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Treatment and Prevention of Recurrence of Multinodular Goiter: An Evidence-based Review of the Literature

Jacob Moalem · Insoo Suh · Quan-Yang Duh

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Abstract
Background Reportedly, 10−15% of patients with goiters ultimately require operative intervention, and recurrences of multinodular goiter (MNG) account for up to 12% of all thyroid operations.
Methods We performed an evidence-based review of articles published in the English language between January 1987 and October 2007 relevant to the subject.
Results Medical treatment with T4 appears to be associated with a greater proportion of patients whose nodules decreased in size by more than 50% (22% vs. 10%; range = 14–39% vs. 0–20%). Recurrence rates of benign nodular goiter after total thyroidectomy were essentially nonexistent (range = 0–0.3%) compared with those after subtotal thyroidectomy (range = 2.5–42%) and more limited resections (range = 8–34%). There was no difference between total and less-than-total thyroidectomy with respect to temporary recurrent laryngeal nerve (RLN) injury (1–10% vs. 0.9–6%, respectively) or permanent RLN palsy (0–1.4%). There was, however, a significantly higher rate of transient hypocalcemia after total thyroidectomy than less extensive operations (9–35% vs. 0–18%, respectively). In relation to redo surgery, permanent hypoparathyroidism appeared to be far more common in the redo group (0–22% vs. 0–4%) Moreover; the redo group had more frequent RLN injury, both temporary (0–22% vs. 0.5–18%) and permanent (0–13% vs. 0–4%). About half the studies examined conclude that postoperative TSH suppression is effective in reducing recurrences, while the other half state that it is not.
Conclusion The definitive management and prevention of recurrence of benign nodular goiter is primarily surgical. Total thyroidectomy essentially eliminates the risk of recurrence without an accompanying increased risk of permanent hypoparathyroidism or RLN injury. Therefore, total thyroidectomy should be considered the procedure of choice for benign multinodular goiter whenever possible, especially considering that reoperations for goiter are significantly more morbid than any initial operation.

J. Moalem · I. Suh · Q.-Y. Duh
Endocrine Surgery, University of California, San Francisco, CA 94143, USA

Q.-Y. Duh (✉)
Surgical Service, Veteran Affairs Medical Center, 4150 Clement Street, San Francisco, CA 94121, USA
e-mail: Quan-yang.duh@med.va.gov

Introduction

Goiters affect 5–7% of the world's population [1, 2] and are the second most common endocrinopathy worldwide [3]. In some endemic areas, up to half of the population has enlarged thyroid glands [2]. Moreover, up to 60% of American adults develop thyroid nodules detectable by sonography [4] or by autopsy [5]. While the vast majority of patients with goiters live in these endemic areas, some 100 million patients with goiters hail from developed countries where iodine prophylaxis is commonplace [6]. Reportedly, 10–15% of patients with goiters ultimately require operative intervention [7], and recurrences of multinodular goiter (MNG) account for up to 12% of all thyroid operations [8, 9]. This is partially due to the fact that recurrence from surgery for MNG is common, with rates as high as 78% [10].

History of therapy

The fascinating history of treatment for goiters dates back to 2700 B.C., when iodine-rich seaweed was used [1]. Many consider the medieval medical school in Salerno to be the birthplace of thyroidology [11], as it was there, in the 1200s, where a variety of pharmacologic remedies for goiters were developed. When these failed, patients underwent surgery either via the seton method or ultimately by scalpel.

Surgery for the thyroid gland did not gain widespread acceptance until 1874 when Emil Theodor Kocher published the results from his first 13 goiter operations (with only 2 deaths). Dr. Kocher was awarded the 1909 Nobel Prize in Physiology or Medicine for his multidisciplinary work on the thyroid gland, and by 1912 he had performed more than 2000 thyroid operations. Kocher's pioneering work was later refined by surgical greats such as Halstead, Lahey, Crile, and Mayo, who perfected the technique of thyroidectomy. Today, more than 100 years after Dr. Kocher's first thyroidectomy, debate still continues over the extent of resection for benign and malignant thyroid pathologies. The crux of the disagreement lies in the balancing act between the morbidity associated with total thyroidectomy compared with that incurred by performing a less radical operation and increasing the risk of recurrent disease.

In this article we discuss the various surgical and nonsurgical treatment methods to address the problem of MNG, with particular attention paid to surgical morbidity and recurrence.

Methods

Study design

In our review of the most widely discussed clinical issues pertaining to treatment for recurrent benign goiters, we focused on two broad questions. First, we sought to identify the best initial treatment, both surgical and medical, with respect to the risk of recurrence. Second, we compared the frequency of surgical complications as a function of the extent of thyroidectomy. In addition, we compared initial and "redo" operations in the specific setting of MNG.

Literature search

Our initial search was limited to all articles published in the English language between January 1987 and October 2007, excluding review articles and studies reported only as abstracts. Key references from before 1987 were also included when necessary. The search terms were identified in the title, abstract, text word, or medical subject heading; the key words included *thyroidectomy*, *thyroid stimulating hormone*, *thyroxine*, *goiter*, *recurrent, reoperation*, and *complications*. A search of the Cochrane Library failed to identify any relevant publications. We screened the summaries and abstracts of the studies for exclusion/inclusion criteria and relevance to our clinical questions. Only the studies that passed the initial screening were further assessed and thoroughly reviewed. Relevant data from each study were extracted and analyzed.

Literature classification

We ranked each publication and assigned a grade of recommendation according to the American Association of Clinical Endocrinologists' protocol for standardized production of clinical practice guidelines as previously described [12]. Well-controlled, generalizable, randomized trials that were adequately powered, well-controlled multicenter trials, and large meta-analyses with quality ratings were categorized as level 1 evidence. Randomized controlled trials with limited data, well-conducted prospective cohort studies, and well-conducted meta-analysis of cohort studies were ranked as level 2. Level 3 evidence included methodologically flawed randomized clinical trials, observational studies, case series or case reports, and trials with conflicting evidence with weight of evidence supporting the authors' recommendation. Level 4 evidence encompassed expert consensus, expert opinion based on experience, "theory-driven conclusions," and "unproven claims."

Results

Does thyroid hormone suppression effectively reduce nodule size? Two recent meta-analyses help shed light on this important and controversial topic. The first, published by Castro et al. in 2002 [13], identified 13 studies that evaluated the impact of T4 on single nodules. Of these, six randomized controlled trials met the trial's inclusion criteria, and a total of 346 patients were included in their analysis. Although not statistically significant, T4 treatment was associated with greater a proportion of patients whose nodules decreased in size by more than 50% (22% vs. 10%; range = 14–39% vs. 0–20%).

This publication sparked a number of subsequent studies seeking to validate or refute the Castro et al. findings. These follow- up trials were included in a second meta-analysis, published by Sdano et al. in 2005 [14]. This study included nine randomized controlled trials (only 3 trials that were not included in Castro's study), and a total of 609 patients. Of the 310 patients who received T4 suppression, 69 (22%) had a 50% decrease in nodule size. Of the

remaining 299 patients who received no treatment or placebo, 30 (10%) had a 50% decrease nodule size. Among the trials included in this meta-analysis, the reported ranges of response were 12–39% for the treatment arm and 0–20% in the control arm. Although these results are statistically significant, eight patients need to be treated in order to have one patient benefit.

One study included in the Sdano et al. meta-analysis is worthy of separate discussion. Koc et al. [15], designed a two-arm crossover study to look for a dose-related response to TSH suppression. This well-designed trial's two groups, low dose and high dose, were further subdivided and randomized to receive a year's course of T4 before or after placebo. Equivalent (about 35%) volume reduction and response rate (40% of patients) were shown for both the high- and low-dose treatment arms.

Interestingly, the volume reduction that was noted in patients who were initially treated with T4 reversed with crossover to placebo. Similarly, patients in the two subgroups that were randomized to receive placebo first demonstrated nodule growth prior to crossover (not significant). Subsequent T4 suppression resulted in significantly decreased nodule size.

A multi-institutional double-blind, placebo-controlled study authored by the French Thyroid Research Group was also recently published [16]. In this trial, T4 therapy (verified by regular TSH measurements) resulted in greater decrease in nodule volume than placebo (-0.36 ± 1.71 ml vs. $+0.62 \pm 3.67$ ml). Moreover, a larger proportion of patients (27% vs. 17%) responded to therapy and had a clinically significant decrease in nodule size.

Does extent of surgery influence the rate of recurrence in patients with benign nodular goiters? We found 15 publications in the past 20 years that offered data on recurrence rates after specific types of thyroidectomy for benign nodular disease (Table 1). Most were in the form of retrospective analyses (12/15), and only four of these were comparative. As Table 1 shows, the ways in which different investigators defined primary disease, treatment groups, length of follow-up, and recurrence were markedly varied and therefore precluded meta-analysis.

There was one well-designed prospective randomized controlled trial (level 1 evidence) that compared total versus subtotal thyroidectomy for MNG at a single institution in Italy [17]. The rate of goiter recurrence after a mean follow-up of 14 years was 14% for patients who had undergone subtotal thyroidectomy versus 0% for those who had undergone total thyroidectomy. These rates are consistent with the range of recurrence rates from the pooled data of the 14 other studies.

Overall, recurrence rates of benign nodular goiter after total thyroidectomy were essentially nonexistent (range = 0–0.3%) compared to those after subtotal thyroidectomy (range = 2.5–42%) and more limited resections (range = 8–34%). Surprisingly, recurrence rates seemed to depend more on whether *any* thyroid tissue was left behind rather than how much, a finding that disagrees with those from studies that suggest that recurrence correlates with bilaterality of disease and resected thyroid volume [18, 19].

Is total thyroidectomy associated with a higher complication rate in patients with benign nodular goiters compared with lesser operations? We identified 13 studies in the past 20 years that have examined complications after various types of operations for benign nodular goiter (Table 2). Eight were comparative studies and three were prospective controlled trials. Since many recent studies advocate total thyroidectomy for the treatment of MNG, we compared the outcomes from this operation to all other less extensive ones. Our reasoning was that we could presume that total thyroidectomy might be associated with higher complication rates than other operations, which, if anything, would create a bias in favor of the control group. Analysis of just the eight comparative studies showed no differences between total and less-than-total thyroidectomies with respect to temporary recurrent laryngeal nerve (RLN) injury (1–10% vs. 0.9–6%, respectively). Moreover, the frequency of permanent RLN palsy was identical for each (0–1.4%). The results of the three prospective controlled trials in particular agree with the findings from the pooled data [17, 20, 21].

Four studies [21–24] demonstrated a significantly higher rate of transient hypocalcemia after total thyroidectomy than after less extensive operations (9–35% vs. 0–18%, respectively). This increased risk, however, appears to decrease over time, as evidenced by the equivalent rates of permanent hypoparathyroidism between total and less-than-total thyroidectomies (0–4% vs. 0–1.4%, respectively).

Is reoperation associated with a higher complication rate in patients with benign nodular goiters? Ten studies in the past 20 years examined the complications of redo thyroidectomies for recurrent benign nodular goiter (Table 3). Nine were comparative studies. The remaining study [25] was a retrospective series of reoperations for recurrent goiter following initial total thyroidectomy, the only study in our review that reported this phenomenon.

We defined two treatment groups: a "redo" group and a comparison group consisting of all "initial" thyroidectomies (regardless of the extent of resection). There were no differences in transient hypocalcemia between redo and initial thyroidectomies (0–25% vs. 1–27%, respectively). However, permanent hypoparathyroidism appeared to be far more common in the redo group (0–22% vs. 0-4%) Similarly, the redo group had more frequent RLN injury, both temporary (0–22% vs. 0.5–18%) and permanent (0–13% vs. 0–4%).

Table 1 Studies on the association between extent of thyroidectomy and recurrence of benign nodular goiter

Reference	N	Level of evidence	Design	Primary disease	Operation	Mean follow-up (years)	Determination of recurrence	Recurrence
Anderson et al. [35]	185	III	Retro	MNG	LT	10.3	H&P, U/S	15 (8.1%)
Bellantone et al. [18]	268	III	Retro	Unilateral goiter	LT	6.7	H&P, U/S	91 (34.0%)
Cohen-Kerem et al. [6]7	124	III	Retro	MNG	ST	7.8	H&P, U/S, RAI, FNA, surgery	21 (16.9%)
Guberti et al. [59]	99	III	Retro	MNG, UNG	LT	8.8	U/S	29 (29.3%)
Kraimps et al. [8]	1456	III	Retro	Benign goiter	ST	>5	H&P	36 (2.5%)
Marchesi et al. [24]	24	III	Retro	Single nodule	LT	3.3[b]	U/S	5 (20.8%)
	59			MNG	TT			0 (0.0%)
Pappalardo et al. [17]	72	I	RCT	MNG	ST	14.5[b]	H&P, U/S, RAI	10 (13.9%)
	69				TT			0 (0.0%)
Piraneo et al. [68]	60	III	Retro	Benign goiter	LT	7.5	H&P, U/S, FNA	18 (30.0%)[a]
	24				ST			1 (4.2%)[a]
Reeve et al. [69]	853	III	Retro	MNG	ST	?	Surgery	64 (7.5%)
Rios et al. [70]	19	III	Retro	Compressive MNG	LT	8.2	H&P	5 (26.3%)
	13				ST			4 (30.8%)
	120				TT			0 (0.0%)
Rios et al. [71]	11	III	Retro	Toxic MNG	LT	8.2	?	2 (18.2%)
	6				ST			2 (33.3%)
	95				TT			0 (0.0%)
Rojdmark et al. [72]	43	III	Retro	Benign goiter	ST	30.0	H&P	18 (41.9%)
Snook et al. [25]	3044	III	Retro	MNG	TT	4.8	H&P	10 (0.3%)[a]
Subbiah et al. [37]	402	III	Retro	Benign radiation-related nodules	LT	17.7	U/S, RAI, FNA, surgery	122 (30.3%)[a]
	77				ST			6 (7.8%)[a]
	149				TT			0 (0.0%)
Wadstrom et al. [38]	229	III	Retro	MNG presenting as single nodule	LT	14	H&P	28 (12.2%)

Retro = retrospective analysis; RCT = prospective randomized controlled trial; MNG = multinodular goiter; UNG = uninodular goiter; LT = limited thyroidectomy; ST = subtotal thyroidectomy; TT = total thyroidectomy; H&P = history and physical exam; U/S = ultrasound; RAI = radioactive iodine scan; FNA = fine-needle aspiration biopsy; ? = not stated

[a] Significant in original publication

[b] Median values provided in original publication

Does surgeon or hospital volume correlate with recurrence rate? Our search identified no studies that directly related recurrence rate of MNG to surgeon [26] or hospital [27] volume. Reports on the subject do suggest that surgeon and hospital volumes are directly related to the likelihood that a patient will undergo total thyroidectomy.

Does postoperative TSH suppression reduce recurrence rate? There has been much interest in the practice of postoperative TSH suppression in an effort to prevent, or delay, recurrence. Despite marked inconsistencies in the literature, supporters of this widely practiced therapy cite data that suggest it is the only available method in preventing MNG recurrence [28]. Opponents of this practice identify numerous weaknesses in the subset of studies that purport to demonstrate a benefit [29].

Unfortunately, the published studies vary methodologically: Some studies relied on physical exam to detect recurrences [30–34], whereas others used ultrasound evaluation [2, 28, 29, 35]. The studies that used ultrasound are further divided according to the authors' definition of a recurrence: Some [28, 29] looked at total remnant volume, whereas others [10] evaluated specific nodule characteristics. In addition, there is wide variation in the extent of thyroidectomy in the series reported, and many of the published studies are reports from endemic areas [10, 28, 36] where the impact of suppressive therapy may be different than in developed countries where iodine is supplemented.

Two studies used a combination of suppressive and substitutive doses of T4 [10, 36], none of the randomized trials were placebo controlled, and few [29] documented adequate suppression of TSH. Moreover, only four studies had more than 10 years of follow-up [29, 35, 37, 38], and many had 5 years or less [28, 33, 34]. Many studies that

Table 2 Studies on the association between extent of thyroidectomy for benign nodular goiter and postoperative complications

Reference	N	Level of evidence	Design	Initial operation	Definition of hypocalcemia	Routine DL?	Transient-permanent distinction	Transient hypocalcemia	Permanent hypocalcemia	Transient RLN injury	Permanent RLN injury
Colak et al. [20]	95	II	NRCT	NT	Sx	No	6 months	9 (9.5%)	0 (0.0%)	6 (6.3%)	0 (0.0%)
	105			TT				12 (11.4%)	1 (1.0%)	10 (9.5%)	1 (1.0%)
Delbridge et al. [73]	1838	III	Retro	NT	?	Yes		?	4 (0.2%)	?	4 (0.2%)
	1251			TT				?	5 (0.4%)	?	6 (0.5%)
Erbil et al. [21]	112	I	RCT	NT	Ca < 8 mg/L	Yes	3 months	11 (9.8%)[a]	0 (0.0%)	1 (0.9%)	0 (0.0%)
	104			TT				27 (26.0%)[a]	0 (0.0%)	1 (1.0%)	0 (0.0%)
Friguglietti et al. [22]	164	III	Retro	NT	Sx	No	2 months	4 (2.4%)[a]	2 (1.2%)	2 (1.2%)	1 (0.6%)
	563			TT				65 (11.5%)[a]	3 (0.5%)	15 (2.7%)	1 (0.2%)
Karanikolic et al. [79]	131	III	Retro	NT	Ca < 1.7 mmol/L, sx	Yes	6 months	7 (5.3%)	1 (0.8%)	5 (3.8%)	1 (0.8%)
	73			TT				16 (21.9%)	3 (4.1%)	5 (6.8%)	1 (1.4%)
Lang and Lo [75]	297	III	Retro	TT	Ca < 1.7 mmol/L, sx	Yes	1 year	54 (18.2%)[a]	4 (1.3%)	19 (6.4%)	4 (1.3%)
Liu et al. [23]	98	III	Retro	TT	Ca < 9 mg/L, sx	No	6 months	26 (26.5%)[a]	0 (0.0%)	2 (2.0%)	0 (0.0%)
Marchesi et al. [24]	24	III	Retro	NT	?	?		0 (0.0%)[a]	0 (0.0%)	1 (4.2%)	0 (0.0%)
	59			TT				13 (22.0%)[a]	0 (0.0%)	3 (5.1%)	0 (0.0%)
Pappalardo et al. [17]	72	I	RCT	NT	Ca < 2.1 mmol/L, sx	No	6 months	13 (18.1%)	1 (1.4%)	2 (2.8%)	1 (1.4%)
	69			TT				24 (34.8%)	2 (2.9%)	2 (2.9%)	0 (0.0%)
Reeve et al. [69]	738	III	Retro	NT	?	Yes		12 (1.6%)	2 (0.3%)	15 (2.0%)	1 (0.1%)
	115			TT				10 (8.7%)	0 (0.0%)	2 (1.7%)	0 (0.0%)
Rios et al. [71]	45	III	Retro	TT	Ca < 8.5 mg/L, sx	No	1 year	6 (13.3%)	1 (2.2%)	7 (15.6%)	0 (0.0%)
Zambudio et al. [76]	301	III	Retro	TT	Ca < 8.5 mg/L, sx	No	1 year	29 (9.6%)	2 (0.7%)	26 (8.6%)	1 (0.3%)
Serpell and Phan [77]	232	III	Retro	TT	Ca < 2.0 mmol/L, sx	No	6 months	33 (14.2%)	4 (1.7%)	?	0 (0.0%)

NRCT = prospective nonrandomized controlled trial; Retro = retrospective analysis; RCT = prospective randomized controlled trial; sx = symptoms; Ca = total serum calcium concentration; DL = direct laryngoscopy; ? = not stated

[a] Significant in original publication

critically evaluated factors that lead to recurrence of MNG cited mean times to recurrence of about 10 years, with a range of less than 1 year to more than 25 years [8]. Taken as a whole, these studies are split in their conclusions: About half conclude that postoperative TSH suppression is effective in reducing recurrences, while the other half state that it is not (Table 4).

To clarify the possible impact of TSH suppression on MNG recurrence, Subbiah et al. [37] recently reviewed their cohort of 632 patients with a history of radiation exposure in childhood who had benign nodules found at surgery. Of these, 226 (36%) had total or subtotal thyroidectomy, and the remainder had a lobectomy or nodulectomy. At a mean follow-up of 17.7 years, 129 patients (21%) developed a recurrence. Of the 424 patients (67%) who received suppressive doses of T4, 60 (14%) developed a recurrence, in contrast with 67 (34.2%) in the 196 patients who did not.

Discussion

Total thyroidectomy is the most effective operation for preventing recurrence of benign nodular goiters. To reduce the inherent bias of comparing total thyroidectomy's recurrence rate of essentially 0% [25, 37] to that of any other lesser procedure, we stratified the pooled operations into three groups: total thyroidectomy; subtotal thyroidectomy; and "limited" thyroidectomy, which encompassed all other resections that left a significant amount of thyroid tissue *in situ* (e.g., enucleation, lobectomy). As Table 2 shows, all resections other than total thyroidectomy are

Table 3 Studies on the association between redo thyroidectomy for benign nodular goiter and postoperative complications

Reference	N	Level of evidence	Design	Type of operation	Definition of hypocalcemia	Routine DL?	Transient-permanent distinction	Transient hypocalcemia	Permanent hypocalcemia	Transient RLN injury	Permanent RLN injury
Delbridge et al. [73]	3089	III	Retro	Initial	?	Yes	?	?	9 (0.3%)	?	10 (0.3%)
	205			Redo				?	0 (0.0%)	?	2 (1.0%)
Erbil et al. [60]	125	III	MCC	Initial	Ca < 8 mg/L, sx	No	2 months	4 (3.2%)[a]	0 (0.0%)	2 (1.6%)*	0 (0.0%)*
	125			Redo				22 (17.6%)[a]	1 (0.8%)	15 (12.0%)*	4 (3.2%)*
Friguglietti et al. [22]	563	III	Retro	Initial	Sx	No	2 months	65 (11.5%)	3 (0.5%)*	15 (2.7%)	1 (0.2%)*
	60			Redo				5 (8.3%)	5 (8.3%)*	3 (5.0%)	3 (5.0%)*
Gibelin et al. [19]	244	III	MCC	Initial	Ca < 2.0 mmol/L, sx	Yes	6 months	3 (1.2%)[a]	0 (0.0%)	14 (5.7%)	1 (0.4%)
	122			Redo				13 (10.7%)[a]	1 (0.8%)	15 (12.3%)	1 (0.8%)
Liu et al. [23]	98	III	Retro	Initial	Ca < 9 mg/L, sx	No	6 months	26 (26.5%)	0 (0.0%)	2 (2.0%)	0 (0.0%)
	8			Redo				2 (25.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
Menegaux et al. [74]	4126	III	Retro	Initial	Ca < 2.0 mmol/L, sx	No	2 months	42 (1.0%)[a]	9 (0.2%)*	21 (0.5%)*	25 (0.6%)*
	202			Redo				6 (3.0%)[a]	2 (1.0%)*	5 (2.5%)*	2 (1.0%)*
Muller et al. [2]	4571	III	Retro	Initial	?	No	?	132 (2.9%)	32 (0.7%)	146 (3.2%)*	32 (0.7%)*
	949			Redo				23 (2.4%)	5 (0.5%)	46 (4.8%)*	33 (3.5%)*
Pappalardo et al. [17]	141	I	RCT	Initial	Ca < 2.1 mmol/L, sx	No	6 months	37 (26.2%)	3 (2.1%)	4 (2.8%)	1 (0.7%)
	9			Redo				2 (22.2%)	2 (22.2%)	2 (22.2%)	1 (11.1%)
Rios et al. [71]	112	III	Retro	Initial	Ca < 8.5 mg/L, sx	No	1 year	18 (16.1%)	4 (3.6%)	20 (17.9%)	4 (3.6%)
	112			Redo				0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Snook et al. [25]	10	III	Retro	Redo	?	Yes	?	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

[a] Significant in original publication

Retro indicates retrospective analysis; MCC, matched case-control study; RCT, prospective randomized controlled trial; Ca, total serum calcium concentration; sx, symptoms

Table 4 Studies on the effect of postoperative TSH suppression on recurrence of benign nodular goiter

Reference	N	Level of evidence	Design	Endemic region?	TSH-suppressive therapy?	Mean follow-up (years)	Determination of recurrence	Recurrence
Miccoli et al. [10]	28	I	RCT	Yes	Yes	3.0	U/S	6 (21.4%)
	32				No			25 (78.1%)
Bistrup et al. [33]	40	I	RCT	No	Yes	9.0	H&P	5 (12.5%)
	60				No			11 (18.3%)
Feldkamp et al. [28]	55	II	RCT	Yes	Yes	1.0	U/S	3 (5.5%)
Hegedus et al. [29]	100	I	RCT	No	Yes	10.0	U/S	19 (19.0%)
	102				No			27 (26.5%)
Berglund et al. [78]	29	III	Retro	No	Yes	6.0	H&P	3 (10.3%)
	186				No			20 (10.8%)
Berghout et al. [32]	20	III	Retro	No	Yes	7.5	H&P	1 (5.0%)
	93				No			10 (10.8%)
Geerdsen et al. [31]	104	III	Retro	No	Yes	8.8	H&P	10 (9.6%)
	71				No			8 (11.3%)
Anderson et al. [35]	14	III	Retro	No	Yes	10.2	U/S	6 (42.9%)[a]
	171				No			9 (5.3%)[a]
Ibis et al. [36]	62	III	Retro	Yes	Yes	7.8	?	25 (40.3%)
	148				No			116 (78.4%)
Persson et al. [34]	121	III	Retro	No	Yes	5.0	H&P	8 (6.6%)
	76				No			3 (3.9%)
Banchuin et al. [30]	141	III	Retro	No	Yes	1.0	H&P	31 (22.0%)[a]
	73				No			5 (6.8%)[a]
Wadstrom et al. [38]	28	III	Retro	No	Yes	14.0	?	6 (21.4%)
	175				No			22 (12.6%)
Subbiah et al. [37]	426	III	Retro	No	Yes	17.7	U/S	60 (14.1%)
	196				No			27 (13.8%)

RCT = prospective randomized controlled trial; Retro = retrospective analysis; U/S = ultrasound; H&P = history and physical exam

[a] Significant in original publication

associated with anywhere from 2.5% to 42% recurrence, regardless of how much thyroid is actually left behind. Furthermore, these findings also suggest that an inadequate initial resection may be the most important predictor of recurrence.

TSH suppression of goiters

The practice of suppressive thyroid hormone supplementation is now over a century old [8]. The aim is to create a thyrotoxic state and minimize TSH release and is based on the knowledge of thyroid-stimulating hormone's trophic effects on follicular cells. This practice has been shown to lead to goiter regression in up to 85% of patients with diffuse goiter [39], and it is also considered to be the postoperative standard of care for differentiated malignancies of the thyroid gland.

TSH suppression is also very common for treatment of MNG. In surveys of American and European endocrinologists [40, 41], more than 40% state that they would use TSH suppression as the treatment of choice for MNG. TSH suppression for MNG was initially bolstered by several studies in the 1960s [42, 43] that supported its effectiveness. Subsequent studies demonstrated up to a 20–30% decrease in MNG size with thyroid suppression therapy in patients who had not undergone surgery [44, 45]. In regions of iodine deficiency, iodine supplementation has also been shown to effectively reduce thyroid nodule volume [46].

Enthusiasm for thyroid hormone suppression for benign disease, however, began to wane in the 1980s and 1990s because of reports that either contradicted [47] or did not confirm [46, 48] the initial supportive studies. Moreover, recent data that reported possible negative side effects of long-term exogenous thyroid hormone supplementation [49, 50] have rekindled interest in the effectiveness of suppressive therapy of multinodular goiter. Increased incidence of atrial fibrillation [51] and other arrhythmias [52] are well-recognized cardiovascular complications of thyrotoxicosis. The negative effects of TSH suppression on bone mineralization are also well recognized. One study

[53] showed that women with a low TSH level were three times more likely to sustain a hip fracture and four times more likely to sustain a vertebral fracture than euthyroid patients.

Although early studies of the utility of primary TSH suppression for nodular disease regression or improved course of disease reported conflicting results, later studies are far more unified in their conclusions: TSH suppression appears to be effective and can produce a clinically significant decrease in nodule size in a subset of patients (up to 40%) [15]. In two well-designed studies [15, 16], the average nodule size decreased by about one-third in response to TSH suppression. Nevertheless, because some nodules (average = 10%, range = 0–20%) demonstrate spontaneous regression, it is estimated that eight patients need to be treated in order to have one patient benefit [14]. As a result, we believe that most authors would agree that TSH suppression cannot be recommended for routine use, but may have a role in the management of certain, particularly high-risk, patients. This therapy should be monitored closely for patient response because unsupervised use would lead to many patients being treated unnecessarily.

Postoperative TSH suppression

Fewer studies have examined postoperative TSH suppression for decreasing the likelihood of goiter recurrence. Because of methodologic inconsistencies, these studies cannot be grouped and cannot be used to make practice recommendations. Moreover, the two best studies offer conflicting results: The best-designed prospective randomized study of the subject evaluated T4 vs. no treatment in 202 patients and demonstrated no treatment effect [29]. The most recent retrospective study, which had 17 years of follow-up data, found a significantly higher recurrence rate among 600 patients who did not receive postoperative thyroid hormone suppression.

The reasons why postoperative TSH suppressions fails to reduce the rate of recurrence are not entirely clear. Certainly the heterogeneity of the examined studies can account for much of the disparity in results. However, it is also increasingly evident that at least some thyroid nodules are autonomous and are no longer subject to the classical hypothalamus-pituitary-thyroid axis of hormonal regulation. This is supported by findings that nodules in recurrent goiters are predominantly polyclonal [54, 55] and may therefore be subject to multiple regulatory pathways. Moreover, nodules have been found to differentially express goitrogenic insulin-like growth factors (IGFs) and their binding proteins (IGFBPs) [7].

Two studies of postoperative TSH suppression contribute to our knowledge about this subject without directly addressing MNG recurrence: Rather, these authors used the degree of TSH suppression [56] and ultrasound measurements of remnant size [29] as surrogate endpoints. In their study of the impact of dose schedules, Goretzki et al. [56] compared the standard daily dose of 0.1 mg/day of L-thyroxine with a larger dose of 1.0 mg once a week. Sixty-four patients who underwent bilateral subtotal thyroidectomy were enrolled, and similar reduction of TSH was achieved in both groups. In another study, Hegedus et al. [57] randomized 110 consecutive patients to receive T4 or no treatment; they found that the average remnant size decreased by a similar amount (−11 vs. −15%) at 12 months.

Another study that used thyroid remnant size as its primary endpoint was conducted in an endemic area [58]. In this study, 139 patients who underwent partial thyroidectomy were randomized to receive T4 alone or T4 with supplemental iodine. The average decrease in remnant volume with T4 was −10%, and in the study group this was augmented significantly when dietary iodine was added (−39.7%). Although the quantitative effect of TSH suppression is similar to that demonstrated by Hegedus et al. [29], both groups in this study exhibited wide ranges of variance (+85% to –89% for T4 alone, +91% to −89% for the iodine + T4 group).

Other variables influencing risk of recurrence of multinodular goiter

Some variables other than extent of initial operation and TSH suppression have been traditionally accepted risk factors for goiter recurrence; those most commonly mentioned include a positive family history, young age at presentation, bilateral disease, and multinodular vs. single nodules [18, 19, 27, 32, 59]. The most recent efforts to elucidate their significance have come from a small number of univariate and multivariate analyses by various European investigators on their respective patient populations [18, 19, 59]. The first of these, by Gibelin et al., was a retrospective case-control study comparing 244 patients with and without recurrence after initial thyroidectomy. They found that younger age and multinodularity were significant risk factors ($p < 0.0001$ and $p = 0.005$, respectively), whereas positive family history and bilateral disease showed only a trend toward predicting recurrence ($p = 0.07$ and $p = 0.09$, respectively) [19]. This was followed by another univariate analysis in Turkey that appeared to confirm the increased risk of younger age ($p < 0.001$) and multinodularity (no statistics presented), but not of positive family history ($p > 0.05$) [60]. One criticism of both studies is that neither utilized more robust multivariate statistics, thus potentially confounding their results. This weakness was partially addressed by Bellantone et al. [18], who retrospectively reviewed 268 patients

in Italy who had undergone lobectomy for unilateral nodular goiter. Multivariate analysis found that female gender was an independent risk factor for recurrence ($p = 0.016$), weight of the initial surgical specimen was an independent risk factor for reoperation ($p < 0.0001$), and multinodularity and lack of postoperative TSH suppression increased the risk for both ($p = 0.017$ and 0.0009 for recurrence, and 0.008 and 0.0005 for reoperation, respectively) [18]. Of note, age was found not to be an independent risk factor for recurrence in this study, and the impact of a positive family history was not studied.

While there is a significant body of literature regarding patient-related and medical therapy-related predictors of MNG recurrence, the evidence is insufficient to make preventive recommendations. Nevertheless, regardless of the mechanism, all discussions of goiter recurrence assume that the initial surgeon had left a remnant of thyroid tissue, however small, that would grow over time and cause clinically recurrent disease. In practice, however, even what were initially considered "total" thyroidectomies appear to lead to occasional recurrences that require reoperation. A recent study by Snook et al. [25] retrospectively examined a series of over 3000 consecutive total thyroidectomies performed at the University of Sydney and identified a small subset of patients who subsequently developed recurrent benign multinodular goiter requiring surgery. The investigators found that most (8/10) of these recurrences were due to inadequate resection of embryologic remnant thyroid tissue along the thyrothymic or pyramidal tract. Interestingly, the importance of complete removal of the pyramidal lobe was first emphasized 50 years ago [61] and reiterated by Makeieff [62]. Snook et al. [25] concluded that total thyroidectomy, with careful attention to identifying and removing the entire thyroid gland along its embryologic descent, should effectively abolish benign goiter recurrence.

Total thyroidectomy is generally agreed to be more effective than lesser resections for the prevention of goiter recurrence. However, is it associated with increased perioperative morbidity? Despite the potential for greater morbidity with the more extensive dissection required for total thyroidectomy, our review suggests that this is not the case. In fact, frequency of temporary and permanent vocal cord dysfunction is identical after total thyroidectomy and after lesser operations. While rates of temporary hypocalcemia are slightly higher after total thyroidectomy than they are for lesser operations, the frequency of permanent hypoparathyroidism is not different. Equally important is the evidence that reoperations for recurrent goiters have significantly higher rates of permanent vocal cord dysfunction and hypoparathyroidism than initial operations (Table 3), which further bolsters the assertion that total thyroidectomy should be the operation of choice for multinodular goiter.

Our institutional practice

As is increasingly the practice worldwide, our tendency at the University of California, San Francisco, is to perform total thyroidectomy for most patients with MNG who require a resection. Occasionally, a patient at high risk for RLN injury will present with ultrasound evidence of unilateral disease, i.e., one dominant nodule or multiple unilateral nodules with a homogeneous-appearing small contralateral lobe. In this situation, we have considered (and have performed) total lobectomy on the affected side. Similarly, when performing a total thyroidectomy for MNG, surgeons may be unsatisfied with the progress of the operation for one reason or another. If a surgeon suspects involvement of the RLN or has failed to identify the RLN, he or she may contemplate ending the procedure at a lobectomy. The primary reason for this staged approach is to avoid bilateral injury to the RLNs and the need for tracheostomy. This way, the tissue planes around the contralateral lobe remain undisturbed, and a completion thyroidectomy may be performed safely after vocal-cord function is evaluated laryngoscopically.

Recurrent goiters often present with local symptoms such as airway obstruction, superior vena cava syndrome, dysphagia, or dysphonia. Surgery is indicated when any of these symptoms is present and whenever the presence of a malignancy cannot be definitively excluded. In high-risk patients, such as those with a prior history of radiation exposure, nodularity in the thyroid gland is associated with a 40% chance of malignancy, which may not necessarily be within the suspicious nodule. In addition, any nodule that grows rapidly should be resected.

Intrathoracic goiters constitute another category of recurrence, and we believe almost all (even if asymptomatic) mandate reoperation, although the discussion of intrathoracic goiters is beyond the scope of this review. Finally, a patient's desire for resection, for cosmetic or other reasons, may be an indication for some reoperations.

When a recurrent MNG is being resected, bilateral RLN injury must be avoided. All patients who require reoperation should undergo preoperative laryngoscopic evaluation, since as many as 20% may have existing permanent RLN palsy [9] and up to 32% of these are known to be asymptomatic [63]. In patients at high risk for postoperative complications, we have staged the resection of bilateral recurrences. Recently, we have been increasingly using RLN monitoring for this situation. Starting the resection on the symptomatic side, the contalateral lobe is resected only after the nerve and parathyroid glands are identified and preserved. Otherwise, the operation is terminated with the patient's symptoms addressed.

Several practical considerations that must be mentioned include the paramount importance of intimate familiarity

with normal anatomy and common variants. While the RLN most commonly lies within the tracheoesophageal groove, in approximately one-third of cases the nerve is lateral to the trachea, and in approximately 1% the nerve is anterior to the trachea [64]. Moreover, while many consider the planes anterior to the inferior thyroid artery as safe, this relationship is also variable: Surgical [64] studies and autopsy [65] studies demonstrate that approximately one-third of RLNs are found either anterior to or interdigitating with branches of the inferior thyroid artery. These relationships are even further obscured when there is scarring from a previous operation.

Reoperations for multinodular goiter

Some experts advocate the lateral approach to reoperations on the thyroid gland [2, 9]. In this method, the patient's old Kocher incision is either reopened or excised, a subplatysmal plane is elevated, and the strap muscles are identified. Rather than reopening the median raphe, however, the straps are retracted medially and a plane anterior to the sternocleidomastoid is entered. In many cases, this approach obviates the need to dissect through scar tissue anteriorly, but the risk to the RLN does not change if the nerve is surrounded by adhesions. In fact, one series demonstrated a slightly higher frequency of RLN paresis in patients who had reoperations via the lateral approach. This higher frequency may be due to the differences in the appearance of the surgical field through this approach and relative unfamiliarity of this view.

There is consensus that regardless of the approach used, the best method to preserve vocal cord function is to identify the RLN early in the operation, before dividing any structures. In the classic study by Dralle et al. [66], rates of RLN injury were inversely related to the effort made to identify the nerve. In this large study, the subgroup of patients with the highest risk for postoperative vocal cord paresis were those undergoing reoperative surgery.

Recently, much attention has been paid to the relationship between outcomes and surgeon and hospital volumes. A cross-sectional study [26] in Maryland found that although the highest-volume surgeons accounted for only 0.6% of all surgeons in the state, they performed the highest percentage of total thyroidectomies. Moreover, this subset of surgeons also had the fewest complications and their patients had the shortest length of stay in the hospital. Unlike surgeon experience, hospital volume had no impact on complications or length of stay. A prospective multicenter study in Germany evaluated the impact of hospital volume on outcomes [27]. It found no relationship between hospital volume and complications, but it concluded that high-volume centers performed significantly more total lobectomies and thyroidectomies than lower-volume centers. While neither study had adequate follow-up to comment on its recurrence rates, it follows that the patients who undergo subtotal resection are at greater risk for recurrence.

Limitations of this review

One of the limitations of this review is that most of the studies we found were retrospective analyses, which generally offer a lower level of evidence than prospective randomized studies. Another limitation was our exclusion of articles in journals published in languages other than English, which could have missed studies on goiter recurrence. Excluding such studies could potentially be even more relevant since most regions with endemic goiter are primarily non-English-speaking. Finally, the heterogeneous way important variables like goiter recurrence, length of follow-up, and hypocalcemia were defined prevented us from performing pooled statistical analyses.

Conclusion

Medical management with TSH suppression as primary treatment does not halt the progression of MNG in a significant number of patients. Furthermore, there is insufficient evidence to support the claim that postoperative TSH suppression decreases the rate of goiter recurrence. Therefore, the definitive management for prevention of recurrence of benign nodular goiter is primarily surgical. Total thyroidectomy essentially eliminates the risk of recurrence, without an accompanying increased risk of permanent hypoparathyroidism or RLN injury. Therefore, total thyroidectomy should be considered the procedure of choice for benign MNG whenever possible, especially considering that reoperations for goiter are significantly more morbid than any initial operation.

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