

Comparison and Contrast of Surgical and Medical Treatment for Adult Patients (age 20
and older) with Multinodular Goiter

Submitted by

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A project presented to the Department of
Physician Assistant of Wichita State University

In partial fulfillment of the
Requirements for the degree
of Master of Physician Assistant

May 2006

Wichita State University
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We hereby recommend that the research project prepared under our supervision by Velitchka H. Kouneva-Skerleva entitled Comparison and Contrast of Surgical and Medical Treatment for Adult Patients (age 20 and older) with Multinodular Goiter will be accepted as partial fulfillment for the degree of Master of Physician Assistant.

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Abstract

Introduction: Multinodular nontoxic goiter is defined as a benign enlargement of the thyroid gland in a subject living in an iodine insufficient area. The causes of MNG are not completely understood, but include autoimmune, genetic, and extrinsic factors. Symptoms vary widely among patients, from those with no symptoms and an incidentally discovered goiter to those with tracheal compression and stridor. The treatment goals for patients with a benign MNG include relief of local compressive symptoms or cosmetic deformity, prevention of progressive thyroid enlargement, and treatment of associated thyroid dysfunction. There are three main treatment options for MNG: thyroidectomy, levothyroxine suppression, and radioactive iodine. Methodology: The purpose of this paper was to compare and contrast medical versus surgical treatment of patients with multinodular goiter through a systemic review of the literature, so that primary care practitioners can use evidence-based criteria when treating or recommending treatment. Articles from 1975 to the present were reviewed that included adult patients ranging in age from twenty years old and older who were diagnosed with benign MNG. Variables included thyroidectomy, antithyroid suppressive therapy and radioiodine therapy. Results: Twenty articles matched the criteria and were reviewed using evidence-based methods. After close analysis of the presented data, disagreement remains in the current treatment of asymptomatic MNG and no optimum treatment has been established. Conclusion: There still is considerable controversy about the optimum treatment and efficacy of using different suppressive medications versus surgical treatment for patients with asymptomatic MNG. Treatment decisions for nontoxic multinodular goiter must be individualized and based on the clinical examination and adequate follow up.

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Acknowledgements

I would like to say thank you to my family, for their support and encouragement. Without them I would have never been able to graduate from the WSU Physician assistant program.

Thank you to my friend, Astrid, and my mother who were always there for me when I needed them in difficult times. At last I would like to say thank you to my research advisor, Pat Bunton, for her patience and dedication to students.

Introduction

A multinodular goitre is defined as a structurally and functionally heterogeneous thyroid enlargement. It is present in 500 to 600 million people and it is usually secondary to endemic iodine deficiency. This is why multinodular goitre is a relatively common condition in areas of mild to moderate iodine deficiency. Despite adequate iodine intake, 4% to 6% of American adults are goitrous. Sporadic nodular goiter ensues from the natural heterogeneity of thyroid follicular cells, which, when amplified by yet unidentified trophic stimuli, results in episodes of proliferating, rapidly dividing micronodules. The initial small diffuse goiter evolves into a multinodular goiter with one or more dominant nodules that may or may not be autonomous. Recent data suggests that 50% of patients with single thyroid nodule have other nodules demonstrated by careful ultrasonography¹⁵. Most multinodular goitres are slow growing and the majority of them are benign. . The incidence of carcinoma is up to 10% in multinodular goiters. These require no operative intervention unless there is suspicion of malignancy. Growing goitres usually come to clinical attention when noted by the patient, as an incidental finding during routine physical examination, or during a radiological procedure.

In patients with multinodular goiter, the history, physical examination, and diagnostic evaluation should be thorough to detect any potential clues for thyroid hormone dysfunction, compression from large goiters, and nodules suspicious for malignancy. The serum TSH should be the initial screening test to assess thyroid The indications for treatment of multinodular goitre include compression–induced symptoms attributed to the goiter (compression of adjacent structures, most notably the trachea, the esophagus, or the large veins of the neck), suspected malignancy, and in some instances

cosmetic concerns of the patient¹⁶. If treatment is required, L-thyroxine, thionomides, surgery and radioiodine (I-131) are effective in selected patients^{1,15,16}.

Nontoxic multinodular goitre has been a subject of research for decades but there remains considerable controversy about the optimum treatment and efficacy of using different suppressive medications versus surgical treatment for patients with this condition.

Literature Review

Multinodular goitre has become a highly endemic thyroid disease that affects people all over the globe, mainly populations exposed to relatively low supply of iodine. This type of goitre progresses from a diffuse enlargement of the thyroid in young adults to a multinodular structure with advancing age. Moreover, in elderly people it is very commonly observed that the long-standing goitre (having this thyroid condition for more than 20 years) descends into the upper mediastinum, causing compression of the trachea and other cervical structures.

Surgery has long been considered the standard and choice procedure for patients with multinodular goitres³. The performance of total thyroidectomy in multinodular disease has been reserved for exceptionally larger goitres. Opponents of total thyroidectomy claim that the procedure is not justified in multinodular disease, as the risk for malignancy is low but associated complication rates are high. It has been documented that total thyroidectomy can be performed safely in benign nodular goitre. However, the relative risk for permanent complications has been found to be higher in subsequent surgeries for recurrent disease than in primary operations with extensive resection⁹.

In addition, some patients refuse surgery because of side effects such as reduced bone mineral content in totally thyroidectomised patients, a possible effect of Calcitonin deficiency⁴. Enlarged multinodular toxic and nontoxic goitres can be reduced by radioiodine (RAI) and because anti-thyroid medications cannot be expected to effect a permanent cure, it is a frequently chosen treatment. The study of Silva et al.² is the first to show that the efficacy of radioiodine therapy of nodular goitres can be improved by pretreatment with TSH. Treatment of benign nodular goitre with mildly suppressive doses of L-thyroxin decreases nodule size⁵.

Arrest of growth in multinodular goitre can occur spontaneously at any stage making it uncertain whether patients with minimal or no symptoms should be treated or merely observed. The study of Bhagat⁶ showed a lack of consensus in the management of multinodular goitre. According to that study there are clinically significant differences between endocrine surgeons and endocrinologist in the management of non-toxic multinodular goitre.

Purpose of Study

Multinodular goitres may be treated with antithyroid suppressive drugs, surgical thyroidectomy, or radioiodine ablation. Unskilled management of multinodular goitre drug therapy can lead to problems with either under- or overdose, including reactions such as agranulocytosis and resulting life-threatening infections.

With inappropriate referral for, or performance of, thyroidectomy, the surgical complications can include hoarseness, vocal cord paralysis, and hypoparathyroidism requiring calcium and vitamin D therapy for life⁴. Without expert management multinodular goiter patients may be at greater risk for worsening their conditions. The

review of literature reveals that optimum treatment for multinodular symptomatic patients is not well established. The purpose of this study is to compare and contrast medical versus surgical treatment of adult patients (20 and older) with multinodular goitre so that primary care practitioners can use evidence-based criteria when treating or recommending treatment.

Methodology

The search was conducted utilizing the keywords of non-toxic multinodular goitre, medical treatment, and surgery.

Major sources of evidence-based format were:

- PUBMED-Medline
- COCHRANE Database of Systematic Reviews
- MESH TERMS
- PROQUEST Nursing

Studies were selected describing outcomes in surgically and medically treated patients with multinodular goitre from 1975 to the present date. Classification of studies was done based on comparison and contrast of different treatments for multinodular goiter.

Results

From 1975 through 2005, twenty articles met inclusion criteria. The review concluded that some articles addressed more than one outcome, therefore there is some overlap in the result section. Three of the articles contained background information regarding non-toxic multinodular goiter.^{1,15,16} This included information concerning

pathogenesis, diagnostic evaluation, laboratory testing and different treatment options for asymptomatic multinodular goiter.

Eight articles discussed the benefits of surgery as a standard treatment for multinodular goiter and compared it with other possible treatments. Thyroidectomy leads to rapid decompression of vital structures and prevents from recurrence.^{1,3,6,9,10,13,16,19}

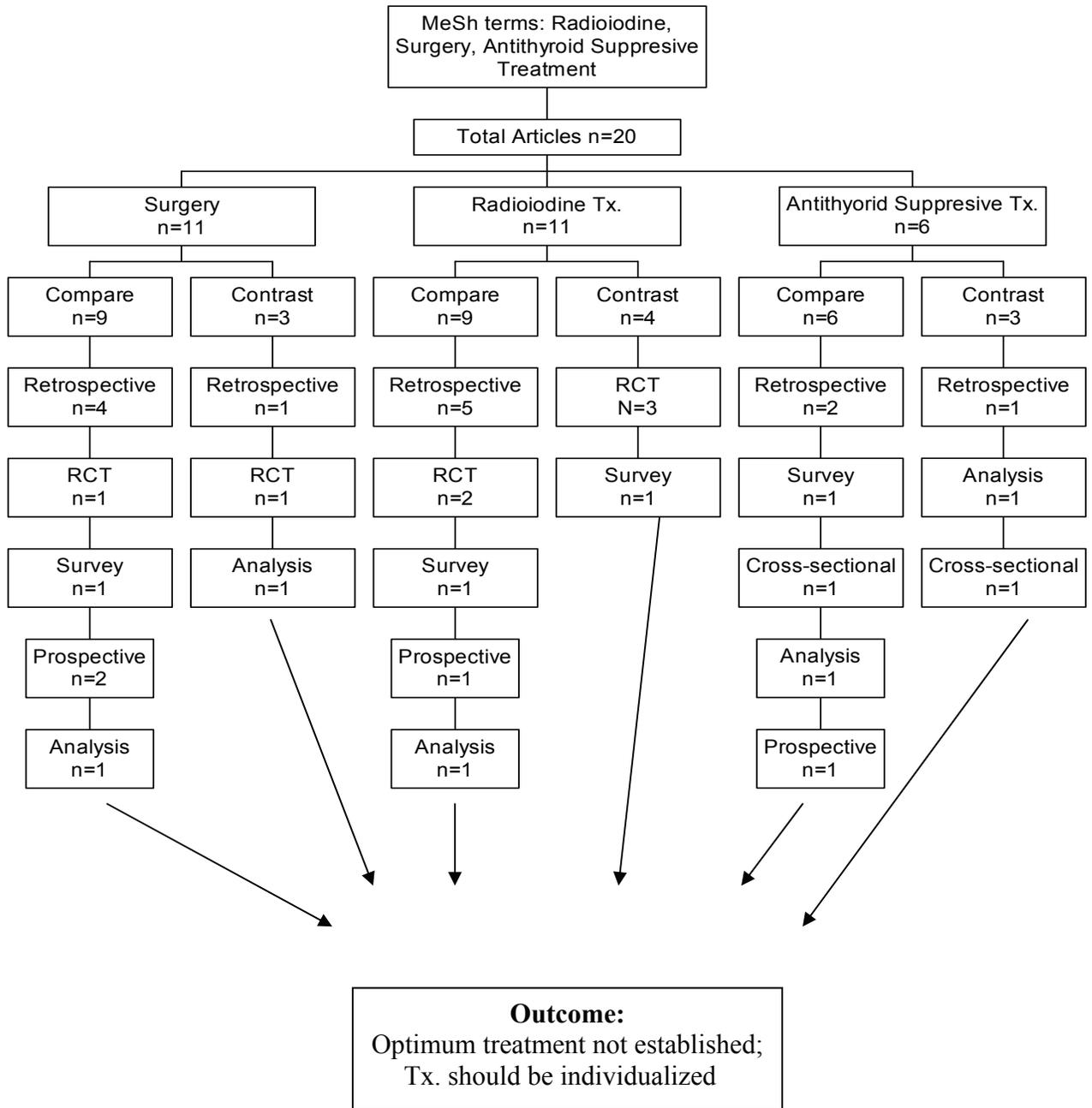
Three articles revealed different postoperative adverse affects of surgical incision-such as: postoperative tracheal hemorrhage or tracheomalacia, injury to the recurrent laryngeal nerve, hypoparathyroidism, voice changes due to superior / laryngeal nerve damage, decrease calcitonin level and hypothyroidism.^{4,15,16}

Eight studies revealed that radioiodine treatment is effective in reducing thyroid volume in most patients with non-toxic multinodular goiter.^{1,2, 11,12,14,16,18,19} Two of the eight studies compared the advantages and the disadvantages of the radioiodine therapy. Side effects include mild radiation thyroiditis as an early event and hypo- and hyperthyroidism.^{2, 17,18}

Another alternate treatment for non-toxic multinodular goiter is suppressive antithyroid therapy. Five studies were found that addressed the issue of prescribing thyroid hormone in an attempt to reverse growth of benign nontoxic goiters or prevent new nodule formation.^{1,5,6,16,19} Three of these studies also discussed the possibility of substantial decrease in bone mineral density at the lumbar spine, the proximal femur and the radius in post-menopausal women receiving long-term suppression therapy with thyroid hormone as well as some cardiac adverse effect (Figure 1).^{1,5,16}

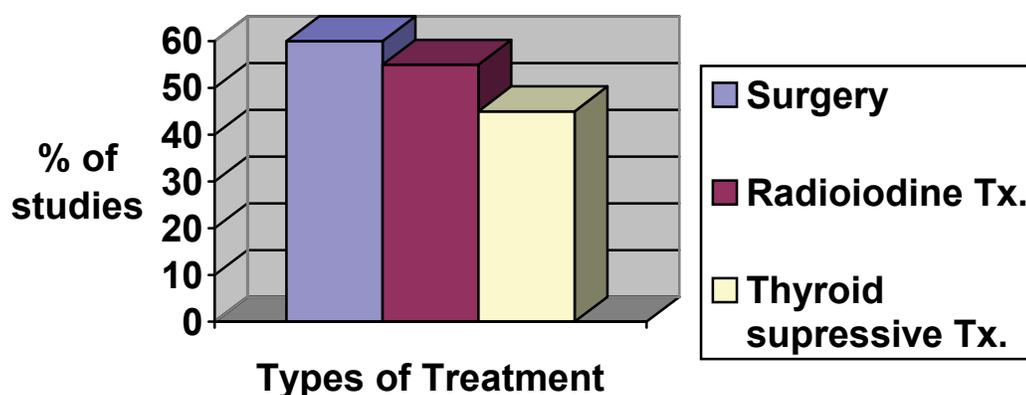
Figure 1. Literature Review Flow Sheet

Comparison and Contrast of Surgical and Medical Treatment
for Adult Patients with Multinodular Goitre



Overall, 60 % of the articles found that surgery is an important part of the treatment of non-toxic multinodular goiter. 55 % supported the importance of radioiodine treatment and 45 % of the articles discussed the need of adding thyroid suppressive therapy. These articles represented Levels I and II as shown at the appendices and can be further graded as A or B evidence. (Figure 2)

Figure 2: Treatment Recommendations



Discussion

Multinodular goitre growth can occur at any time bringing the uncertain question whether patients with minimal or no symptoms should be treated medically or surgically. It remains a debated and controversial point whether thyroidectomy should be undertaken in the patient with a nontoxic multinodular goitre, or medical treatment would be in the patient's best interest. Such controversy of comparing and contrasting surgical vs. medical treatment has led to this systematic review of evidence-based literature. Twenty

articles meeting the inclusion criteria were selected and divided into surgical and medical treatment.

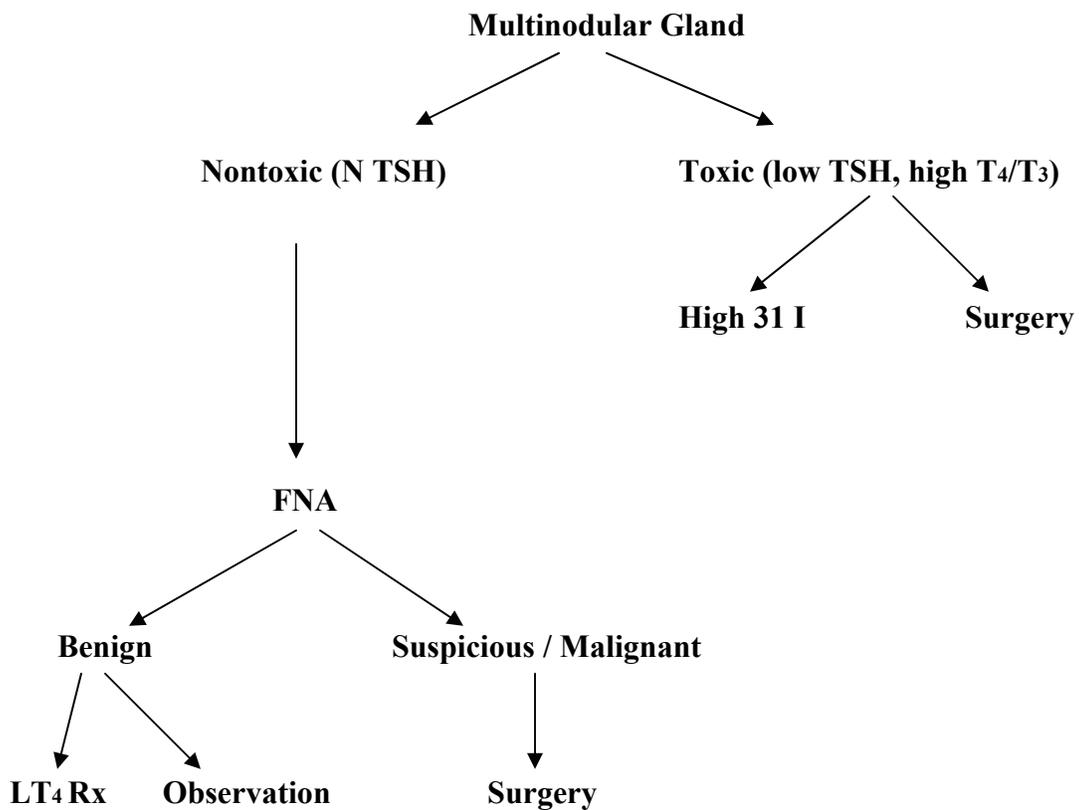
Surgery

The main indications for the treatment of patients with nontoxic multinodular goiter are compression of the trachea or esophagus and venous-outflow obstruction. Another indication is growth of the goitre, especially where there is intrathoracic extension. Such goiters are inaccessible to palpation and fine needle aspiration biopsy, and they may cause acute airway symptoms. Sometimes treatment is sought because of neck discomfort or cosmetic issues.

For large nontoxic multinodular goiters surgery remains the standard therapy^{1,3,6,9,10,13,16,19}. Surgery effectively relieves compressive symptoms but the indications for surgery in asymptomatic patients are not well established. When surgery is recommended there is a strong preference for total or near-total thyroidectomy, especially for patients with bilateral multinodular goiter. However, the practice of surgery should always be based on achievable benefits of the procedure that outweigh the potential complications. Thyroidectomy is justifiable only if it can be done safely with minimal damage to the laryngeal nerves and the parathyroid glands. The potential benefits of total thyroidectomy relate to adequate removal of the goiter and the prevention of recurrence³. Mary Samuels, M.D., Division of Endocrinology, Oregon Health Sciences University, Portland Oregon states “ I believe that thyroidectomy is a suitable option in SNG, tailored to the patient’s general health, size of goiter, symptoms, and available surgical expertise”¹⁶

Recommending surgery to a patient with an asymptomatic multinodular goiter must depend upon the statistical likelihood of underlying cancer. In 10% of all cases of multinodular goiter the presence of occult malignancy has been found and obviates the need for completion surgery (Figure 3).

Figure 3. Management of patients with multinodular goiters.



The study of Alexopoulou et al, states that all patients that underwent surgery because they were either considered at risk for thyroid cancer or because a nodular goiter had to be removed for mechanical or cosmetic reasons. The study clarifies that goiters with nodules that increase rapidly in size, and appear dominant on scintigraphy and have low echogenicity on ultrasound should be considered at high risk of malignancy and

therefore further investigated by surgery. The study goes on to emphasize that the size of the nodules are also important. Nodules that are larger than 3cm according to the ultrasound report should also be removed, as they are associated with a higher risk of clinical cancer.

Although surgery has been recommended as the standard therapy for patients with multinodular goiter, the possibilities of postoperative adverse effects are cause for considering an alternate treatment. Surgical morbidity includes postoperative tracheal obstruction due to hemorrhage or tracheomalacia, injury to the recurrent laryngeal nerve, hypoparathyroidism, voice changes due to superior / laryngeal nerve damage, and hypothyroidism. The rate of goiter recurrence after surgery increases with time.¹

Patients who have undergone total or near-total thyroidectomy have shown significantly lower basic calcitonin levels. In the study of Michael McDermott, 6 males and 12 females who had previously undergone near/total thyroidectomy were compared with the same group of normal male and female patients. Thyroidectomized males had a significantly lower mean bone mineral content (BMC) than the control group; among the females the thyroidectomised group did not reach statistical significance for low mean BMC. In conclusion the authors believe that the decreased BMC found in thyroidectomized patients provides further evidence that calcitonin deficiency plays a role in the development of osteoporosis in these patients.

Medical Treatment

Radioiodine Therapy

The first report of the use of radioactive iodine to treat large multinodular goiter appeared in 1960s and was followed by a number of uncontrolled studies. Radioiodine

therapy has shown to be highly useful for goiter reduction in nontoxic multinodular goiter producing forty to sixty percent shrinkage in volume within two years.¹⁸ An important fact is the finding that compressive symptoms decrease in the majority of patients. According to Hermus et al there was significant tracheal widening as measured by MRI and this widening was accompanied by improvement in respiratory function (Figure 4).

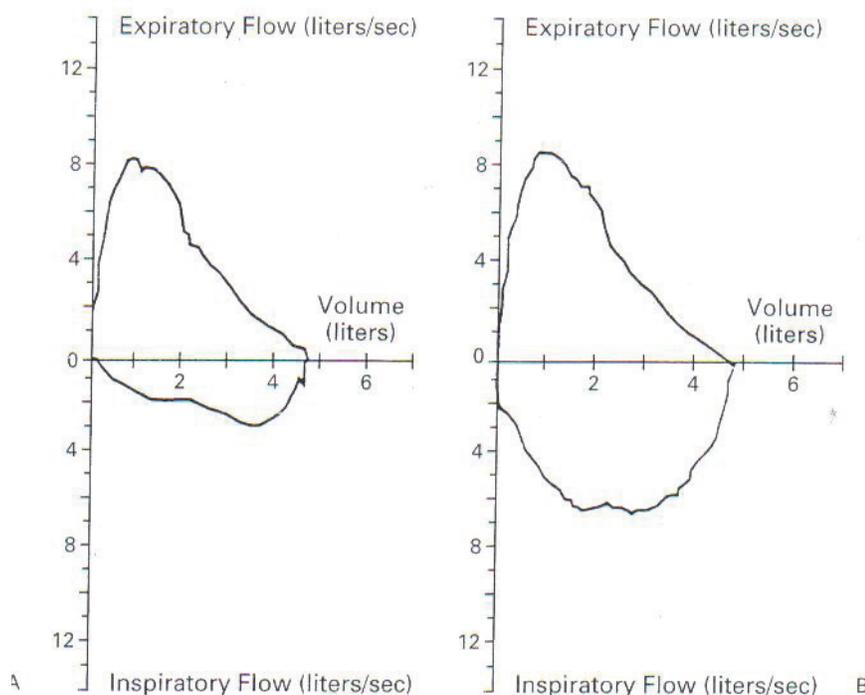


Figure 4. Flow-volume loop curves in a patient with a multinodular goiter before (panel A) and one year after (panel B) radioiodine therapy.

Radioiodine treatment is especially attractive in elderly patients who have a high operative risk and in those who refuse surgery. The study of Silva et al is the first to show that the efficacy of radioiodine therapy of nodular goiters can be improved by pretreatment with recombinant human TSH (rhTSH). The main indication is in the treatment of large goiters in elderly patients with subclinical hyperthyroidism and suppressive serum TSH values. Pretreatment with rhTSH stimulates the uptake of

radioiodine by most nodules of MNG, possibly with a more extensive distribution of the radioisotope within the nodules.^{2,17}

For non-toxic multinodular goiter, radioiodine treatment is not yet often chosen, although it is becoming increasingly popular in some countries. One theoretical drawback is the failure of radioiodine to reach cold areas or nodules within a MNG. Side effects include mild radiation thyroiditis as an early event and hypo- and hyperthyroidism.^{2,8,10,17}

Early side effects (pain in the thyroid region, radiation thyroiditis, increase in compressive symptoms, and esophagitis) are rare, and when present they are usually mild and transient. The development of autoimmune (Graves') hyperthyroidism is the most important complication, occurring several months after therapy in approximately five percent of patients.¹ However, thyrotoxicosis occurring late after radioiodine treatment for nontoxic multinodular goiter has suggested being a result of release of autoantigens that may trigger an autoimmune response¹⁴.

Based on the measurements of whole-body radiation exposure, there is slight increase in the estimated lifetime risk of nonthyroid cancer of about 1.6% because of the large doses of radioiodine used in patients with very large goiters. The risk is much less (about 0.5%) in patients above the age of 65 years, but no data exists for the incidence of RAI-induced malignancy in the treatment of multinodular goiter patients of any age.¹⁵

Thyroid Hormone Suppressive Therapy

The use of thyroid hormone suppression therapy of MNG is controversial. Thyroid hormone is prescribed in an attempt to reverse growth of benign nontoxic goiters or prevent new nodule formation. Results show that patients with relatively small, nontoxic multinodular goiters, a decrease in goiter size, defined as a decrease in thyroid

volume of more than thirteen percent, occurred in fifty-eight percent of patients treated with thyroxine.¹ In iodine-deficient areas, L-T4 therapy has been advocated as a useful treatment to hinder the recurrence of nontoxic nodular goiter due to the high sensitivity to TSH of the iodine-depleted thyroid gland. The prospective randomized study of Carella et al. leads to the conclusion that, patients living in a moderate iodine-deficient area and undergoing thyroid surgery for nontoxic goiter, lowering the plasma TSH concentration attains the nonsuppressive L-thyroxine (L-T4) therapeutic effectiveness. With the addition of iodine salt to daily diet the effects of L-T4 on remnant size are significant.⁷

To avoid the development of toxic symptoms thyroid hormone should not be used in patients with suppressed serum TSH levels. Thyroxine therapy in doses sufficient to suppress serum thyrotropin may have adverse effects. A meta-analysis of all controlled cross-sectional studies of the effect of thyroid hormone therapy on bone mineral density demonstrated substantial decreases (5 to 9 percent) in bone mineral density at the lumbar spine, the proximal femur and the radius in post-menopausal women receiving long-term suppression therapy with thyroid hormone. No negative effect of therapy on bone mineral density was found in premenopausal women or men.¹

A low serum thyrotropin concentration in persons 60 years of age or older is also associated with a tripling of the risk of atrial fibrillation in the subsequent decade. Therefore it is not unreasonable to assume that suppression therapy with thyroid hormone might have adverse cardiac effects. The therapy increases left ventricular mass, but whether it causes cardiac dysfunction is not clear.¹ Research revealed that after discontinuation of thyroid suppressive therapy, goiter size returned to base line.

Furthermore, there is no evidence that long-term thyroxine therapy alters the natural history of multinodular goiter.^{1,8}

Conclusion

Primary care physicians, endocrinologists, surgeons, and otolaryngologists encounter nodular goiters commonly in clinical practice. Epidemiological data suggests that in the United States, the incidence of such goiters is approximately 0.1% to 1.5% per year, translating into 250,000 new nodules annually. Nodular goiters are more common in women than in men. Another risk factor is advancing age and exposure to external irradiation. These goiters may be asymptomatic, with normal TSH levels (nontoxic).

Indications for treatment in patient with multinodular goiter include hyperthyroidism, local compression symptoms attributed to the goiter, cosmetics, and concerns about malignancy based on diagnostic results. The use of levothyroxine suppression therapy to effectively decrease and control multinodular goiter size is controversial. Thyroid hormone should not be used, however, in patients with suppressed serum TSH levels, to avoid the development of toxic symptoms. Management of toxic multinodular goiters by surgery is well established. Radioiodine is also effective therapy for many of these patients. When treatment is necessary for nontoxic multinodular goiters, surgical excision is preferred. For patients who have small, nontoxic multinodular goiters that are clinically asymptomatic, who are biochemically euthyroid according to serum TSH levels, and who have prominent palpable benign nodules, yearly evaluation with serum TSH determinations and thyroid palpation is sufficient. Patients with moderate size but stable multinodular goiters and normal serum TSH levels may

also be managed by yearly clinical observation. For large nontoxic multinodular goiters with local compression symptoms, the preferred treatment is surgery.

After close analysis of the presented data, it appeared there was controversy in the current treatment of asymptomatic MNG and not optimum treatment is established. Treatment decisions for nontoxic multinodular goiter must be individualized and based on the clinical examination and adequate follow up.

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Appendix A
Raw Data

<i>Study Year</i>	Research addresses	<u>Levels of evidence</u>	<i>Demographics</i>	<i>Findings</i>	Supportive of Research
	1. Surgery 2. Radioiodine Tx. 3. Thyroid sup. Tx. 4. All of them 5. Background	1. random control 2 .retrospective 3. background	Main data		1. Surgery preferred 2. Surgery has AE 3. Radioiodine preferred 4. Radioiodine AE 5. Thyroid STx. 6. AE of Thyroid STx. 7. Background
Hermus et al 1998	4 5	3	N/A	Bilateral thyroidectomy is a standard Tx. 40% reduction of thyroid volume in 1 year	6
Silva et al 2004	2	1	34 pts. with long-standing MNG were treated with RAI	Pretreatment with rhTSH results in a more effective RAI	3
Hishman et al 2001	1	2	98 pts. With MNG underwent total thyroidectomy	Total thyroidectomy is treatment of choice for benign thyr.disorders when the entire gland is involved	1
McDermot et al 1982	1	1	18 pts. who had previously undergone near-total thyroidectomy	Totally thyroidectomised pts.had decreased BMC-evidence of decreased calcitonin associated with osteoporosis	2

Baldini et al 2002	3	2	89 female pts. with non-toxic MNG followed for 2 years after being treated with L-thyroxine	Reduction of nodule size more than 30% was considered Significant	6
Bhagat et al 2003	4 5	2	A questionnaire containing a hypothetical case and 11 variations on the case was sent to endocrinologists and endocrine surgeons	Difference between endocrine surgeons and endocrinologists in the management of non-toxic goiter	1 3 5
Carella et al 2002	3	1	139 pts. living in a moderate iodine-deficient area	Remnant volume reduction	5
Derwahl et al 2000	5	3	N/A	Background information, introduction, etiology, diagnosis, and treatment options and adverse effects	6
Giles et al 2004	1	1	218 pts. with MNG underwent total or near-total thyroidectomy	Recommended surgery to eliminate complications of thyroid cancer	1
Huysmans et al 2004	2	2	Pretreating pts. with low serum TSH before iodine treatment for volume reduction of nodular goiter.	Good for high operative risk pts. and iodine leads to significant decrease in nodule size.	5
Alexopoulou et al 2004	1	1	80 pts. with MNG underwent surgery; considered at risk for thyroid cancer of for cosmetic or mechanical reasons	Nodules that are > 3 cm. should be considered for surgery	1

Dent et al 1975	1	2	156 pts. with thyroidectomy	Operation for pt. with asymptomatic MNG must depend upon the statistical likelihood of underlying cancer	1
Buchanan et al 2001	1	2	158 pts. with hemithyroidectomy	All pts. should have preoperative circulating TAA measurements because of possibility of developing hypothyroidism	2
Huysmans et al 1997	2	2	3 pts. treated with radioiodine for volume reduction of a large MNG	Severe autoimmune hyperthyroidism may occur after radioiodine treatment	4
Hurley et al 1996	5	3	N/A	Prevalence, pathogenesis, and treatment	6
Samuels 2001	5	3	N/A	Treatment for MNG	6
Nieuwlaat et al 2005	2	2	26 pts. with MNG referred for radioiodine treatment to reduce thyroid volume	Pretreatment with single dose of rhTSH improves the efficacy of radioiodine treatment	3
Bonnema et al 2005	4	2	Questionnaire circulated in ATA. Index case presented: 140 responses retained	Disagreement on treatment recommendations among North American clinicians	6

Huysmans et al 1994	2	2	19 pts. with a large compressive goiter and high operative risk or refused to have thyroid surgery	Treatment with I-131 is an effective alternative to surgery for elderly pts.	3
Moli et al 1999	2	2	50 pts. with MNG treated with I-131	Goiter size decreased on average of 50%	3

Vita

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