Journal of Endocrinological Investigation

Thyroid nodule recurrence following lobo-isthmectomy: incidence, patients characteristics, and risk factors

--Manuscript Draft--

Manuscript Number:	JENI-D-18-00163R2
Full Title:	Thyroid nodule recurrence following lobo-isthmectomy: incidence, patients characteristics, and risk factors
Article Type:	Original Article
Funding Information:	
Abstract:	Purpose: This study was aimed at assessing the incidence and timing of thyroid nodules recurrence, defined as appearance of new benign or malignant nodules in contralateral lobe in patients with unilateral benign thyroid nodules or thyroid microcarcinoma treated with lobo-isthmectomy. Patient's characteristics and risk factors associated with this phenomenon were also investigated. Methods: A retrospective study was performed by evaluating 413 patients undergoing lobo-isthmectomy with a minimum follow-up of 1 year. Clinical characteristics, surgical interventions and complications, histological diagnosis,thyroid function at last follow up were collected. Results: Single or multiple thyroid nodule recurrence equally occurred in 80 patients (23%) with a median time to relapse of ~5 years (range 0.3-34.5 years) after lobo-isthmectomy. Recurrence was significantly associated with younger age (<46 yrs), family history of nodular goiter, and number of pregnancies in women. Development of hypothyroidism was not rare either (~10%) and appeared in 3 to 19 months; a preoperative TSH level >2.43mIU/L was associated with the need of l-thyroxin replacement therapy after surgery. The most frequent surgical complication was transient hypoparathyroidism (4.6%), while the rate of permanent hypoparathyroidismsignificantly increased in patients submitted to CT (5.3%). Conclusions: Thyroid nodules recurrence following lobo-isthmectomy is not a rare event and occurs within 5 years after surgery, more frequently in younger patients with family history of nodular goiter and in women with multiple pregnancies. Pre-surgical TSH levels may predict the development of post-surgical hypothyroidism, possibly improving the management of patients addressed to surgery.
Corresponding Author:	Maria Chiara Zatelli, M.D. Universita degli Studi di Ferrara ITALY
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Universita degli Studi di Ferrara
Corresponding Author's Secondary Institution:	
First Author:	Maria Chiara Zatelli, Dr.
First Author Secondary Information:	
Order of Authors:	Maria Chiara Zatelli, Dr.
	Livia Lamartina
	Domenico Meringolo
	Emanuela Arvat
	Luca Damiani
	Giorgio Grani
	Alice Nervo
	Cosimo Durante

	Laura Giacomelli
Order of Authors Secondary Information:	
Author Comments:	Dear Editor we submit a further revision of our multicenter study investigating thyroid nodule recurrence. We tried to address all the issues raised by the Reviewer and believe that the manuscript improved. We believe this manuscript may be of interest to the readers of the Journal of Endocrinological Investigation. Best regards Maria Chiara Zatelli
Response to Reviewers:	Dear Editor We thank you for the opportunity to revise our manuscript and thank the Reviewer for the accurate re-evaluation of the manuscript and the constructive comments, which we try and address as follows: 1)the Reviewer indicates that in the conclusion we reported that young age, pregnancy and familial history are predictor factors for recurrent thyroid nodules. Indeed, family history did not reach statistically significant association with recurrences in both uni and multivariate analysis. Therefore, in keeping with the reviewer suggestion, we modified the conclusions by removing the indication of family history as a predictive factor of nodule recurrence. The sentence has been modified as follows (lines 268 – 270): “In conclusion, our study shows that thyroid nodule recurrence following lobo-isthmectomy is a frequent event, involving more closely younger patients and women with multiple pregnancies.” 2)the Reviewer underlines that the identified TSH cut-off has a good PPV but very low NPV and sensitivity, indicating that in patients with TSH above the cut-off the probability to have normal thyroid function after lobectomy is only 40% and, consequently, more than half of patients will develop hypothyroidism after lobectomy. We agree with the reviewer and we added this consideration in the Discussion section as follows (lines 256 - 260): “In addition, the low NPV and sensitivity of the identified TSH cut-off indicates that in patients with TSH above the cut-off before surgery the probability to have normal thyroid function after lobo-isthmectomy is only 40% and consequently, more than half of patients will develop hypothyroidism after lobectomy. Therefore, our results indicate that thyroid function monitoring is mandatory in patients submitted to lobo-isthmectomy.” In addition, as indicated by the Reviewer, we reviewed our conclusions as follows (lines 270 – 272): “Pre-surgical TSH levels may predict the development of post-surgical hypothyroidism, possibly improving the management of patients addressed to surgery by monitoring post-surgical thyroid function.”
Suggested Reviewers:	Luciano Pezzullo l.pezzullo@istitutotumori.na.it Expert surgeon in the thyroid field.
	Giuseppe Costante giuseppe.costante@bordet.be Expert Endocrinologist in the thyroid field

Thyroid nodule recurrence following lobo-isthmectomy: incidence, patients characteristics, and risk factors

Maria Chiara Zatelli[1], Livia Lamartina[2], Domenico Meringolo[3], Emanuela Arvat[4], Luca Damiani[1], Giorgio Grani[2], Alice Nervo[4], Cosimo Durante[2], Laura Giacomelli[5].

[1]Section of Endocrinology and Internal Medicine, Department of Medical Sciences, University of Ferrara, Ferrara, Italy.

[2]Department of Internal Medicine and Medical Specialties, University of Rome 'Sapienza', Rome, Italy.

[3]Endocrinology Unit, AUSL Bologna-Bentivoglio Hospital, Bologna, Italy.

[4]Division of Oncological Endocrinology, Department of Medical Sciences, Azienda Ospedaliera Città della Salute e della Scienza, Turin, Italy.

[5]Department of Surgical Sciences, University of Rome 'Sapienza', Rome, Italy.

Corresponding author:

Maria Chiara Zatelli, MD

Phone: +39-0532 236682

e-mail: ztlmch@unife.it

Acknowledgments: GG and LL contributed to this paper as recipients of the PhD program of Biotechnologies and Clinical Medicine of the University of Rome, Sapienza.

Abstract

Purpose: This study was aimed at assessing the incidence and timing of thyroid nodules recurrence, defined as appearance of new benign or malignant nodules in contralateral lobe in patients with benign thyroid nodules or thyroid microcarcinoma treated with lobo-isthmectomy. Patient's characteristics and risk factors associated with this phenomenon were also investigated.

Methods: A retrospective study was performed by evaluating 413 patients undergoing lobo-isthmectomy with a minimum follow-up of 1 year. Clinical characteristics, surgical interventions and complications, histological diagnosis, thyroid function at last follow up were collected.

Results: Single or multiple thyroid nodule recurrence equally occurred in 80 patients (23%) with a median time to relapse of ~5 years (range 0.3-34.5 years) after lobo-isthmectomy. Recurrence was significantly associated with younger age (<46 yrs)~~, family history of nodular goiter,~~ and number of pregnancies in women. Development of hypothyroidism was not rare either (~10%) and appeared in 3 to 19 months; a preoperative TSH level > 2.43mIU/L was associated with the need of l-thyroxin replacement therapy after surgery. The most frequent surgical complication was transient hypoparathyroidism (4.6%), while the rate of permanent hypoparathyroidism significantly increased in patients submitted to completion thyroidectomy (5.3%).

Conclusions: Thyroid nodules recurrence following lobo-isthmectomy is not a rare event and occurs within 5 years after surgery, more frequently in younger patients with family history of nodular goiter and in women with multiple pregnancies. Pre-surgical TSH levels may predict the development of post-surgical hypothyroidism, possibly improving the management of patients addressed to surgery.

Key words: thyroid lobectomy, thyroid nodules, recurrence, incidence, risk factors.

INTRODUCTION

Thyroid nodules are common in the general population, with a prevalence ranging from 1 to 5% for palpable nodules [1–3] and from ~20 to~70% for nodules identified by neck ultrasound (US)[4–6]. A recent cross-sectional study confirmed a higher prevalence in females and found a positive correlation with age, identifying smoking and body mass index as independent risk factors for thyroid nodules [7]. As underlined by the last American Thyroid Association Guidelines [8], the clinical relevance of thyroid nodules depends on their benign or malignant nature, with important consequences on their management. When surgery is needed, an important issue regards the extent of gland removal. Lobo-isthmectomy is associated with a lower rate of complications compared with total-thyroidectomy [9]. The actual rate of surgical complications following lobo-isthmectomy depends on the expertise of the surgeon. Complications are similar between lobo-isthmectomy and total-thyroidectomy, and include peri-operative bleeding, wound infection, transient or permanent laryngeal nerve damage. Thyroid lobectomy virtually eliminates the risk of hypoparathyroidism and spares a certain proportion of endogenous thyroid hormones production. On the other hand, lobo-isthmectomy may expose the patients to the risk of thyroid nodule recurrence in the contralateral lobe. All current studies, however, have been performed in single institutions with a pooled nodule-recurrence incidence of ~34%. A previous study identified female sex, multiple nodules and lack of postoperative levo-thyroxine (LT4) therapy as predictive factors of recurrence [10], but data are again coming from a single center.

The primary aim of our study was to assess rate and timing of recurrences, defined as appearance of new benign nodules or thyroid cancer relapse in the contralateral lobe, in patients with unilateral benign thyroid nodule or thyroid microcarcinoma treated with lobo-isthmectomy and referred to three Italian centers. We also assessed the risk factors for recurrence, the rate of surgical complications, the need for LT4 replacement, the rate of completion thyroidectomy (CT) due to relapsing disease and the rate of surgical complications of CT.

MATERIALS AND METHODS

Patients

All patients undergoing thyroid lobo-isthmectomy for unilateral benign thyroid nodule or microcarcinoma in three Italian centres (Section of Endocrinology and Internal Medicine, Dept. of Medical Sciences, University of Ferrara; Endocrinology Unit, AUSL Bologna-Bentivoglio Hospital, Bologna; Division of Oncological Endocrinology, Department of Medical Sciences, Azienda Ospedaliera Città della Salute e della Scienza, Turin) with at least 1 year of follow-up were enrolled in the study. Inclusion criteria were the availability of reports on periodical assessment of neck US and TSH levels. All patients provided permission for disclosing their anonymized data.

Evaluated parameters

We assessed patient characteristics at the time of the primary surgery, including age, sex, number of pregnancies in women, preoperative TSH levels, positivity for antithyroid antibodies, coexistence of Hashimoto's thyroiditis, post-operative histological diagnosis. Serum anti-thyroglobulin antibodies (ATG) and anti-thyreoperoxidase antibodies (ATPO) levels were defined as positive according to local institutional cut-offs.

During the follow-up period, the development of nodule recurrence, interval between surgery and the development of recurrence, TSH levels, interval between surgery and the development of hypothyroidism and the use of LT4 replacement therapy, the occurrence of surgical complications (i.e., transient or permanent hypoparathyroidism; recurrent laryngeal nerve palsy) following the primary and/or secondary surgery were recorded.

Recurrence was defined as the sonographic appearance, after the first surgery, of new nodules (benign or malignant) in contralateral lobe in patients with thyroid nodule treated with lobo-isthmectomy.

Hypoparathyroidsm was defined as the need for temporary (<6 months) or chronic (≥6 months) calcium and/or vitamin D supplementation. As for recurrent laryngeal nerve palsy, this was

established at laryngoscopy in all symptomatic patients, and was considered permanent if lasting for at least 6 months.

Statistical analysis

Data are expressed as median and range. Patients were grouped according to the presence of nodule relapse during the follow-up. Categorical variables were compared between subgroups using the Fisher exact test or the Pearson chi-square test, when appropriate. Continuous variables were compared using the Mann-Whitney test. Univariate and multivariate logistic regression analyses were performed to evaluate the association between nodular relapse and several potential predictive factors. Furthermore, the association between the need of LT4 therapy after lobo-isthmectomy and potential predictive factors – such as TSH level before surgery and history of thyroiditis – was assessed by univariate and multivariate logistic regression analyses. The Odds ratios (OR) are reported along with their 95% confidence intervals (CI). Two tailed Fisher exact text was performed to assess the strength of the association between two independent variables. To propose a cutoff of pre-surgery TSH to predict hypothyroidism, a Receiver Operating Characteristic (ROC) curve analysis was performed. All tests used a two-sided α of 0.05. Data analysis was performed using IBM SPSS Statistics 22.0 (Armonk, NY: IBM Corp.).

RESULTS

Patients' characteristics at baseline

Data on 413 patients who underwent lobo-isthmectomy for unilateral thyroid nodule were collected at the three involved Centers. Among the recruited patients, 59 were excluded because they underwent CT within 1 year, while 354 patients constituted the study population and were followed-up for 71.7 ± 3.7 months (range 2 – 459 months) after lobo-isthmectomy.

The characteristics of the study population at the time of the primary surgery (i.e., lobo-isthmectomy) are reported in Table 1. Before surgery, median TSH levels were 1.3 mIU/L (range

0.01 to 9.7 mIU/L). It is noteworthy that 105 patients (30%) were on LT4 replacement therapy. ATG and ATPO were positive in 20 and 28 patients, respectively, with a total number of patients with positive anti-thyroid antibodies summing up to 34 (10%). Among the 274 female patients, 134 had at least one pregnancy (range 1 -8 pregnancies) and 83 were on menopause at the time of surgery. Family history was positive for nodular goiter and for chronic autoimmune thyroiditis in ~20% and 1% of the patients, respectively.

Lobo-isthmectomy was indicated for diagnostic purposes (indeterminate cytology) in 52% of the cases. Therapeutic lobo-isthmectomy was indicated for mass effect and for hyperthyroidism in 33% and 4% of the patients, respectively. In 92% of the patients, histology showed a benign lesion, mostly represented by adenomas (57%) and hyperplastic lesions (36.5%). Thyroid cancer was found in 6% of the patients including 18 papillary thyroid carcinomas (PTC) and 4 follicular thyroid carcinomas (FTC). Histological evidence of thyroiditis was found in 9%of the specimens.

Development of recurrences

Among the 354 patients submitted to lobo-isthmectomy, 80 (22.5%) showed nodule recurrence mainly in the contralateral lobe (94%), with 3 cases showing bilateral recurrence. The median time to recurrence was 59 months (range: 4 months- 34.5 years), with no significant difference between males and females. A longer time to recurrence was observed for multiple recurrent nodules (66 months) as compared to single recurrent nodules (49 months), but the difference did not reach statistical significance.

Among recurrent nodules, 24 were submitted to fine-needle aspiration biopsy and the cytology report was consistent with a benign category in the majority of cases (79%), and with an indeterminate and suspicious class in 3 and 1 nodule, respectively. Among these patients, CT was indicated in 8 patients and median time to surgery was 19 years (range 1.6 to 30.8 years). Histology disclosed benign lesions in 5 cases and PTC in 3 cases.

Predictive factors of recurrence

We then analyzed the possible predictive factors of recurrence. On univariate analysis, no clinical characteristic was significantly associated with recurrence (Table 2). In particular, we did not find any significant difference in TSH levels measured before and after surgery between patients with nodule relapse as compared to those without. On multivariate analysis, family history of multinodular goiter approached statistical significance (OR, 2.137; 95% CI, 0.983 – 4.647; p= 0.055) and older age at surgery was an independent risk factor for nodule recurrence (OR, 0.976; 95% CI, 0.954 – 0.998; p=0.03 for each year of age increase) (Table 3). In female patients, the number of pregnancies was identified as independent risk factor (1.7 ± 0.18 vs. 1.24 ± 0.07 in women with recurrence vs. women without recurrence - OR, 1.591; 95% CI, 1.102-2.297; p=0.013) and age (OR 0.968; 95% CI 0.94 – 0.99; p 0.029 for each year of age increase) was identified as an independent protective factor for the development of thyroid nodule recurrence (Table 4

LT4 replacement therapy after lobo-isthmectomy

When we evaluated the need for LT4 replacement therapy after lobo-isthmectomy we found that it significantly associated with pre-surgical TSH levels (OR, 1.524; 95% CI, 1.002-2.317; p=0.049) in patients that were not on LT4 therapy before surgery. A preoperative TSH level > 2.43 mIU/L (OR, 7.11; 95% CI, 2.06-24.59; p=0.002) was significantly associated with the development of post-surgical hypothyroidism, which appeared in 9.8% of the patient in a time frame ranging from 3 to 19 months, independently of the presence of thyroiditis. The proposed TSH cut-off value has a specificity of 93.9% (95% CI 83.1-98.7%) and a sensitivity of 31.7% (95% CI 22.8-41.7%), with a positive predictive value of 91.4% (95% CI 76.9-98.2%) and a negative predictive value of 40% (95% CI 31-49.5%).

Rate of surgical complications

The majority of the patients did not experience surgical complications after lobo-isthmectomy. Two cases (0.6%) of transient and 3 cases (0.8%) of permanent laryngeal nerve palsy were recorded, while transient or permanent hypoparathyroidism developed in 19 (5.3%) and in 1 case (0.3%), respectively.

Surgical complications of completion thyroidectomy

Among the 59 patients who underwent CT within 1 year from lobo-isthmectomy, final histology showed benign lesions in 6 cases (10%), PTC in 33 cases (56%), and follicular thyroid carcinoma (FTC) in 20 cases (34%). Surgical complications of CT were represented by transient (2%) or permanent (5%) hypoparathyroidism and by permanent recurrent laryngeal nerve palsy (2%). The rate of permanent recurrent laryngeal nerve palsy was found to be significantly higher after CT as compared to lobo-isthmectomy (p=0.0068).

DISCUSSION

This retrospective multicenter study shows that thyroid nodule recurrence after lobo-isthmectomy is not an uncommon event, occurring in 1 out of 4.4 patients within a median of 5 years. The risk factors associated to recurrence were younger age (i.e. < 46 years old) and, in the subgroup of female patients, age and number of pregnancies. The need for thyroid hormone replacement therapy was significantly higher in patients with a preoperative TSH level above 2.43 mUI/L.

When interpreting the results of this research, however, certain limitation with regard to the outcome of this study should be kept in mind. The retrospective design leads to incomplete data set, thus exposing to potential selection bias. Surgery and follow up were performed in different institutions with, possibly, a heterogeneous management protocol. Nevertheless, these figures better represent the real-life challenges. The institutions involved in this study are experienced referral centers for thyroid disease management. They include highly skilled surgeons, even if patients

operated elsewhere were not excluded. In any case, the rate of surgical complications found after lobo-isthmectomy was very low (<1%). The range of post-surgical follow-up time was variable but reached a median of 71.7 months.

A nodule recurrence rate similar to that found in our study was observed in a paediatric population followed-up for a mean of 45 months [11], where, however, the need for replacement therapy was higher as compared to our population, mostly composed of adult subjects. On the contrary, a greater incidence rate of recurrence was found by Lytrivi et al. [12], accounting for almost half of the 270 patients submitted to lobo-isthmectomy and followed-up for a median of 78 months. In this study, preoperative contralateral lobe volume and resected thyroid weight were identified as significant predictors of recurrence. In addition, they found that family history of thyroid disease was a potential predictive factors of nodular recurrence. In our series we found that age at surgery <46 years and number of pregnancies in women represent independent risk factors for the development of thyroid nodule recurrence. These data would support a role for estrogens in thyroid nodule development, also taking into consideration that menopausal women had a lower chance to develop recurrence. It is well known that estrogens are potent growth factors, influencing normal and cancer thyroid cell proliferation both via genomic and non-genomic actions, as well as influencing tumor microenvironment, angiogenesis and metastasis [13, 14]. Therefore, our data are in line with a growth-promoting effect of estrogens also on normal thyroid follicular cells, since recurrence was higher in women with a higher number of pregnancies in their clinical history. In addition, higher estrogens exposure during reproductive years may confer an increased risk of developing thyroid cancer [15].

The importance of a predisposing genetic background for the development of nodule recurrence after lobectomy is suggested by the finding that family history of multinodular goiter approached closely a statistical significant value for recurrence prediction. Evidence for familial clustering, with an autosomal dominant pattern of inheritance, and female predominance for multinodular goiter is consolidated [16] and contribution of genetic susceptibility to goiter

development in endemic regions has been calculated to be ~40% [17]. Previous genetic studies identified different candidate loci, such as MNG-1 [18, 19] and Xp22 [20] in different families, indicating an important genetic heterogeneity. Indeed, despite benign nodules display a unique molecular signature [21], the specific genes involved in goiter development have not been fully clarified and a multifactorial pathogenesis, involving environmental factors and emotional stress on a peculiar genetic background, is more likely [15, 22]. This hypothesis is further strengthened by the evidence that family history of thyroid nodular disease did not predict recurrence in a study with pediatric subjects [11], while it was significantly associated with recurrence in a single centre retrospective study involving mainly adult patients [12]. Furthermore, recent evidences challenge the canonically accepted natural history and pathogenesis of goiter [23].

The development of thyroid nodule recurrence did not have an important clinical impact in our series, since the majority of recurrent nodules (56 out of 80, 70%) had not been further investigated, indicating that they were not clinically and sonographically suspicious for malignancy. Among the 24 recurrent nodules requiring a re-assessment (including fine-needle aspiration biopsy), 3 (12.5%) turned out to hide a cancer, thus supporting the need for long-term follow-up and accurate monitoring in these patients.

In addition, our data confirm that the chance for surgical complications significantly increases in patients who had a lobo-isthmectomy with the need for subsequent CT compared to those treated with lobo-isthmectomy alone. Given the absolute low rate of surgical complication, it is unlikely that this phenomenon is linked to the expertise of surgeons, but rather to the consolidated evidence that a re-operative thyroid surgery is associated with a greater likelihood of complications [24, 25]. Only clinically evident recurrent laryngeal nerve palsy was considered in the study and the actual rate of palsy may have been underestimated.

In our series we found that a preoperative TSH level >2.43 mIU/L was significantly associated with the development of hypothyroidism after surgery, independently on the presence of thyroiditis. Therefore, our results are in line with previous studies showing that the incidence of

post-operative biochemical hypothyroidism is not rare (22% for subclinical and 4% for overt hypothyroidism) [26]. In addition, the low NPV and sensitivity of the identified TSH cut-off indicates that in patients with TSH above the cut-off before surgery the probability to have normal thyroid function after lobo-isthmectomy is only 40% and consequently, more than half of patients will develop hypothyroidism after lobectomy. Therefore, our results indicate that thyroid function monitoring is mandatory in patients submitted to lobo-isthmectomy. However, we failed to identify any correlation with autoimmune thyroid disease, differently from previous reports [27, 28], probably due to the heterogeneity of diagnostic criteria [29] and to the different patient populations taken into account. The identification of a TSH threshold may be very useful to identify those patients that are at greater risk to develop post-surgical hypothyroidism, in order to plan a tighter biochemical follow up. Indeed, in our series the development of hypothyroidism varies widely over time, presenting up to more than 1.5 years after surgery. Once again, this evidence further supports the need for long-term follow-up and accurate monitoring in these patients.

In conclusion, our study shows that thyroid nodule recurrence following lobo-isthmectomy is a frequent event, involving more closely younger patients ~~with family history of nodular goiter~~ and women with multiple pregnancies. Pre-surgical TSH levels may predict the development of post-surgical hypothyroidism, possibly improving the management of patients addressed to surgery by monitoring post-surgical thyroid function. Further prospective studies are needed to identify more accurate predictive factors of recurrence in order to improve the management of these patients.

CONFLICT OF INTEREST

The Authors declare they have no conflict of interest that may influence the content of this manuscript.

ETHICAL STATEMENT

The Authors declare that manuscript complies with the ethical standards indicated in the Instruction for Authors of the Journal.

REFERENCES

1. Filetti S, Durante C, Torlontano M (2006) Nonsurgical approaches to the management of thyroid nodules. Nat Clin Pract Endocrinol Metab 2:384–394 . doi: 10.1038/ncpendmet0215
2. Vander JB, Gaston EA, Dawber TR (1968) The significance of nontoxic thyroid nodules. Final report of a 15-year study of the incidence of thyroid malignancy. Ann Intern Med 69:537–540
3. Tunbridge WM, Evered DC, Hall R, et al (1977) The spectrum of thyroid disease in a community: the Whickham survey. Clin Endocrinol (Oxf) 7:481–493
4. Lamartina L, Deandreis D, Durante C, Filetti S (2016) ENDOCRINE TUMOURS: Imaging in the follow-up of differentiated thyroid cancer: current evidence and future perspectives for a risk-adapted approach. Eur J Endocrinol 175:R185-202 . doi: 10.1530/eje-16-0088
5. Tan GH, Gharib H (1997) Thyroid incidentalomas: management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. Ann Intern Med 126:226–231
6. Guth S, Theune U, Aberle J, et al (2009) Very high prevalence of thyroid nodules detected by high frequency (13 MHz) ultrasound examination. Eur J Clin Invest 39:699–706 . doi: 10.1111/j.1365-2362.2009.02162.x
7. Jiang H, Tian Y, Yan W, et al (2016) The Prevalence of Thyroid Nodules and an Analysis of Related Lifestyle Factors in Beijing Communities. Int J Environ Res Public Health 13:442 . doi: 10.3390/ijerph13040442
8. Haugen BR, Alexander EK, Bible KC, et al (2016) 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid 26:1–133

9. Rosato L, Avenia N, Bernante P, et al (2004) Complications of thyroid surgery: analysis of a multicentric study on 14,934 patients operated on in Italy over 5 years. World J Surg 28:271–276 . doi: 10.1007/s00268-003-6903-1

10. Bellantone R, Lombardi CP, Boscherini M, et al (2004) Predictive factors for recurrence after thyroid lobectomy for unilateral non-toxic goiter in an endemic area: results of a multivariate analysis. Surgery 136:1247–1251 . doi: 10.1016/j.surg.2004.06.054

11. Akkari M, Schmitt D, Jeandel C, et al (2014) Nodular recurrence and hypothyroidism following partial thyroidectomy for benign nodular thyroid disease in children and adolescents. Int J Pediatr Otorhinolaryngol 78:1742–1746 . doi: 10.1016/j.ijporl.2014.07.037

12. Lytrivi M, Kyrilli A, Burniat A, et al (2016) Thyroid lobectomy is an effective option for unilateral benign nodular disease. Clin Endocrinol (Oxf) 85:602–608 . doi: 10.1111/cen.13088

13. Hima S, Sreeja S (2016) Modulatory role of 17β-estradiol in the tumor microenvironment of thyroid cancer. IUBMB Life 68:85–96 . doi: 10.1002/iub.1462

14. Derwahl M, Nicula D (2014) Estrogen and its role in thyroid cancer. Endocr Relat Cancer 21:T273-283 . doi: 10.1530/ERC-14-0053

15. Moleti M, Sturniolo G, Di Mauro M, et al (2017) Female Reproductive Factors and Differentiated Thyroid Cancer. Front Endocrinol 8:111 . doi: 10.3389/fendo.2017.00111

16. Krohn K, Führer D, Bayer Y, et al (2005) Molecular pathogenesis of euthyroid and toxic multinodular goiter. Endocr Rev 26:504–524 . doi: 10.1210/er.2004-0005

17. Greig WR, Boyle JA, Duncan A, et al (1967) Genetic and non-genetic factors in simple goitre formation: evidence from a twin study. Q J Med 36:175–188

18. Bignell GR, Canzian F, Shayeghi M, et al (1997) Familial nontoxic multinodular thyroid goiter locus maps to chromosome 14q but does not account for familial nonmedullary thyroid cancer. Am J Hum Genet 61:1123–1130 . doi: 10.1086/301610

19. Neumann S, Willgerodt H, Ackermann F, et al (1999) Linkage of familial euthyroid goiter to the multinodular goiter-1 locus and exclusion of the candidate genes thyroglobulin,

thyroperoxidase, and Na+/I- symporter. J Clin Endocrinol Metab 84:3750–3756 . doi: 10.1210/jcem.84.10.6023

20. Capon F, Tacconelli A, Giardina E, et al (2000) Mapping a dominant form of multinodular goiter to chromosome Xp22. Am J Hum Genet 67:1004–1007 . doi: 10.1086/303095

21. Ye L, Zhou X, Huang F, et al (2017) The genetic landscape of benign thyroid nodules revealed by whole exome and transcriptome sequencing. Nat Commun 8:15533 . doi: 10.1038/ncomms15533

22. Knobel M (2016) Etiopathology, clinical features, and treatment of diffuse and multinodular nontoxic goiters. J Endocrinol Invest 39:357-373. doi: 10.1007/s40618-015-0391-7.

23. Grani G, Bruno R, Lucisano G, et al (2017) Temporal Changes in Thyroid Nodule Volume: Lack of Effect on Paranodular Thyroid Tissue Volume. Thyroid Off J Am Thyroid Assoc 27:1378–1384 . doi: 10.1089/thy.2017.0201

24. Vasica G, O'Neill CJ, Sidhu SB, et al (2012) Reoperative surgery for bilateral multinodular goitre in the era of total thyroidectomy. Br J Surg 99:688–692 . doi: 10.1002/bjs.8684

25. Kurmann A, Herden U, Schmid SW, et al (2012) Morbidity rate of reoperation in thyroid surgery: a different point of view. Swiss Med Wkly 142:w13643 . doi: 10.4414/smw.2012.13643

26. Verloop H, Louwerens M, Schoones JW, et al (2012) Risk of hypothyroidism following hemithyroidectomy: systematic review and meta-analysis of prognostic studies. J Clin Endocrinol Metab 97:2243–2255 . doi: 10.1210/jc.2012-1063

27. Kandil E, Krishnan B, Noureldine SI, et al (2013) Hemithyroidectomy: a meta-analysis of postoperative need for hormone replacement and complications. ORL J Oto-Rhino-Laryngol Its Relat Spec 75:6–17 . doi: 10.1159/000345498

28. Grani G, Carbotta G, Nesca A, et al (2015) A comprehensive score to diagnose Hashimoto's thyroiditis: a proposal. Endocrine 49:361–365

Table 1. Characteristics of the study population at the time of the primary surgery (lobo-isthmectomy)

Patient characteristics	**Study population** (n=354)
Age (yrs) - *median (range)*	47.5 (7-80)
Gender- *n. (%)*	
- female	274 (77)
- male	80 (23)
Pregnancy - *n. (%)*	
- None	41 (15)
- 1	55 (20)
- 2	62 (23)
- 3	11 (4)
- 4	3 (1)
- >4	3 (1)
- at least 1	99 (36)
Thyroid nodules diagnosis - *n. (%)*	
- Clinical (auto-palpation, physical examination)	121 (34)
- Asymptomatic (screening/incidentaloma)	141 (40)
- Not specified	92 (26)
Nodular goiter - *n. (%)*	
- Uninodular	186 (53)
- Multinodular unilateral	43 (12)
- Multinodular bilateral	83 (23)
- Multinodular NA	2 (1)
- At least one nodule (not better specified)	40 (11)
Larger nodule maximum diameter (mm) - *median (range)*	30 (2 - 90)

Table 2. Predictive factors of nodule recurrence: univariate analysis in the whole cohort

Variable	Relapse/all patients	*p*	OR (95% CI)
Gender- *n. (%)*			
- Male	13/80 (16%)		1
- Female	67/274 (24%)	0.13	1.67 (0.8 – 3.5)
Age (yrs) at surgery - *median (range)*	46.4 (14 - 81)/ 50 (13 - 81)	0.06	0.980 (0.96-1.00)
Family History of nodular goiter - *n. (%)*			
- No	50/181(28%)		1
- Yes	10/59 (17%)	0.12	0.54 (0.2 – 1.2)
- NA	20/114 (18%)	0.05	0.56 (0.3 – 1.0)
Pregnancy (N=274 female patients) - *n. (%)*			
- **No**	8/42(19%)		1
- **Yes**	36/134 (27%)	0.41	1.5 (0.6 – 4.2)
- **NA**	23/98 (21%)	0.66	1.26 (0.5 – 3.6)
Number of pregnancies (N=274 female patients) - *median (range)*	1 (0 - 8)/ 1 (0 - 8)	0.059	1.31 (0.99-1.72)
Menopause (N=274 female patients) - *n. (%)*			
- Yes	23/83 (28%)		1
- No	4/26 (15%)	0.30	0.48 (0.1 - 1.6)
- NA	40/165 (24%)	0.64	0.84 (0.4 – 1.6)
Cigarette smoke - *n. (%)*			
- No	38/130 (29%)		1
- Yes	7/34 (21%)	0.39	0.63 (0.2 – 1.6)
- NA	35/190 (18%)	0.03	0.55 (0.3- 0.96)
Thyroiditis - *n. (%)*			
- No	72/303 (24%)		1
- Yes	8/51 (16%)	0.28	0.60 (0.2 – 1.4)
Nodular goiter - *n. (%)*			
- Uninodular	44/186 (24%)		1
- Multinodular	24/128 (19%)	0.33	0.75 (0.4 – 1.3)
- Not specified	12/40 (35%)	0.42	1.38 (0.6 – 3.1)
Nodular goiter - *n. (%)*			
- Multinodular unilateral	52/234 (22%)		1
- Multinodular bilateral	15/83 (18%)	0.53	0.77 (0.4 – 1.5)
- Not specified	13/37 (35%)	0.09	1.89 (0.8 – 4.2)
Histology - *n. (%)*			
- Benign	74/326 (23%)		1
- PTC	6/18 (33%)	0.39	1.70 (0.5 – 5.1)
- FTC	0/4	0.58	-
- Other	0/6	0.34	-
Benign histology - *n. (%)* (N=316)			
- Adenoma/Thyroiditis	42/185 (23%)	0.759	1
- Hyperplasia	32/131 (24%)	1	1.08 (0.65–1.81)
- NA	3/16 (19%)		1.27 (0.33 – 7.28)

Table 3. Predictive factors of nodule recurrence: multivariate analysis in the whole cohort

Variable	p	OR	95% CI
Family history of nodular goiter	0.055	2.137	0.983 – 4.647
Age at time of surgery	0.030	0.976	0.954 – 0.998

Table 4. Predictive factors of nodule recurrence: multivariate analysis in female subjects

Variable	p	OR	95% CI
Family History of nodular goiter	0.650	1.233	0.498 – 3.051
Number of pregnancies	0.013	1.591	1.102 – 2.297
Age at time of surgery	0.029	0.968	0.940 – 0.997

Patients with missing data were excluded from multivariate analysis.