



Unilateral benign multinodular versus solitary goiter: Long-term contralateral reoperation rates after lobectomy[☆]



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ARTICLE INFO

Article history:

Accepted 17 April 2018

Available online 8 November 2018

ABSTRACT

Background: Few long-term studies define the appropriate extent of surgery and recurrence rates for unilateral multinodular goiter. We compared the rate and time to reoperation in patients with multinodular goiter who underwent lobectomy to that of patients with benign solitary nodule.

Methods: Retrospective study of a prospective database of all patients who underwent lobectomy for multinodular goiter or solitary nodule from 1991 to 2017. We analyzed reoperation rates and time to reoperation. Reoperation was defined as the need for completion thyroidectomy determined the following criteria: nodule greater than 3 cm, multiple nodules, nodule growth or suspicion for malignancy by ultrasound or fine-needle aspiration biopsy, or compressive symptoms.

Results: Included in the study were 2,675 lobectomies; 852 (31.85%) for multinodular goiter. In total, 394 patients (14.7%) underwent reoperation: 261 (30.6%) with a previous multinodular goiter and 133 (7.29%) with solitary nodule ($P < .0001$). A total of 80% of the patients with multinodular goiter and 67.66% with solitary nodule recurred as multinodular goiter; 3.5% of all recurrences were carcinomas. The mean time to reoperation was 14.8 years, without difference between groups ($P = .5765$). Patients without reoperation were younger (47 ± 15 vs 54 ± 13 years of age, $P < .0001$) and more likely to be male ($P < .0001$).

Conclusion: Lobectomy for unilateral multinodular goiter is the procedure of choice given the length of time to reoperation. Patients and surgeons should be aware of the need for long-term surveillance.

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Introduction

Benign multinodular goiter (MNG) refers to an enlarged thyroid gland with nodules within it, frequently owing to iodine deficiency. It is the most common endocrine disorder worldwide. It can affect the thyroid gland diffusely (bilateral MNG), or it can be restricted to a single lobe (unilateral MNG). MNG becomes symptomatic when compressive symptoms develop, such as dysphagia, dyspnea, or vascular compression of the neck vessels. Surgery for MNG is indicated for several reasons, including the development of compressive symptoms, suspicion of malignancy by ultrasound (US) or fine-needle aspiration biopsy (FNAB), association with hyperthyroidism, or because of patient preference.

Although much has been written about the appropriate extent of thyroid surgery for bilateral MNG, controversy remains centered around the discussion of recurrence rates and safety of total or near-total thyroidectomy versus subtotal thyroidectomy or Dunhill's procedure.^{1–11} A total of 4 randomized controlled trials and a meta-analysis concluded that total thyroidectomy (TT) is the procedure of choice for bilateral MNG because of the almost negligible recurrence rates and high safety profile in experienced hands at high-volume centers.^{1,9,10,12,13}

Controversy regarding the procedure of choice for unilateral MNG still remains. Thyroid lobectomy (hemithyroidectomy plus isthmusectomy) is regarded by some authors as the procedure of choice because of its lower morbidity, low need for thyroxine supplementation, and low rate of short-term recurrence.^{14–19} However, there are few long-term studies describing the recurrence rates after a lobectomy for unilateral MNG.^{14,17,18,20}

The aim of this study was to evaluate the rate and time to reoperation at long-term follow-up of patients with initial unilateral MNG versus a benign solitary nodule (SN) who underwent a lobectomy.

[☆] Presented at the 2018 American Association of Endocrine Surgeons 39th annual meeting, Durham, North Carolina, May 6–8, 2018.

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Materials and methods

We conducted a retrospective study of a prospectively maintained database of consecutive patients who underwent thyroid surgery from January 1991 to January 2017 at our institution (a tertiary referral hospital with an endocrine surgery unit performing over 500 thyroid procedures per year). All patients who underwent a lobectomy for benign MNG or benign SN were included in the study. In all cases both the initial and reoperative procedure had been performed at our institution, and all operations were performed by or under direct supervision of a senior endocrine surgeon (J.L.K.). Lobectomy was defined as a hemithyroidectomy plus isthmusectomy with preservation of the contralateral lobe. Intraoperative nerve monitoring was used in all reoperative cases. Fiber-optic flexible laryngoscopy and serum calcium levels are routinely performed in all patients on the first postoperative day. We analyzed patient records for age, sex, histopathology of the surgical specimen for benign versus malignant pathology, recurrence rates of nodular disease and time to recurrence, and immediate complications. We excluded duplicate records, patients who had undergone subtotal thyroidectomy or isthmusectomy, patients with Graves' disease, final pathology reports of cancer after the first surgery, concomitant neck dissections, absence of records for preoperative US, and an absence of recorded operative findings. The primary outcome was the number of patients who underwent a completion contralateral lobectomy. The secondary outcome was the time to clinically significant progression requiring reoperation.

Patients who initially underwent a lobectomy for benign thyroid pathology had unilateral nodular thyroid disease and no nodules on the contralateral lobe, confirmed by preoperative US. All patients received long-term postoperative follow-up from their primary care physician with annual physical examination or neck US and TSH at their doctor's discretion. In cases where the primary care physician determined that clinically significant recurrence had occurred, the patient was referred back to our institution for evaluation by an endocrine surgeon. Recurrence requiring completion thyroidectomy was defined by the endocrine surgeons as a clinically significant disease in the remnant lobe^{15–17,21}: a nodule greater than 3 cm, multiple nodules, nodule growth on consecutive US per American Thyroid Association (ATA) guidelines at the time of surgery (20% increase in at least 2 nodule dimensions with a minimal increase of 2 mm or a more than 50% increase in volume),²¹ suspicious nodule by US or FNAB per ATA guidelines at the time of surgery, compressive symptoms, or patient preference.

Quantitative data were expressed as mean $\pm$ standard deviation or median (interquartile range). Qualitative variables were given as number (percentage) of patients. Comparisons were conducted using *t*-test or Wilcoxon test for respectively normally and

Table 1
Characteristics of patients with and without reoperation.

Characteristic	Reoperation <i>n</i> = 394	No reoperation <i>n</i> = 2,281	<i>P</i> value
Male	39 (10%)	484 (21%)	<.0001
Age (yrs)	54 $\pm$ 13	47 $\pm$ 15	<.0001

non-normally distributed continuous variables. Comparisons for categorical variables were performed with a χ^2 test. Kaplan-Meier curves were generated to assess recurrence-free survival.

Results

Between January 1991 and January 2017, a total of 11,013 thyroid surgeries were performed at our institution; of these, 3,231 were lobectomies for benign thyroid pathology. A total of 2,675 lobectomies were included in the study: 852 (31.85%) for unilateral MNG and 1,823 (68.15%) for SN. A clinically significant recurrence requiring completion thyroidectomy was present in a total of 394 patients (15%). Of these reoperations, 261 (30.60%) were in patients with a previous MNG and 133 (7.29%) were in patients with a previous SN ($P < .0001$, Fig. 1). Of the patients with MNG, 80% ($n = 208$) recurred as an MNG and only 20% as an SN. Similarly, of the patients with an SN, 67.66% ($n = 90$) recurred as an MNG and only 32.33% as an SN (Fig. 1). Of all the patients that presented with a recurrence requiring reoperation, only 3.5% had a thyroid carcinoma in the final histopathological analysis of the surgical specimen.

The mean time to reoperation for the population studied was 178 months (14.8 years), with a mean follow-up time of 173.8 months (14.48 years, range 1 to 26 years). There was no difference in mean time to reoperation for patients with MNG versus SN ($P = .5765$; mean [interquartile range]: 170 [146] vs 182 [146]). However, the patients with an initial diagnosis of unilateral MNG had a shorter time to reoperation ($P < .0001$; Fig. 2).

There were some statistically significant differences of note between the patients without recurrence and those with recurrence requiring completion thyroidectomy. Patients without reoperation were younger (47 ± 15 vs 54 ± 13 years of age; $P < .0001$); given that the mean time to reoperation was 14.8 years, this indicates that patients with recurrence requiring completion surgery were younger at the time of the first surgery. Also, male patients were less likely to present with a recurrence ($P < .0001$; Table 1).

The complication rates are summarized in Table 2. There was a greater incidence of hypoparathyroidism (13% vs 0.61%) and hypothyroidism (3.5% vs 100%) at the 1-month follow-up in the completion thyroidectomy group ($P < .0001$). All other complication rates were similar in both groups. Because long-term follow-up

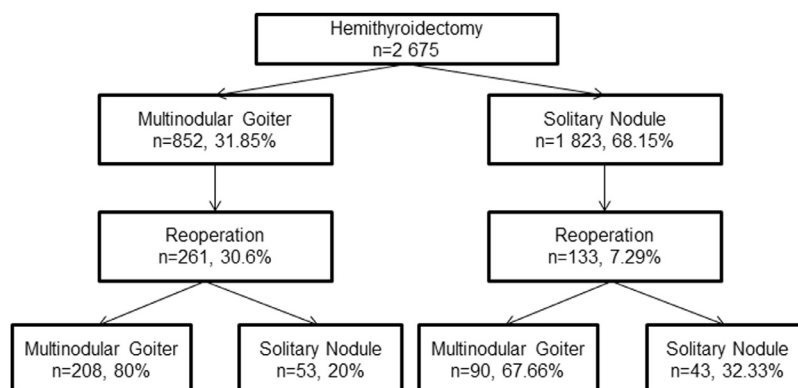


Fig. 1. Patient distribution. In the population studied, there were 394 recurrences (15%); there is a statistically significant difference in the rate of reoperation between patients with unilateral multinodular goiter ($n = 261$, 30.6%) and patients with SN ($n = 133$, 7.29%; $P < .0001$).

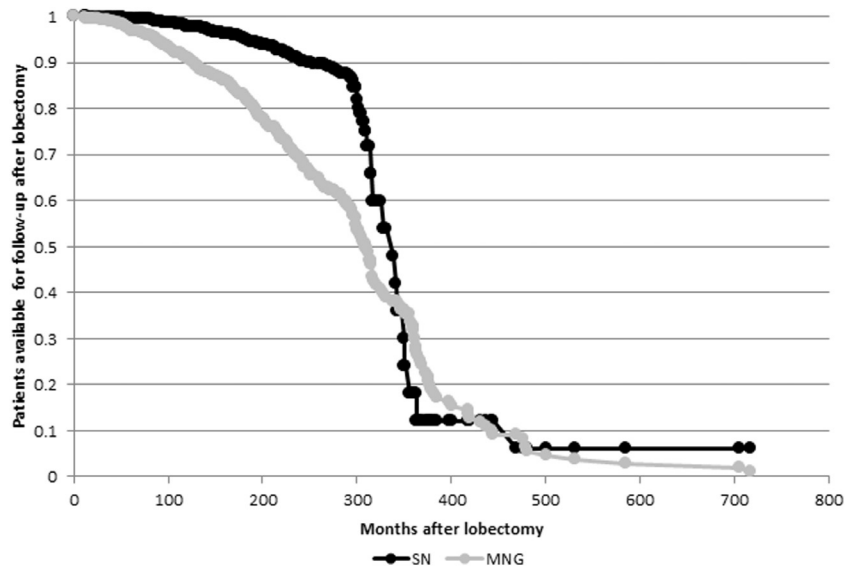


Fig. 2. Kaplan-Meier estimate of time to reoperation after lobectomy for multinodular goiter (MNG) versus solitary nodule (SN). The mean time to reoperation was 178 months (14.8 years); there is a statistically significant difference between the time to reoperation between patients with unilateral MNG and patients with SN ($P < .0001$).

Table 2
Complication rates in hemithyroidectomy versus completion thyroidectomy.

Complication	Hemithyroidectomy (<i>n</i> = 2,281)	Completion thyroidectomy (<i>n</i> = 394)	<i>P</i> value
Hypothyroidism	3.50%	100%	<.0001
Hypoparathyroidism	0.61%	13.03%	<.0001
Compressive hematoma	0.70%	0.75%	.7553
Unilateral RLN injury	4.90%	4.26%	.5713

RLN =

is provided by the patient's primary care physician, we have no records for transient versus temporary hypoparathyroidism and recurrent laryngeal nerve injury.

Discussion

It is generally believed that the pathological process of MNG involves the whole thyroid gland, therefore MNG is a known risk factor for recurrence after an incomplete thyroid surgery. This is supported by the results in our study where 80% of the recurrences of MNG and 68% of the recurrences of SN recurred as MNG in the remaining thyroid lobe. However, it is difficult to justify a TT over a lobectomy if the contralateral thyroid lobe has a completely normal appearance preoperatively on US because of the increased risk of complications accompanying bilateral surgery. The surgical procedure of choice for the treatment of MNG remains controversial, especially in patients with proven unilateral disease. In recent years, TT has become the standard of care for MNG in many centers because of its negligible recurrence rate and low complication rate when performed by experts.^{1,9,10,12,13} However, there are very few studies with long-term data defining the appropriate extent of surgery in patients with confirmed unilateral MNG.^{14,17,18,20}

Although this is a retrospective study with its inherent limitations (patients lost to follow-up, incomplete patient records), it is unique in the number of patients analyzed, the long-term follow-up, and the description of a cohort of truly unilateral MNG confirmed by preoperative US. It represents 1 of the few studies with long-term surveillance and a large number of patients with unilateral benign nontoxic nodular thyroid disease.

Previous authors have reported recurrence rates of 11% to 55% after surgery for unilateral MNG,^{14,17,18,20} with a reoperation rate

of 7.4% to 11%^{14,17,18} at a mean of 5 to 12 years follow-up. It is difficult to analyze this data because different authors have used varying criteria to define asymmetric MNG: some authors have defined it by negative palpation of the contralateral lobe during surgery,¹⁷ whereas others have accepted micronodular disease by US in the contralateral lobe,¹⁴ yet others used strict preoperative ultrasonographic criteria of absence of nodular disease in the contralateral lobe.^{18,20} There has also been discrepancy in defining a recurrence, be it entirely new nodules, the growth of a remnant on follow-up US,^{14,18,20} or the appearance of clinically significant disease with symptoms that require reoperation.¹⁷ All of our patients had a preoperative US confirming unilateral nodular disease, with no nodular disease in the contralateral lobe. Our mean time to clinically significant recurrence requiring completion thyroidectomy was 14.8 years, with a reoperation rate of 30.6% for patients with MNG and 7.3% for patients with SN. Because long-term follow-up is provided by the patients' primary care physician, it is possible to have lost patients in the cohort. However, the health care system in our country always refers back to the same institution as long as the patient does not migrate from the region. It is important to highlight that this study has the largest number of patients in the published literature, with a total of 2,675 patients of which 852 had MNG.

When considering a lobectomy versus a TT, it is important to correctly justify a TT, because the complication rates can significantly affect the patient's quality of life, although the rates of TT performed by experts are low. The complications affecting quality of life after TT are temporary recurrent laryngeal nerve injury in 1.9% to 8%,^{4,5,8,21,22} permanent recurrent laryngeal nerve injury in 0% to 3%,^{4,6–8,21,22} bilateral recurrent laryngeal nerve injury of 0.4%, transient hypoparathyroidism in 13% to 30%,^{2–4,7,21} and permanent hypoparathyroidism in 0.1% to 20%.^{4,6–8,14,21} In patients undergoing a thyroid lobectomy there is no risk of permanent hypoparathyroidism or bilateral recurrent laryngeal nerve injury.^{15,17} In our population there was no significant difference in complication rates between patients undergoing hemithyroidectomy or completion thyroidectomy with respect to compressive hematoma (0.70% vs 0.75%) or unilateral recurrent laryngeal nerve injury (4.90% vs 4.26%). There was a greater rate of hypoparathyroidism after completion of thyroidectomy versus hemithyroidectomy (13.03% vs 0.61%). Unfortunately, it was not possible to determine transient versus permanent rates of recurrent laryngeal nerve

injury or hypoparathyroidism given that long-term follow-up is provided by the patients' primary care physician and not our endocrine surgery department. However, our group previously published the morbidity associated with reoperative surgery for recurrent benign nodular goiter, with an incidence of transient and permanent RLN paralysis of 6.18% and 0.77%, respectively, and transient and permanent hypoparathyroidism of 13.5% and 1.54% after completion of thyroidectomy or hemithyroidectomy.²³ This is in accordance with Olson et al who demonstrated that patients who underwent reoperation did not have higher complication rates than in the initial surgery.¹⁷ For this reason it is important to confirm unilateral disease by preoperative US to avoid dissecting the contralateral lobe to confirm absence of nodules during the initial procedure. Therefore, although the recurrence rates for MNG are 30%, 70% of all patients would require no further surgery. If surgery for recurrence is required, the operation can be performed with no significant increase in morbidity, with one analysis showing no symptomatic hypocalcemia, permanent hypoparathyroidism, or bilateral recurrent laryngeal nerve injury in these patients.¹⁷ Also, given that the patients with recurrence in our study presented at a mean of 14.8 years after the initial operation, it is difficult to justify an initial TT exposing them to the potential quality-of-life altering complications when they could remain disease free for a long period of time.

The requirement for supplemental postoperative hormone therapy is also a factor to be considered when evaluating the extent of initial surgery. The rate of hypothyroidism requiring supplemental hormone therapy in patients with a lobectomy for benign disease ranges from 8% to 30%.^{14,15,20} Thus, at least two-thirds of previously euthyroid patients subjected to a thyroid lobectomy will not require hormone supplementation compared with 100% of the patients who undergo TT.

In our study, patients with no recurrence were older than people with recurrence, which is in keeping with the observation that young age at first operation (less than 45 years) is a major risk factor for goiter recurrence.¹⁴ We also found that male sex was a protective factor for recurrence. This may be due to the influence of hormonal factors in the development of thyroid nodules, but additional studies would be needed to test this hypothesis.

In other studies the rate of incidental thyroid cancer in patients with MNG has been cited as 5% to 16.6%.^{2,4,5,7,8,10,24,25} This incidence has been used to justify performing a TT in patients with MNG. In our study the rate of thyroid cancer in recurrences was 3.5%, which is less than that reported in other studies and the incidence of 7% to 15% of cancer in thyroid nodules reported by the ATA.²¹ With a careful follow-up of patients with neck US and FNAB of suspicious nodules, performing a lobectomy does not put patients at an increased risk of invasive thyroid cancer, which would justify a TT.

The rate of reoperation for recurrent MNG is 30% at almost 15 years; the complication rate for completion surgery is not significantly different from the initial procedure, and TT has a greater complication rate than thyroid lobectomy because of the greater extent of surgery. Therefore, a lobectomy with close long-term clinical and US surveillance should be considered the procedure of choice in patients with unilateral MNG.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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Discussion



Dr Mira Milas (Phoenix, AZ): Thank you for a very well-conducted long-term study and a review of a lot of patients.

My question relates to the role of ultrasound during the long time period of patients included in your study which started, if I remember correctly, in 1991 when ultrasound really was not part of routine decision making. I am curious whether you analyzed subsets of your patient population in time brackets when ultrasound was or was not part of decision making, the implication being that in the era where ultrasound was able to detect the presence of multiple nodules in the contralateral lobe, whether that may have changed the outcomes that you saw in the earlier cohorts.

Dr Beatriz de Rienzo-Madero: Unfortunately, there was no way for us to analyze when all patients got an ultrasound or at what point patients that had a palpable nodule underwent an ultrasound. However, all patients that went to surgery got an ultrasound, and we confirmed that the contralateral lobe was completely clean before they had a lobectomy.

Dr Mira Milas (Phoenix, AZ): So all of the patients by virtue of inclusion had a preoperative ultrasound and no nodules in that contralateral lobe?

Dr Beatriz de Rienzo-Madero: That's correct.

Dr Tricia Moo-Young (Evanston, IL): Great talk about a very relevant topic. This is a challenge that I think myself and a lot of people in this room deal with when we are trying to educate our patients about the best choice of operation.

Did you track family history? If there were prior family members that had goiters, maybe bilateral disease, even if your patients presented with unilateral disease, was that taken into account in the study in terms of the influence of potential reoperation?

Based on your conclusions, how would you counsel a patient who presented with a unilateral nodule in terms of their options of choosing a total versus a lobectomy? Because I think a lot of us recognize that patients play a lot into this in terms of their willingness to do follow-up ultrasounds versus wanting to choose to go onto medications to avoid follow-up.

Dr Beatriz de Rienzo-Madero: It is an important factor to look into family history and patient history. We tried to capture this. However, not all the patient records were complete, so we didn't have enough information from all the patient records to be able to do a sub-analysis on that.

In terms of your second question, I think it's important to present the patient with both options, and then take into account if they have family history or how willing they are to undergo follow-up with consecutive ultrasounds and clinic visits, and with this, counsel the patient and arrive at a decision.

Dr Shelby Holt (Dallas, TX): I'm curious about how if the contralateral lobe was sonographically normal and you had benign pathology on the side of the lobectomy, why the recommendation for follow-up ultrasounds? The more that you ultrasound these patients, the higher the rate of completion thyroidectomy. They are going to grow very weary of surveillance. So I'm curious if you didn't follow these patients with ultrasound at all, how would that have affected your reoperation rate?

Dr Beatriz de Rienzo-Madero: Actually, in our group, all patients after surgery go back to their primary care physician, and the follow-up is pretty much up to them. They usually watch out for any change in physical exam or new compressive symptoms. If they consider that it's needed, they'll do a follow-up ultrasound, and then refer them back to our institution when necessary.

Dr Sareh Parangi (Boston, MA): Thanks for this very useful presentation. For me in my practice, this is probably 1 of the most common questions patients ask me: What are the chance I'll need to come back for surgery? And based on the literature, I have been approximating 20%, so I am glad that my numbers match your big study.

Do you think the solitary nodules were really adenomas? Actual tumors as opposed to colloid goiter? Currently we may be picking those up with RAS mutations. Did you notice a pattern in your analysis?

Dr Beatriz de Rienzo-Madero: We wanted to use a solitary nodule group to be able to compare against. To be included in the study, all of these had to have a final benign diagnosis by pathology. So all of the solitary nodules that were included in the study were benign adenomas in the end.

About 70% of these recurred as a multinodular goiter and then had to undergo reoperation because of symptoms or greater nodule size. But I do believe that with the new ultrasound characteristics and molecular testing, that the number of patients that are undergoing surgery for solitary nodules will go down.