Simple clinical and laboratory features predict successful outcome of ^{131}I treatment of hyperthyroidism

Boelaert K, Syed AA, Manji N, Sheppard MC, Holder RL, Gough SC, Franklyn JA. Prediction of cure and risk of hypothyroidism in patients receiving ^{131}I for hyperthyroidism. Clin Endocrinol (Oxf) 2009;70:129-39.

SUMMARY

BACKGROUND There is no consensus concerning the most suitable amount of ^{131}I that should be administered to patients with hyperthyroidism. The aim of this study was to define the most effective fixed amount of ^{131}I that should be administered to patients with hyperthyroidism and to define the clinical and biochemical factors that predict outcome in individual patients.

METHODS This is a large retrospective study of patients with hyperthyroidism treated with a fixed amount of ^{131}I at Queen Elizabeth Hospital (University Hospital Birmingham England) from January 1984 through April 2006. The two outcomes assessed were the probability of curing hyperthyroidism and the risk of developing hypothyroidism following a single ^{131}I treatment. Patients were stratified into three diagnostic categories: (1) Graves' disease, (2) toxic nodular hyperthyroidism (TNH), and (3) indeterminate etiology (IDE). Graves' disease was defined as the presence of an elevated serum free thyroxine (T_4) level, with or without an elevated serum triiodothyronine (T_3), and an undetectable serum thyrotropin (TSH) level together with two of the following three conditions: Graves' ophthalmopathy, a palpably diffuse goiter, or elevated serum thyroid peroxidase antibodies (anti-TPOAb) with or without thyroglobulin antibodies. TNH was defined by a palpable nodular goiter, and patients who did not fulfill the criteria for Graves' disease or TNH were defined as having IDE, which comprised a mixture of Graves' disease and TNH. Goiter was assessed by neck palpation and classified as follows: none (normal size gland or impalpable) and medium (palpable) or large (visible) goiter. Graves' ophthalmopathy was defined according to the NOSPECS acronym (no signs or symptoms, only signs of lid retraction and stare, soft-tissue involvement, proptosis of 3 mm or greater, extraocular muscle involvement, corneal involvement and vision loss, and secondary optic-nerve disease). The following factors were defined at the time of diagnosis: Graves' ophthalmopathy; the presence, size, and type of goiter; anti-TPOAb titer, and serum free T_4 and TSH concentrations, which were available for analysis in 1165 patients. The protocol for selecting patients for ^{131}I therapy was unchanged for the duration of the study; however, in 1995 the ^{131}I dosage was increased from 5 to 10 mCi (185 to 370 MBq) until 2000, when it was increased again to 16 mCi (600 MBq) because a local audit demonstrated unacceptably low cure rates with 5 and 10 mCi of ^{131}I. If antithyroid drugs (ATDs) had been administered, they were withdrawn a week before ^{131}I therapy and were not restarted for a minimum of 1 week thereafter.

RESULTS The study group comprised 1278 patients, 543 (43%) with Graves' disease, 233 (18%) with TNH, and 502 (39%) with IDE. A total of 428 patients (79%) were female and 115 (21%) male. The mean(±SEM) patient age was 49.7±0.6 years, which was significantly higher in those with TNH (62.5±0.9) and IDE (51.5±0.8) as compared with Graves' disease (42.7±0.6) (P<0.0001). There were significantly more males in the Graves' disease group (21%) as compared with those with TNH (11.2%) (P<0.001).

The 485 patients treated with a single 16-mCi dose of ^{131}I had a greater cure rate (84%) as compared with those treated with either 5 mCi(63%) or 10 mCi (75%) (P<0.001) (Figure 1). Within

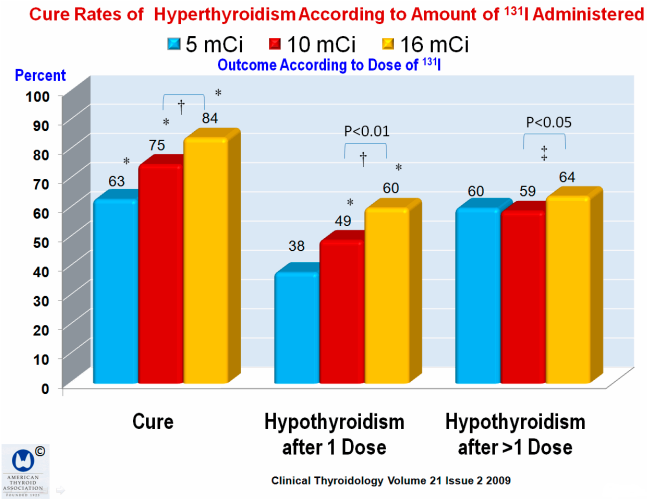

Figure 1. The prevalence and cure of hypothyroidism 1 year after a single fixed dose of ^{131}I. *P<0.001, comparing 5 vs. 10 mCi, and 5 vs. 16 mCi. †P<0.01, comparing 10 vs. 16 mCi. ‡P<0.05, comparing 10 and 16 mCi. Adapted from Figure 1 from Boelaert et al. Here and elsewhere percentages are rounded to a single integer.

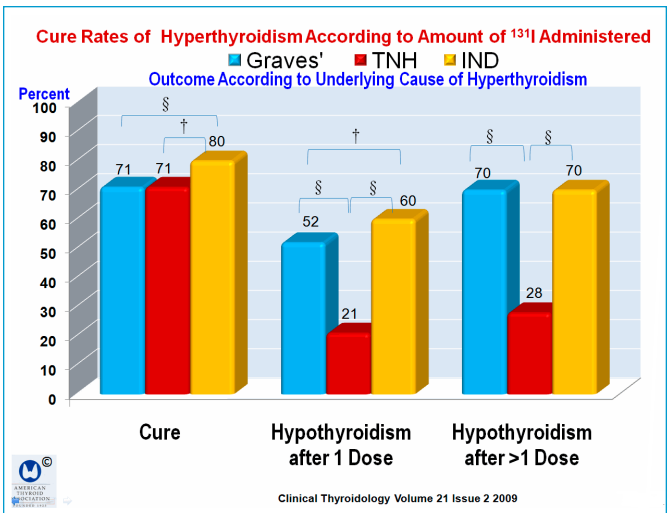

Figure 2. Outcome according to the underlying cause of hyperthyroidism. TNH is nodular hyperthyroidism, and IND is indeterminate cause of hyperthyroidism (features of both Graves' disease and nodular goiter). §P<0.0001. †P<0.01. Brackets show the comparisons that are statistically significant. Adapted from Figure 1 from Boelaert et al.

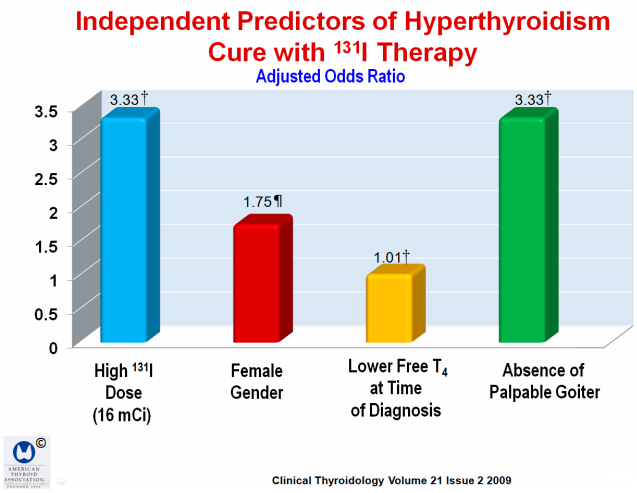

Figure 3. Independent predictors of hyperthyroidism cure according to binary logistic-regression analysis. Results are shown as adjusted odds ratios. †P<0.01. ¶P = 0.002.

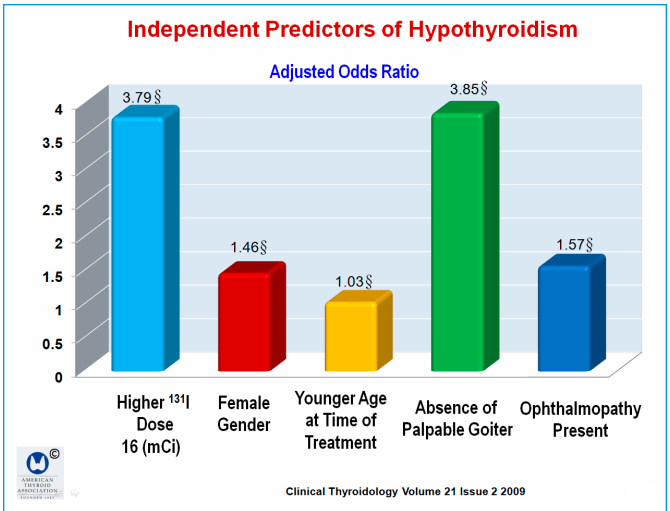

Figure 4. Independent predictors of hypothyroidism 1 year after initial therapy according to binary logistic-regression analysis. Results are adjusted odds ratios. §P<0.0001. ¶P = 0.002.

1 year, the incidence of hypothyroidism was significantly higher (60.4%) in patients treated with larger doses of ^{131}I (16 mCi) as compared with 38% of the patients treated with 5 mCi and 49.2% treated with 10 mCi (P = 0.001) (Figure 1).

The cure rates of hyperthyroidism were 71.3% in patients with Graves' disease and 71.2% in patients with TNH (P = not significant). However, 1 year after therapy there were significantly lower rates of hypothyroidism in patients with TNH (21%) as compared with Graves' disease (51.8%) (P<0.01) (Figure 2).

The use of ATDs 2 weeks before or after ^{131}I treatment (n = 845) was not associated with an increased risk for treatment failure, but was significantly associated with an increased risk for hypothyroidism, (adjusted odds ratio [AOR], 1.46; range, 1.16 to 1.85; P = 0.001), which was still present after correcting for the amount of ^{131}I administered or the underlying cause of hyperthyroidism.

Binary logistic-regression analysis found the following to be independent predictors of cure: a 16-mCi dose of ^{131}I (AOR, 3.33; range, 2.28 to 4.85; P<0.001); female gender (AOR, 1.75; range, 1.23 to 2.47; P = 0.002); lower serum free T_4 concentration at the time of diagnosis (AOR, 1.01; range, 1.01 to 1.02; P<0.001); and absence of a palpable goiter (AOR, 3.33; range, 2.00 to 5.56; P<0.001) (Figure 3). The independent predictors that identified hypothyroidism 1 year after therapy were as follows: 16 mCi of ^{131}I (AOR, 3.79; range, 2.66 to 5.38; P<0.001); female gender (AOR, 1.46; range, 1.05 to 2.02; P = 0.02); younger age (AOR, 1.03; range, 1.01 to 1.04; P<0.0001); absence of a palpable goiter (AOR, 3.85; range, 2.38 to 5.88; P<0.001); and presence of ophthalmopathy (AOR, 1.57; range, 1.06 to 2.31; P = 0.02) (Figure 4).

Based on the results from the binary logistic-regression analysis, the authors derived a formula to predict the probability of cure, which is summarized in Tables 2, 3 and 4 in the article, which they use in practice using a mathematical model available at http://medweb4.bham.ac.uk/websites/boelaert/index.asp.

CONCLUSION Successful treatment of hyperthyroidism with one dose of ^{131}I can be predicted by the administration of larger amounts of ^{131}I, and by female gender, younger age, low disease severity, and small goiter size. Independent predictors of ^{131}I-induced hypothyroidism are female gender, absence of palpable goiter, and larger amounts of ^{131}I.

COMMENTARY

Radioactive iodine (^{131}I) was first introduced as a novel treatment of hyperthyroidism in 1941 (1) and over the ensuing six decades became the preferred initial therapy in North America for patients with Graves' hyperthyroidism (2,3). Despite wide regional variations in its early use, ^{131}I has become first-line therapy for hyperthyroidism in many regions around the world (4-6). Yet its use continues to spark debate on a number of levels, including the amount of ^{131}I that is optimal for therapy(7) and the best technique to administer the treatment(4,7,8). In addition, there is concern about the efficacy of a single therapeutic dose of ^{131}I and the possibility of inducing hypothyroidism, thus precipitating the lifelong need for levothyroxine-replacement therapy. This is of special concern when larger amounts of ^{131}I are administered. The converse concern is persistent hyperthyroidism that may occur when smaller amounts of ^{131}I are administered. Indeed, it is highly unlikely that this dosage conundrum can be solved. There also is ongoing debate about administering ATDs shortly before or after ^{131}I has been administered.

A number of studies have shown that fixed doses of ^{131}I are as good as more elaborately calculated doses (9), which are clearly less cost-effective and more cumbersome for the patient than is the use of predetermined standard doses (5,7-9). In fact, most physicians prefer to give fixed doses of 5 to 15 mCi; yet doing this leaves little chance of accurately predicting the success rate or the probability

of inducing lifelong hypothyroidism (5). For example, the cumulative incidence of hypothyroidism may be as high as nearly 56% at 1 year and 86% at 10 years after initial ^{131}I therapy (10); the same study found that independent risk factors predicting hypothyroidism were the presence of thyroid autoantibodies, no ATD therapy prior to ^{131}I, and a high dose of ^{131}I.

The use of ATDs around the time that ^{131}I is administered seems to interfere with the effects of ^{131}I, although there is disagreement about the importance of this effect. A meta-analysis of 14 randomized, controlled trials with a total of 1306 participants found that ATD therapy was associated with an increased risk for ^{131}I treatment failure (relative risk, 1.28; P = 0.006) and a reduced risk of hypothyroidism (12). The study found no difference in summary estimates for different ATDs or for whether they were given before or after ^{131}I treatment.

Boelaert et al. address all of these issues. The main strengths of this study are the large number of patients and the completeness of follow-up. The study has a few limitations, namely that goiter size was determined by palpation and that routine ultrasound evaluation was not performed. It also is not clear why patients treated with ATDs 2 weeks before and after ^{131}I therapy did not have an adverse effect on therapeutic outcome, which is contrary to prospective randomized studies (11).

Boelaert et al. found that the independent factors predicting the highest cure rates were a single 16-mCi dose of ^{131}I, female gender, less severe hyperthyroidism, and an absence of palpable goiter. Conversely, the independent factors predicting the highest rates of hypothyroidism were a single 16-mCi dose of ^{131}I, female gender, younger age, an absence of a palpable goiter, and the presence of ophthalmopathy. The highest cure rates were in patients with IDE, comprising patients with both Graves' disease and TNH. Nearly half (49.8%) of this group had impalpable goiters.

In summary, a small number of simple clinical and biochemical factors can be used to identify patients who should receive doses of ^{131}I that are more likely to increase the chance of cure while identifying others at high risk for hypothyroidism. The authors developed a model to help identify patients who are likely to achieve a cure and those who are at risk for hypothyroidism. The model is on a website that provides an estimate of risk that may be useful to practitioners. However, the authors provide the caveat that the validity of the model must be evaluated in different patient populations, especially those living in environments affecting iodine intake. Nonetheless, this website model might facilitate thoughtful discussion for patients undergoing counseling concerning the pros and cons of ^{131}I therapy for hyperthyroidism.

In my view, this is an article that should be read by all who are administering ^{131}I to patients with hyperthyroidism.

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