Importance of radioiodine dosage in the treatment of patients with toxic nodular and toxic multinodular goiter

Toksik nodüler ve toksik multinodüler guatr hastalarının tedavisinde radyoaktif iyot dozunun önemi

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Özet

Amaç: Toksik multinodüler guatr (TMNG) ve toksik nodüler guatr (TNG) hastalarında verilen radyoaktif iyot (RAI) tedavisinin dozla ilgili etkinliğini ve yan etkilerini değerlendirmek

Gereç ve Yöntem: Çalışmamıza 2003-2006 yılları arasında hastanemizdeki klinik muayene ve laboratuvar testleri sonucu TMNG ve TNG tanısı almış 57 hasta dahil edildi. Hastalara tiroid fonksiyon testleri (TFT), tam kan sayımı, biyokimya testleri, tiroid ultrasonografi (TUSG), tiroid sintigrafisi ve 4/24 saatlik RAI tedavisi gören hastalarda radyoaktif iyot *uptake* testleri uygulanarak tanı konuldu. RAI tedavisi gören hastalarda TUSG ve TFT radyoaktif iyot tedavisi öncesi ve tedaviden 12 ay sonra tekrar değerlendirildi. RAI tedavi öncesi ve sonrası tiroid loblarının ve nodüllerin volümleri değerlendirildi.

Bulgular: TMNG ve TNG hastalarına uygulanan ortalama RAI tedavi dozu 15.6 mCi idi. Tedavinin 12. ayında hastaların %52.6'sında (30/57) ötiroidizm ve %26.4'ünde (15/57) hipotiroidizm gelişirken sadece %21'inin (12/57) tirotoksik kaldığı izlendi. Hem tiroid loblarında hem de nodüllerin volümlerinde başlangıç boyutlarına göre istatistiksel olarak belirgin azalma vardı ($p<0.001$). RAI tedavi dozu ile tiroid loblarının ve nodüllerin volümündeki azalmada anlamlı bir fark yoktu. On iki aylık takip sırasında hipotiroidi dışında hiçbir yan etki rapor edilmedi.

Sonuç: RAI tedavisi, TMNG ve TNG hastalarında başarılı bir şekilde hastaların semptomlarını kontrol etmiştir. RAI tedavisi, hem tiroid lobları üzerinde hem de nodüller üzerinde yararlı etkisini dozdan bağımsız olarak göstermektedir. Ortalama 15 mCi RAI tedavisi TMNG ve TNG hastalarının tedavisinde yeterlidir.

Anahtar sözcükler: toksik nodüler guatr, radyoaktif iyot tedavisi

Abstract

Aim: Our aim was to evaluate the dose-related effects and side effects of radioactive iodine (RAI) treatment on toxic multinodular goiter (TMNG) and toxic nodular goiter (TNG) patients.

Material and Methods: Our study includes 57 patients diagnosed with TNG and TMNG, as a result of clinical examination and labotatory tests, in our hospital between the years 2003-2006. Patients were diagnosed through complete blood count, biochemical tests, thyroid function tests (TFT), thyroid ultrasonography (TUSG), thyroid scintigraphy and 4/24 hours radioactive iodine uptake (RAIU) test. For the patients receiving RAI treatment, TFT and TUSG were repeated at 12th month controls. The volumes of thyroid lobes and nodules were compared by TUSG before and after treatment.

Results: Mean 15.6 mCi RAI treatment was given to patients with TMNG and TNG. After a 12-month treatment, euthyroidism developed in 30/57 (52.6%) and hypothyroidism in 15/57 (26.4%) of patients, but 12/57 (21%) of patients were still thyrotoxic. Decrease in thyroid lobe and nodule volumes was statistically significant ($p<0.001$). No significant difference was observed between RAI dosage and percentage decrease in the thyroid lobes and nodules. At the 12th month follow-up, no side effects, except hypothyroidism, were observed.

Conclusions: RAI treatment is successful in controlling the disease and symptoms in TMNG and TNG. Its beneficial effect on thyroid lobe and nodule volumes as well as side effect rate is independent of RAI dosage. Mean 15 mCi RAI treatment is sufficient for disease control in TMNG and TNG.

Keywords: toxic nodular goiter, radioactive iodine treatment

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Introduction

Toxic nodular goiter (TNG) and multinodular goiter (TMNG) are important thyroid disorders in many countries. As they are particularly thyroid disorders of elderly population, the diagnosis, follow-up and treatment require special consideration.[1] There are several studies on the effectiveness of radioactive iodine (RAI) treatment in such patients, which consider RAI a safer method compared to surgery, since surgical therapy can not be performed in elderly patients and sometimes surgical complications may have life-threatening results.[1,2]

However, there are still controversial results on the dosage of RAI given to TMNG and TNG patients. Treatment options in TNG and TMNG vary according to the nodule size, patient age, RAI uptake (RAIU) test as well as whether there are symptoms due to compression or not, or co-existence of other diseases, patient occupation and preference, pregnancy or lactation status.[3-5]

Various authors recommend that RAI treatment should be given in different forms and doses in TMNG and TNG. Therefore, we planned this study to evaluate the hormonal control and ultrasonographic alterations in relation to the RAI dosage in the nodule size of the patients with TMNG and TNG.

Material and Methods

Study groups and design

Our study assessed retrospectively a total of 57 patients who received RAI treatment in our hospital between the years of 2003-2006 following the assessment of clinical features and the results of laboratory tests. Initially, patients were examined by complete blood count, routine biochemical tests, thyroid funtion tests (TFT), thyroid ultrasonography (TUSG) and thyroid scintigraphy. In the pre-treatment RAIU test, measurements were performed at the 4th and the 24th h. Patients were assigned to 3 groups according to thyrotropin (TSH), free triiodothyronine (fT3) and free thyroxine (fT4) levels at the 12th month following the treatment. Patients with TSH levels lower than 0.35 μIU/ml were accepted as hyperthyroid. If TFT's results were normal, the patients were regarded as euthyroid, and if TSH was above 4.5 μIU/mL, hypotyroid.

Thyroid function tests

Thyroid function tests (fT3, fT4, TSH), were assayed on Abbott-Architect 2000 and by Chemiluminescence microparticle immunoassay method. Thyroid peroxidase antibody (TPOAb), anti-thyroglobulin antibodies were measured by Roche Elecsys 2010 (United States) device and electroluminescenes immunoassay (United States) (ECLIA) method. To exclude Graves' disease diagnosis, all thyroid autoantibody (Anti thyroidperoxidase, Anti thyroglobulin, TSH receptor antibody) positive patients were excluded.

The patients were separated into 3 groups according to TSH, fT3 and fT4 levels at the 12th month. If TSH, fT4 and fT3 levels of the patients were normal, they were considered as euthyroid, if TSH was supressed, the patient was considered toxic and if TSH was above normal limits, as hypothyroid.

Thyroid volumes

TUSG examinations of the patients were performed by the same endocrinologist before and after the 12- month RAI treatment at the Endocrinology Clinic of the Ankara Numune Education and Research Hospital, using the General Electric LOQIC 400 (Made in Japan, 2003) ultrasonography equipment and the 11 MHz linear probe. Intraobserver error rate was 4.8%. At TUSG, sizes of right and left thyroid lobes and size of the scintigraphic toxic nodule and if present, size of the second active nodule (A=length, B=width, C=height) were measured. Thyroid parenchymal tissue and nodules' features were examined. Thyroid lobes and nodules' volume were calculated by the formulation: Volume (mL) = AxBxCx π/6. (π =3.14).[6] Thyroid fine needle aspiration was performed on the active nodules larger than 2 cm and on nodules with suspected malignancy to exclude possible malignant cases. No malignancy was found in the biopsies. If a single active nodule was present at ultrasonography and scintigraphy, the case was classified as TNG and if more than one active nodule existed, as TMNG.

Radioactive iodine therapy

RAI treatment dosage given to the patients was calculated by nuclear medicine specialists according to the hormonal levels, thyroid gland size, thyroid scintigraphy and 4/24 hrs RAI uptake test results, and according to formulation ^{131}I dosage ={ [thyroid gland weight (g) x 100-180/1000 mCi/g] / 24. h RAIU (%)/100}. Informed consent of all patients was obtained before the RAI treatment.

Patients were injected 5 mCi (185 MBq) ^{99m}Tc pertecnetat intravenously and a glass of water was given to prevent esophageal involvement. After 20-40 minutes, a thyroid scintigraphy was performed with a gama camera with pinhole collimator (ADAC Provivo).

For RAIU test, patients were administered 50μCi ^{131}I in liquid form. Uptake measurements were taken at the 4th and the 24th hours. Normal uptake ranges were accepted as 12-20% for 4th hour and 20-30% for 24th hour. Seven days before the examination, antithyroid medica-

Table 1: Demographic variables of patients before RAI treatment

	N: 57
Male/Female	16/41
Age	58.8±14.6 (27-85)
Smoking (Yes/No)	10/47
Family thyroid disease history (Yes/No)	11/46
Antithyroid drug usage history (Yes/No)	30/27
TSH values before RAI treatment (uIU/mL)	0.32 ± 0.77
Free T3 (pg/mL)	4.66 ±4.28
Free T4 (ng/dL)	1.42 ± 0.91
4th hour RAIU (%)	18.7±13.4
24th hour RAIU (%)	30.2±13.76

Table 2: TFT values of the patients after 12 months of treatment

	Values after 12 months of treatment		
	Toxic (n:12)	Euthyroid (n:15)	Hypothyroid (n:30)
TSH (nIU/mL)	0.12±0.10	1.63±1.03	18.44±27.09
sT4 (ng/dL)	1.21±0.53	0.95±0.15	0.92±0.38
sT3 (pg/mL)	4.20±2.95	2.58±0.36	2.29±0.55

Normal Ranges: TSH: 0.35-4.94 uIU/mL, sT4: 0.70-1.48 ng/dL, sT3: 1.71-3.71 pg/mL

tions of the patients were withdrawn. Hormonal and laboratory assessments were done on the day before the RAI treatment.

Patients were asked to stay away from children and pregnant women for one week after receiving RAI. Following the treatment, the patients were called for regular visits and TFT was performed. At 12th month visits routine laboratory assessments, TFT and TUSG were repated. At USG, thyroid lobes and nodules' volumes were re-calculated.

Statistical Analysis

SPSS 11.5 package programme was used for data analysis. Descriptive analysis was given as mean±standart deviation for continuous variables and % for categorical variables. If the group number was two, between independent groups, significance of difference for means was evaluated with Student's t test or Mann Whitney U test and for independent group number more than two, with One Way Variance Analysis or Kruskal Wallis test. When statistical results of Kruskal Wallis test were significant, Kruskal Wallis multiple comparison test was used to determine the group causing the difference. The significance of difference between the pre-treatment and post-treatment measurements within groups was analysed with dependent-t test or Wilcoxon Sign test. For categorical comparisons, qui- square test was used. To determine the possible statistical linear relations between continuous variables Pearson correlation tests were used. Results $P<0.05$ were considered statistically significant.

Results

Fourty-one of the 57 patients included in the study were female and 16 were male with 58.79 ± 14.57 (27-85) years mean age. Fourty-seven (82.5%) of the patients never smoked. Thyroid gland mean volume was 21.5±16.1 ml for the right lobe, and 19±15.3 ml for the left lobe, with nodule-1 volume 6.8±10.9 ml and nodule-2 volume 4.69±6.1. Twenty-nine of the nodules were mixed, 15 isoechoic, 11 hypoechoic and 2 were cystic. Mean RAIU was 18.7%±13.4 (34-8%) at 4th h and 30,2%±13.76 (44-17%) at 24th h. Demographic parameters of the patients are shown in **table 1**.

The patients were re-evaluated with TFT and TUSG after a 12- month treatment and grouped into 3, according to their TFT results as toxic, euthyroid and hypothyroid (**Table 2** for TFT results). Thyroid autoantibodies were not evaluated at the end of study.

Assessment of RAI treatment dosage in the post-treatment groups showed 15.08±4.12 mCi in the toxic group, 16±4.16 mCi in the euthyroid group and 15.33±3.77 mCi in hypothyroid group ($P>0.05$).

There was no statistically significant relationship between the post-treatment clinical status and patient

Table 3: Comparison of thyroid lobe and nodule volumes before and 12 months after RAI treatment

	Pre-treatment volume (mL)	Post-treatment volume (mL)	Mean change (%)	P value
Right lobe	21.5 ± 16.1	13.2 ± 12.48	35.63%	<0.001
Left lobe	19 ± 15.3	12.3 ± 13.3	24.43%	<0.001
Nodule 1 (*)	6.8 ± 10.9	3.25 ± 5.29	25.52%	<0.001
Nodule 2 (**)	4.69 ± 6.18	3.49 ± 4.12	20.60%	<0.001

* The largest nodule in TMNG (dominant nodule) or single nodule suggesting toxic adenom

** Second largest nodule in TMNG

age, sex and smoking status (p: 0.19, 0.18 and 0.729, respectively).

Pre-treatment antithyroid medication usage was observed in 10/12 (83%) of the post-treatment toxic group, 13/30 (43%) of the euthyroid group and 7/15 (47%) of the hypothyroid group (p=0.055). Of the 30/57 patients who had antithyroid medication history, 29 had used PTU and only one, methimazole (**Table 3**, for a comparison of the pre-treatment and post treatment volumes of nodules and thyroid lobes).

The percent changes in the right thyroid (35.63%) and left thyroid (24.43%) were statistically similar in the male and female patients (p=0.831 and p=0.347, respectively). However, in nodule–1, a statistically more significant percent decrease was observed in the female patients than males (p=0.033). The percent changes of right lobe, left lobe and nodule–1 were similar in the smokers and non-smokers (p=0.413; p=1.000 and p=0.135, respectively). There was no statistically significant linear relationship between age and percent change in the right lobe (r=0.238 and P=0.074). There was a statistically positive linear relationship between age and percent change in the left lobe (r= 0.315 and p=0.017). There was no statistically significant linear relationship between age and percent change in nodule–1 (r=0.132 and p=0.405).

When nodule numbers were taken as sample unit, at the last follow-up compared to the baseline, 61 (88%) of the 69 nodules decreased in size, while 8 (12%) showed increase. On the whole, decrease in nodule size was statistically significant (p<0.001). Statistically significant percent decrease in nodule size was observed more in women than men (P=0.008).

When nodule numbers were taken as sample unit in the toxic, euthyroid and hypothyroid groups, there was also a statistically significant decrease in nodule size at the 12th month compared to the baseline respectively (p=0.017, p<0.001, p<0.002). However, percent change of nodule size at the 12th month of treatment versus baseline was statistically similar in all groups (p=0.698).

When nodule number was taken as a sample unit for all three groups, percent changes in nodule size in each group had no statistically significant linear relationship with age, 4th h uptake, 24th h uptake or treatment dosage (P>0.05).

Patients were also grouped into three groups retrospectively, as 10 mCi, 15 mCi and 20 mCi according to RAI treatment doses calculated by variable scale method. Six (55%) of the 11 patients who received RAI treatment of 10 mCi dose were found to be euthyroid, 3 (27%) were hypothyroid and 2 (18%) were toxic after a 12-month treatment. However, in the group receiving 15 mCi, 12 months after the treatment, 13 (46%) of the 28 patients were euthyroid, 8 (29%) hypothyroid and 7 (25%) toxic. In the group receiving 20 mCi, 11 (61%) of the 18 patients were euthyroid, 4 (22%) hypothyroid and 3 (17%) toxic at the end of the treatment. There was no significant relation between radioactive iodine dosage and the groups that the cases belonged to at the end of the treatment (p=0.902) **(Figure 1)**.

When RAI treatment dosage and change in thyroid lobe volumes were evaluated there was a decrease of 7% in the 10 mCi receiving group, 35% decrease in the 15 mCi group and 36% decrease in the 20 mCi group. However, the relationship between RAI treatment dosage and percent changes in thyroid nodules was not statistically significant (p=0.312) **(Figure 2)**.

The changes observed in all nodules' volumes as a result of RAI treatment were also evaluated. There was a 39% decrease in the 10 mCi group, 15% decrease in the 15 mCi group and 11% in the 20 mCi group. No statistically significant relationship was observed between radioactive iodine dosage and percent changes (p=0.643) **(Figure 2)**.

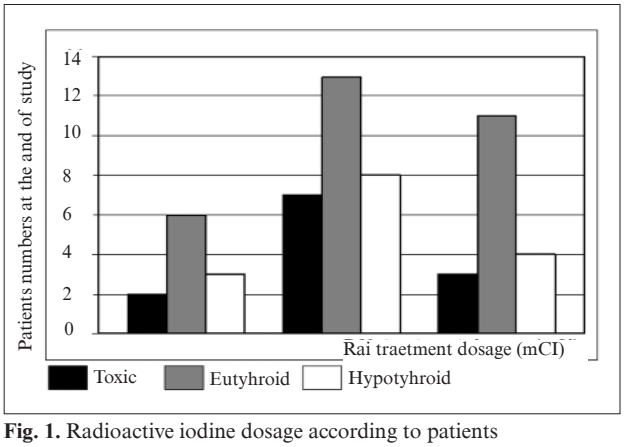

Fig. 1. Radioactive iodine dosage according to patients

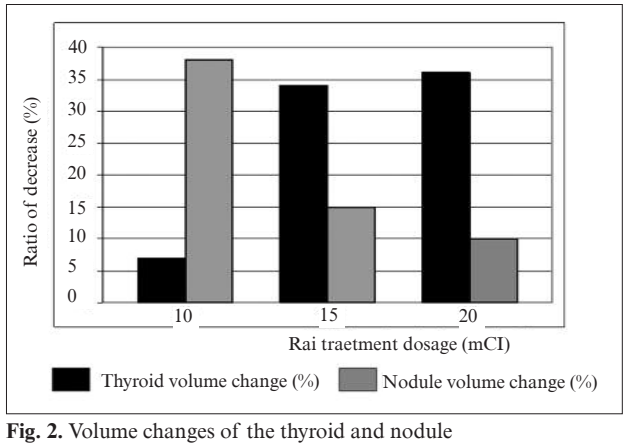

Fig. 2. Volume changes of the thyroid and nodule

Discussion

Surgical therapy has been considered as standard treatment in large compressive goiter patients for many years. However, surgery can not be performed in all elderly patients due to some severe medical problems such as cardiac, pulmonary and several other diseases.[7,8] Besides, some of the patients do not prefer surgical intervention. In such cases, RAI treatment is used in patients with TMNG and nontoxic MNG.[9-11]

In our study, we evaluated 57 patients who received RAI treatment for TMNG and MNG. While in 30/57 (53%) patients included in the study euthyroidism developed, 12/57 (21%) patients remained toxic, and hypothyroidism was observed in 15/57 (26%). Hypothyroidism+euthyroidism rate was approximately 80%. Mean RAI treatment dosage was 15.08±4,12 mCi in the toxic group, 16±4.16 mCi in the euthyroidism group and 15.33±3.77 mCi in the hypothyroidy group. Of the total 69 nodules, in the 12th month of treatment compared to the baseline, 61 (88%) decreased in size. 39% decrease was observed in the 10 mCi group; the decrease was 15% in the 15 mCi group and 11% in the 20 mCi group.

In one study, in RAI group mean time to respond was 5.4 months and goiter sizes decreased in 38% of the cases in TMNG.[12] In another study, three months after treatment, euthyroidism or hypothyroidism was observed in 82% of the surgical and 21% of the RAI treatment group. However, after 2 years, success rates were similar, though hypothyroidism was found significantly higher in the surgical treatment group.[13,14] Similarly, in our study, volume decrease in the nodules was approximately 25% and hypothyroidism+euthyroidism rate was approximately 80% after a 12-month RAI treatment.

RAI is a treatment option which has been used for more than 50 years for its low side effect incidence and high efficacy. The majority of Graves' disease patients can be effectively treated by taking a single dose of RAI.[13,14] A second treatment is required in only 10% of the cases. In the Guidelines of American and German Nuclear Medicine Association, RAI treatment was considered a comfortable, effective and cost-effective option for toxic nodular goiter treatment.[15] TNG patients are more resistant to RAI treatment compared to Graves' disease patients. The reason is not clear, yet it is hypothesized that RAI turnover may be higher in nodules and this may lower the effective dose amount.[16] In a study evaluating 14 studies done between 1952-2006 on the antithyroid medication usage prior to and after RAI treatment, some authors found that using antithyroid drug one week before or after RAI treatment leads to a decrease in RAI treatment effectiveness and hypothyroidism risk.[16] In our study, thirty of 57 (53%) of the patients included in the study had a history of pre-treatment antithyroid medication. This rate was reported to be 64% in another study from Turkey.[19] Again, in our study, there was a pre-treatment antithyroid drug usage history in 10/12 (83%) of the patients in the post-treatment toxic group, in 13/30 (43%) of the euthyroid group and 7/15 (47%) of the hypothyroid group. We observed that 10 (83.3%) of the 12/57 patients who remained toxic after treatment had antithyroid drug usage before RAI treatment. The fact that the group which remained toxic in our study had a high level of antithyroid drug usage suggests that antithyroid medications lower the effectiveness of RAI treatment. We thought that antithyroid treatment and treatment duration affect the effectiveness of RAI treatment. So we recommend that RAI treatment should be performed as soon as possible when the disease is diagnosed before giving any antithyroid drugs.

In a screening study, hypothyroidism rate was 10-20% at the end of RAI treatment.[15] Moreover, in a study, after 3 years of follow-up, hypothyroidims rate was 8% with mean 8.9 mCi dosage.[17] In another study, the hypothyroidy rate was 9%.[17] A study from our country reported that after mean 20 mCi RAI treatment, at the 3rd month, hypothyroidims rate was 5.1, but increased to 10% after 12 months.[18]

In our study, hypothyroidism rate was 26.4% at the 12th month of RAI treatment. In our study, over all, 12 months after mean 15.6 mCi RAI treatment, hypothyroidism rate was 26.4%. The highest percent of hypothyroisim was observed in 8/28 (28.6%) patients who had received 15 mCi RAI. The hypothyroidims rate was 3/11 (27.3%) in the 10 mCi and 4/18 (22.2%) in the 20 mCi receiving group.

Several factors are suggested to cause hypothyroidism in these patients. For instance, excistence of antibodies against thyroid cytoplasm antigens may play a role in the development of hypothyroidism. Hypothyroidism incidence increases with age in patients over 55, and while antithyroid drug usage before treatment lowers hypothyroidy rate, its incidence increases with higher doses. Iodine uptake of extranodular tissue is also a significant factor for hypothyroidism development.[19,20]

In most of the studies, thyroid volume decreased with RAI treatment. In a study of Le Moli R et al., in non-toxic goiter, 50% decrease was observed within 2 years after a single dose of 4-77 MBq/g thyroid RAI treatment. In 8 years of follow-up, hypothyroidy rate was 58%. Anti-TPO antibody positivity, presence of family history and relatively small goiter revealed a higher hypothyroidism incidence.[20] In our study, we excluded the patients who have thyroid autoantibody at the begining of study. So we did not evaluate the thyroid autoantibody positivity at the end of our study.

In another study, 100 hypothyroidism cases treated with RAI during 2000-2001 were evaluated retrospec-

tively; 31 of these cases were treated as Graves' disease, 37 as TMNG and 32 as toxic adenoma. Mean RAI treatment dosage was 14.4 mCi for Graves' disease, 12.9 mCi for TMNG and 12.1 mCi for toxic adenoma. Treatment efficacy (euthyroidy-hypothyroidy) at the end of three years was 87% for Graves' disease, 81% for TMNG and 94% for toxic adenoma. Mean decrease in thyroid volume was 76% for Graves', 33% for TMNG and 69% for toxic adenoma. Temporary nausea and sialadenitis were observed in several patients as a side effect.[21]

In our study, RAI treatment dosage was calculated according to thyroid hormone levels, gland size, thyroid scintigraphy and 4/24 hours RAI uptake results using variable scale method.

Hypothyroidism and Graves ophtalmopathy may sometimes accelerate with RAI treatment, and in large nodular goiters, airway obstruction may occur. Radiation thyroiditis can develop in 2-3% of the cases but generally it is mild with a short duration.[3,22] In our study, we observed no such side effects in 12 month follow-up.

Until the 12th month visit after treatment no side effects were found except hypothyroidy. Hypothyroidy rate was 26.4%. This appeared to be because of the higher age levels in our cases compared to other studies, a lower rate of antithyroid drug usage before treatment and because our patients received higher doses of RAI.

In conclusion, RAI treatment at TMNG and TNG patients is a rather effective treatment option for diminishing thyroid nodules and for hormonal control. No side effects other than hypothyroidism are observed. Regarding patient comfort and cost, it should be considered as a first line of therapy in TMNG and TNG patients. A dosage of mean standard 15 mCi RAI treatment is sufficent for disease control in TMNG and TNG patients.

References

1. Franklyn JA. The management of hyperthyroidism. N Engl J Med 1994;330:1731-1738.
2. Allahabadia A, Daykin J, Sheppard MC, Gough SC, Franklyn JA. Radioiodine treatment of hyperthyroidism-prognostic factors for outcome. J Clin Endocrinol Metab 2001;86:3611-3617.
3. Freitas JE. Therapeutic options in the management of toxic and nontoxic nodular goiter. Semin Nucl Med 2000;30 :88-97.
4. Dietlein M, Dederichs B, Kobe C, Theissen P, Schmidt M, Schicha H. Therapy for non-toxic multinodular goiter: radioiodine therapy as attractive alternative to surgery. Nuklearmedizin 2006;45:21-34
5. Hegedüs L, Bonnema SJ, Bennedbaek FN. Management of simple nodular goiter: current status and future perspectives. Endocr Rev 2003;24:102-132.
6. Knudsen N, Bols B, Bulow I, et al. Validation of ultrasonography of thyroid gland for epidemiologic purpose. Thyroid 1999;9:1069-1074.
7. Hermus AR, Huysmans DA. Treatment of benign nodular thyroid disease. N Engl J Med 1998 14;338 :1438-1447.
8. Samuels MH. Evaluation and treatment of sporadic nontoxic goiter--some answers and more questions. J. Clin Endocrinol Metab 2001;86 :994-997.
9. Chatzopoulos D, Papadopoulose A. Functional autonomy of the thyroid gland and its therapeutic control. Hell J Nucl Med 1999, 2:69-72.
10. Hegedüs L, Hansen BM, Knudsen N, Hansen JM. Reduction of size of thyroid with radioactive iodine in multinodular non-toxic goitre. BMJ 1988;10;297:661-662
11. Wesche MF, Tiel-V Buul MM, Lips P, Smits NJ, Wiersinga WM. A randomized trial comparing levothyroxine with radioactive iodine in the treatment of sporadic nontoxic goiter. J Clin Endocrinol Metab 2001;86:998-1005.
12. Kang AS, Grant CS, Thompson GB, van Heerden JA. Current treatment of nodular goiter with hyperthyroidism (Plummer's disease): surgery versus radioiodine. Surgery 2002;132:916-923
13. Erickson D, Gharib H, Li H, van Heerden JA. Treatment of patients with toxic multinodular goiter. Thyroid 1998;8:277-282.
14. Dietlein M, Lauterbach KW, Schicha H. Treatment of toxic nodular goitres: Comparative costing of radioiodine therapy and surgery. Exp Clin Endocrinol Diabetes 1998;106 Suppl 4:66-70.
15. Reiners C, Schneider P. Radioiodine therapy of thyroid autonomy. Eur J Nucl Med Mol Imaging 2002;29:471-478.
16. Walter MA, Briel M, Christ-Crain M, et al. Effects of antithyroid drugs on radioiodine treatment: systematic review and meta-analysis of randomised controlled trials. BMJ 2007;10;334:514.
17. Nygaard B, Hegedüs L, Nielsen KG, Ulriksen P, Hansen JM. Long-term effect of radioactive iodine on thyroid function and size in patients with solitary autonomously functioning toxic thyroid nodules. Clin Endocrinol (Oxf) 1999;50:197-202.
18. Erdoğan MF, Küçük NO, Anil C, Aras S, Ozer D, Aras G, Kamel N. Effect of radioiodine therapy on thyroid nodule size and function in patients with toxic adenomas. Nucl Med Commun 2004;25:1083-1087.
19. Zingrillo M, Modoni S, Conte M, Frusciante V, Trischitta V. Percutaneous ethanol injection plus radioiodine versus radioiodine alone in the treatment of large toxic thyroid nodules. J Nucl Med 2003;44 :207-210.
20. Le Moli R, Wesche MF, Tiel-Van Buul MM, Wiersinga WM. Determinants of longterm outcome of radioiodine therapy of sporadic non-toxic goitre. Clin Endocrinol (Oxf) 1999;50:783-789.
21. Tarantini B, Ciuoli C, Di Cairano G, et al. Effectiveness of radioiodine (I-131) as definitive therapy in patients with autoimmune and non-autoimmune hyperthyroidism. J Endocrinol Invest 2006;29:594-598.
22. Sarkar SD. Benign thyroid disease: what is the role of nuclear medicine? Semin Nucl Med 2006;36:185-193.