MBq (20–86 mCi). TSH receptor antibodies were all undetectable before treatment and became elevated during thyrotoxicosis (63). Nygaard et al. (61), using a dose of 3.7 MBq (100 μCi)/g, showed no elevation of TSH receptor antibodies in 10 patients monitored up to 18 mo after treatment.

Huysmans et al. (64) concluded that the risk of induction of thyroid cancer for patients treated with ^{131}I for large NTMNG is not higher than that after therapy for small goiters, because the absorbed dose in the thyroid is similar. The absorbed doses in extrathyroidal tissues, however, depend on the total dose administered, and there is an estimated 1.6% lifetime risk of fatal and nonfatal cancer. For people older than age 65, the estimated risk is reduced to 0.5%, which is comparable with the surgical mortality of subtotal thyroidectomy (2).

CONCLUSION

[131]I therapy for NTMNG appears to be an acceptable therapy for large NTMNG, especially for older patients who are at high operative risk, have had previous thyroidectomy with goiter recurrence or refuse surgery. With the recent changes in the release criteria for patients who receive radioactive materials, hospitalization may no longer be necessary for patients who receive large doses of Na[131]I. This makes this form of therapy a more cost-effective choice for patients with large NTMNG.

Risks of acute thyroiditis and swelling are rare, and late complications of either hypo- or hyperthyroidism are easily managed. Patients with large predominantly retrosternal goiter or superior vena cava obstruction may need careful observation. In addition, elderly patients should be observed for transient hyperthyroidism.

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