

## Risk factors for recurrence and morbidity in reoperative thyroid surgery: a different point of view

### *Reoperatif tiroid cerrahisinde nüks ve morbidite oranı için risk faktörleri: farklı bir bakış açısı*

Kalin Vidinov<sup>1</sup>, Georgi P. Georgiev<sup>2</sup>

#### ABSTRACT

**Objective:** Recurrent goiter is a common problem following subtotal thyroid gland resection for multinodular goiter disease. The aim of the present study is to evaluate risk factors for recurrence, ultrastructural particularities of the thyroid and morbidity rate in relation to the side of initial and redo surgery for recurrent disease.

**Methods:** From January 2003 to December 2010 a total of 4,395 patients underwent consecutive thyroid gland surgery for nodular goiter at Department of Endocrine Surgery USBALE "Akad. Iv. Penchev" Hospital. Five hundred fifty one (12.5%) patients underwent redo-surgery for recurrent disease after subtotal resection. All of them with complete follow-up were included in the present study.

**Results:** Recurrent disease was found in 279 (50.7%) patients in the ipsilateral lobe and 272 (49.3%) patients in the contralateral lobe. The incidence of permanent recurrent laryngeal nerve palsy was significantly higher in patients with ipsilateral redo surgery compared to patients undergoing initial operation (3.9% vs. 1.2%;  $p < 0.05$ ) whereas no difference was found in patients with contralateral redo surgery compared to patients undergoing initial operation. Independent risk factors for contralateral recurrent disease were age at primary operation  $< 30$  years and familial history.

**Conclusion:** Our study showed that reoperation on the ipsilateral lobe is associated with a significantly higher morbidity rate compared to initial surgery. Reoperation on the contralateral lobe carries no additional morbidity. Further studies are necessary in order to evaluate whether lobectomy is sufficient for patients with familial history and unilateral goiter. *J Clin Exp Invest* 2013; 4 (4): 417-421

**Key words:** Goiter, recurrence, nodular goiter, thyroid gland, recurrent laryngeal nerve palsy, hypoparathyroidism

#### ÖZET

**Amaç:** Tekrarlayan (nüks) guatr, multinodüler guatr hastalığı tedavisi için yapılan subtotal tiroid bezi rezeksiyonunu takiben gelişen yaygın bir sorundur. Bu çalışmanın amacı; tekrarlayan guatr hastalığının başlangıcı ve redo cerrahi ile ilgili olarak nüks, tiroidin ultrastrüktürel özellikleri ve morbidite oranı yönünden risk faktörlerini değerlendirmektir.

**Yöntemler:** Ocak 2003-Aralık 2010 tarihleri arasında USBALE "Akad. Iv. Penchev" Hastanesi Endokrin Cerrahi bölümünde toplam 4,395 hastaya nodüler guatr tedavisi için ardışık tiroid bezi cerrahisi uygulandı. Hastalardan 551'ine (%12,5) subtotal rezeksiyon sonrası gelişen tekrarlayan hastalık tedavisi için redo cerrahi yapıldı. Takip edilen hastaların tamamı çalışmaya dahil edildi.

**Bulgular:** Tekrarlayan (nüks) guatr hastaların 279'unda (%50,7) ipsilateral lob ve 272'sinde (%49,3) kontralateral lob yerleşimliydi. Kalıcı tekrarlayan laringeal sinir felci açısından, hastalara yapılan ilk operasyon ile karşılaştırıldığında; kontralateral redo cerrahi geçiren hastalarla arasında herhangi bir fark bulunmazken ipsilateral redo cerrahi geçiren hastalarda anlamlı olarak daha yüksekti (3,9% vs. 1,2%;  $p < 0.05$ ). Kontralateral tekrarlayan guatr için bağımsız risk faktörleri; ilk operasyon sırasında 30 yaş altında ve aile öyküsü olmak.

**Sonuç:** Çalışmamız, ilk operasyon ile karşılaştırıldığında ipsilateral lobdaki reoperasyonun anlamlı olarak daha yüksek morbidite oranı ile ilişkili olduğunu gösterdi. Kontralateral lobdaki reoperasyonun morbiditeye etkisi yoktu. Aile öyküsü olan tek taraflı guatr hastalarının tedavisi için lobektominin yeterli olduğunu değerlendirmek amacıyla daha ileri düzey çalışmalara ihtiyaç vardır.

**Anahtar kelimeler:** Guatr, nüks, nodüler guatr, tiroid bezi, tekrarlayan laringeal sinir felci, hipoparatiroidi

<sup>1</sup> USBALE "Acad. Iv. Penchev" Hospital, Department of Endocrine Surgery, Medical University, Sofia, Bulgaria

<sup>2</sup> University Hospital of Orthopaedics "Prof. B. Boychev", Medical University, Sofia, Bulgaria

**Correspondence:** Georgi P. Georgiev,

University Hospital of Orthopaedics, Medical University Sofia, 56 Nikola Petkov Blvd., 1614 Sofia, Bulgaria

Email: georgievgp@yahoo.com

Received: 28.07.2013, Accepted: 04.11.2013

Copyright © JCEI / Journal of Clinical and Experimental Investigations 2013, All rights reserved

## INTRODUCTION

Multinodular goiter is the most common indications for surgery in endemic iodine-deficiency regions. Ever since Theodor Koher proposed surgery for goiter about a century ago, there has been a debate about the best surgical resection for the disease. Nowadays the paradigm shift in thyroid surgery away from Kocher's principles of nodal enucleation or subtotal resection to extended thyroidectomy involving at least hemithyroidectomy (total unilateral lobectomy) is well-accepted approach for the treatment of multinodular goiter disease [1]. Unilateral lobectomy and total thyroidectomy carries no increased risk of morbidity compared with subtotal resection and therefore the more radical approach for benign multinodular disease is reasonable for preventing recurrent goiter [2]. Studies have already documented a significantly higher morbidity rate in redo-surgery after previous thyroid resections compared with initial surgery [3]. However, most studies do not precisely report the side, time, ultrastructure of the thyroid gland, risk factors and its side specific morbidity of reoperation after subtotal resection.

The aim of the present study was to review our experience in redo surgery, to evaluate risk factors for recurrence and morbidity rate in relation to the initial surgery.

## METHODS

From January 2003 to December 2010, 4,395 patients underwent consecutive thyroid gland surgery for nodular goiter at Department of Endocrine surgery USBALE "Akad. Iv. Penchev" Hospital. The majority of patients were women 3,516 (80%) and only 879 (20%) men. As a primary institution and referral center for Bulgaria, we had changed our policy towards extended primary resection for benign thyroid disease (lobectomy for unilateral or total thyroidectomy for bilateral disease) already in 2001. Data of all patients undergoing thyroidectomy were prospectively collected and stored in an electronic database. A total of 551 patients (12.5%) underwent reoperation after subtotal resection. In our institution, we have a strict policy of having all previous documentation before doing redo surgery, so all 551 patients came with complete follow-up (including exact indication, date and extent of initial surgery).

All of initial operations on these patients were performed at an external clinic. The control group to compare morbidity rate and risk factors of initial and redo surgery consisted of 1,000 patients. We used the operative material from 95 of the patients from the control group to evaluate the ultrastructural

changes in the connective tissue elements of the thyroid stroma. Twelve of these patients had reported familial history of thyroid nodules. In order to see the extend of the pathological changes we took tissue samples from the central part of the thyroid nodule, one centimeter from the macroscopic border of the thyroid nodule (macroscopically normal tissue) (zone one) and two centimeters from the thyroid nodule (zone two). For ultrastructural examination, we used routine transmission electron microscopy. The electron microscopy has been made on Hitachi H-500 microscope. All studies in this paper were done in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All patients gave their informed consent prior to their inclusion in the study.

Overall loss of follow-up was <1%. Patients undergoing reoperation were allocated into two groups based on the type of recurrence. The first group (Group I) consisted of those patients with inadequate primary surgery - disease in the previously operated ipsilateral lobe. The second group (Group II) consisted of the patients with "true recurrences" - disease in the non-operated lobe, only. The patients with bilateral recurrence were located in the first group.

Our standard operation for unilateral thyroid disease was lobectomy including resection of the isthmus. When there was bilateral disease the operation was total thyroidectomy. Every patient was evaluated with thyroid function tests - free thyroxin and thyroid stimulating hormone, TAT, MAT and ultrasonography to define the extent of the disease. Preoperatively every patient underwent laryngoscopic examination of the vocal cords and the serum calcium concentration test. The operation was performed by a standard technique of capsular dissection. Recurrent laryngeal nerves and parathyroid glands were routinely identified on both sides. The parathyroid glands with compromised blood supply were excised, diced and reimplanted in the sternocleidomastoid muscle. Removed tissue was submitted for intraoperative frozen-section and fast track histological analyses in all cases. If there was no risk factors for bleeding the wounds were closed without suction drains.

After the operation every patient was asked if his or her voice was changed. If there was a positive answer or if the surgeon suspected postoperative vocal cord palsies during the postoperative period the patients underwent second postoperative laryngoscopic examination of the vocal cords.

Postoperative serum calcium levels were estimated twice for 24 hours after surgery. Calcium supplementation was given if serum calcium levels dropped  $<2.0$  mmol/L. If the patient could be weaned from calcium supplement within six months, hypoparathyroidism was considered transient. If there was laryngoscopic evidence of recurrent laryngeal nerve (RLN) recovery within six months of operation the RLN palsy was defined as transient. Oral thyroxin supplementation was started from the second day after the operation at a dose of 75-150 micrograms per day, according to body weight. Follow up was planned after a month, after three months and after six months. In the absence of any complication, the patients were discharged on the third day.

The data analysis and interpretation was performed on SPSS 19.0 software package program (SPSS Inc., Chicago, IL, USA). Student's t-test was performed to determine the significance between continuous variables, and Fisher's exact test was used to compare proportions. We used chi-square test to determine significant difference between the expected frequencies and the observed frequencies. Logistic regression analysis was performed to analyze risk factors for recurrence. A value of  $<0.05$  was used as the threshold for statistical significance.

## RESULTS

A total of 551 (12.5%) patients underwent reoperation. Recurrent ipsilateral disease was found in 279 (50.7%) patients and 272 (49.3%) patients had recurrence in the contralateral lobe. The patients in group II were younger at the time of the primary

operation than in group I. In group II, 103 patients were below 30 years, 99 were between 30 and 40 years, and 77 were above 40 years. In group I, 75 patients were below 30 years, 97 were between 30 and 40 years, and 100 were above 40 years. This difference between the two groups was statistically significant ( $p=0.026$ ).

Preexisting RLN palsy was observed in the "true recurrence" group (group II) in 6.3% ( $n=17$ ) and in group I in 6.5% ( $n=18$ ) ( $p$  value not significant). There was TSH-suppression therapy in 21 (7.5%) patients in group I and 20 patients (7.4%) in group II. The initial operation in the group I was a subtotal unilateral resection in 30.1% ( $n=84$ ) and a subtotal bilateral resection in 69.9% ( $n=195$ ). Initial operation in the group II was subtotal unilateral resection in 61.7% ( $n=168$ ) and lobectomy in 38.2% ( $n=104$ ). Permanent recurrent laryngeal RLN palsy was significantly higher in patients undergoing redo surgery on the ipsilateral lobe (group I) compared to patients undergoing operation on the non-operated lobe (3.9% vs. 1.2%;  $p<0.05$ ) (Table 1). However there was no difference in patients with contralateral redo surgery compared to patients undergoing initial thyroid operation ( $p>0.05$ ). No difference was found in persistent hypoparathyroidism between the groups (Table 2). Table 2 shows the risk factors for contralateral recurrence in multivariate regression analysis. Significant risk factors for contralateral recurrence were age at primary operation  $<30$  years (95% CI 0.365-0.850,  $p=0.007$ ) and familial history of thyroid nodules (95% CI 0.346-1.06,  $p=0.02$ ). Our analysis showed that gender and TSH-suppression are not statistically significant.

**Table 1.** Comparison between morbidity rate after primary and secondary operations

	Initial surgery ( $n=1000$ )	Group I ( $n=279$ )	Group II ( $n=272$ )	p value
Nerves at risk	1.600	350	272	
Permanent RLN palsy	12 (1.2%)	11 (3.9%)	3 (1.1%)	0.03
Permanent hypoparathyroidism	9 (0.9%)	2 (0.7%)	2 (0.7%)	0.76

**Table 2.** Multivariate analysis for risk factors for contralateral recurrence

	95% CI	p value
Gender	0.352-1.439	0.344
Age at primary operation $<30$ years	0.365-0.850	0.007
TSH-suppression	0.515-14.050	0.241
Familial history of thyroid nodular disease	0.346-1.06	0.020

Our electron microscopic examination showed pathological changes in the ultrastructural charac-

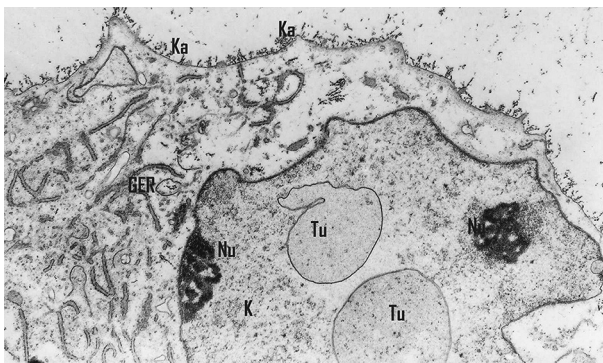
teristics of the thyrocytes in the samples from the center of the thyroid nodule. We saw the features of

medium cell hypertrophy and a decreased nucleocytoplasmic index. Fibroblasts from the stroma of the tumor were with tunnel-like structures in the karion (Figure 1). They had an increased number of endoplasmic reticulum and lysosomes. The thyrocytes has a decrease in the number of microvilli from the inner cell surface. In the same time between the microvilli there were lysosome-like structures (Figure 2). These structures had characteristic features like both simple and complex lysosomes in the different stages of digestive process. The fibro-

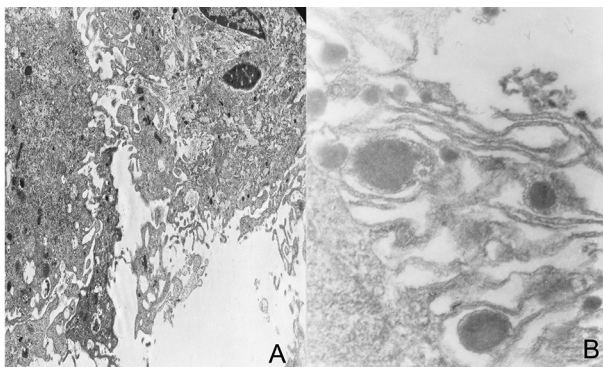
blasts had very well developed endoplasmic reticulum and simple lysosomes. These changes of the thyrocytes and the thyroid stroma were not confined only to the central zone of the thyroid nodule (Table 3). There were ultrastructural changes in the thyrocytes of 88 patients in the zone one and only 11 patients had changes in zone two. All of the patients with changes in zone two had a familial history of thyroid nodules. There were changes in the thyroid stroma in zone one - 84 patients and only 4 patients had changes in zone two.

**Table 3.** Statistical analysis of the ultrastructural changes in patients with goiter

	Patients with ultrastructural changes in the thyrocytes (n)	Patients with ultrastructural changes in thyroid stroma (n)
Central zone of the thyroid nodule	95	95
Zone one (1 cm away from the thyroid nodule)	88	84
Zone two (2 cm away from the thyroid nodule)	11	4
Difference between zone one and zone two	p=0.007	p=0.014



**Figure 1.** Fibroblast with an increased number of granular endoplasmic reticulum (GER) and lysosomes from the stroma of the tumor with tunnel-like structures (Tu) in the karion (K). There were two nucleoli (Nu) in the karion.



**Figure 2.** (A) The thyrocytes has a decrease in the number of microvilli from the inner cell surface; (B) In the same time between the microvilli there were lysosome-like structures

## DISCUSSION

Recurrent goiter is a frequent problem following subtotal resection of the thyroid gland for benign multinodular goiter disease. Recurrent goiter may occur because of the development of new nodules (true recurrence - mostly in the contralateral lobe) or because of the growth of "residual" or persistent macroscopic or microscopic nodules left at the previous thyroid operation [4]. The reported incidence of recurrence rate ranges from 12% to 42% [5,6].

Clear definition concerning the side of recurrence and its morbidity in relation to the previous operation is mandatory and often not mentioned in published series. Our retrospective study shows that the morbidity rate for recurrent disease after subtotal resection was significantly higher for ipsilateral (group I) redo surgery compared to initial surgery, whereas redo surgery can be performed safely on the contralateral lobe (group II). Our findings support the conclusions of Miller et al. [7] and Moalem et al. [8] that during reoperation, fibrosis after previous thyroidectomy makes RLN dissection more difficult, and it is associated with higher morbidity. RLN palsy rates vary from 0% to 14% in the literature, according to various surgeons' experience [9]. Our detailed analysis showed that morbidity rate of reoperation on the ipsilateral lobe is associated with a significantly higher rate of persistent recurrent laryngeal nerve palsy compared to the initial operation due to adhesions. In contrast, reoperation on the contralateral lobe was not associated with

an increased persistent recurrent laryngeal nerve palsy rate compared to initial surgery. Our findings support the conclusions made by Menegaux et al. [3] that reoperation on the contralateral side is not associated with adhesions and tissue conditions are comparable to initial surgery.

Two accepted risk factors for recurrence are noted in the literature - family history and bilateral disease [10]. However, these criteria are controversial [4]. In multivariate analysis, we found that young age at primary operation and familial history of thyroid nodules are independent risk factors for contralateral recurrent disease. This can be explained with the higher probability rate of recurrence, when initial operation was performed at younger age and in patients with familial history of thyroid nodules. Apart from missing some micro nodules on the contralateral side on the initial operation there seems to be a different etiology to explain the recurrences. In their studies, Harrer et al. [11] and Struder et al. [12] explain the recurrences with the fact that the nodules within multinodular goiters in recurrent disease were of polyclonal rather than clonal character. The proliferation of polyclonal nodules suggests that the polyclonal nodules arise from differentiating cells with a higher than average growth potential, due to acceleration of their proliferation rate by unknown superordinate molecular events.

Our ultrastructural studies showed that all patients with familial history had visible pathological changes in the zone two centimeters away from the thyroid nodule. This is a clear proof that if these patients were treated with subtotal thyroidectomy there would definitely be a recurrence of the disease in the near future. This can be explained by the multifactorial etiology based on complex interactions of an individual's genetic makeup and environment. To the same conclusions came Böttcher et al. [13], and Brix and Hegedüs [14] in their studies. Based on the results of our study we cannot determine whether if the thyroid nodule is near the isthmus of the gland the ultrastructural changes exist in the contralateral lobe. However, we agree with the conclusions made by Bauer et al. [15] that if there is a recurrence in these cases the reoperation on the contralateral lobe will not be associated with higher morbidity than primary surgery. For this reason, we will not recommend total thyroidectomy for unilateral disease. The limitations of the study include lack of randomization, the retrospective study design and the absence of genetic tests.

In conclusion, our study showed that reoperation on the ipsilateral lobe is associated with a significantly higher morbidity rate compared to initial

surgery. Reoperation on the contralateral lobe carries no additional morbidity. However, it is essential to prevent surgery in a previously operated thyroid bed. For this reason, we recommend lobectomy for unilateral and total thyroidectomy for bilateral euthyroid goiter. Further studies are necessary in order to evaluate whether lobectomy is sufficient for patients with familial history and unilateral goiter.

## REFERENCES

1. Tezelman S, Borucu I, Senyurek Y, Tunca F. The change in surgical practice from subtotal to near-total. *World J Surg* 2009;33:400-440.
2. Barczyński M, Konturek A, Stopa M, et al. Total thyroidectomy for benign thyroid disease: is it really worthwhile? *Ann Surg* 2011;254:724-730.
3. Menegaux F, Turpin G, Dahman M, et al. Secondary thyroidectomy in patients with prior thyroid surgery for benign disease: a study of 203 cases. *Surgery* 1999;126:479-483.
4. Kraimps JL, Marechaud R, Gineste D, et al. Analysis and prevention of recurrent goiter. *Surg Gynecol Obstet* 1993;176:319-322.
5. Pappalardo G, Guadalaxara A, Frattaroli FM, et al. Total compared with subtotal thyroidectomy in benign nodular disease: personal series and review of published reports. *Eur J Surg* 1998;164:501-506.
6. Wadstrom C, Zedenius J, Guinea A, et al. Multinodular goitre presenting as a clinical single nodule: how effective is hemithyroidectomy? *Aust N Z J Surg* 1999;69:34-36.
7. Muller PE, Jakoby R, Heinert G, Spelsberg F. Surgery for recurrent goitre: its complications and their risk factors. *Eur J Surg* 2001;167:816-821.
8. Moalem J, Suh I, Duh QY. Treatment and prevention of recurrence of multinodular goiter: an evidence-based review of the literature. *World J Surg* 2008;32:1301-1312.
9. Peix JL, Van Box Som P, Olagne E, et al. Results of reoperations for goiter. *Ann Chir* 1997;51:217-221.
10. Berghout A, Wiersinga WM, Drexhage HA, et al. The long-term outcome of thyroidectomy for sporadic nontoxic goitre. *Clin Endocrinol (Oxf)* 1989;31:193-199.
11. Harrer P, Bröcker M, Zint A, et al. The clonality of nodules in recurrent goiters at second surgery. *Langenbecks Arch Surg* 1998;383:453-455.
12. Studer H, Gerber H, Zbaeren J, Peter HJ. Histomorphological and immunohistochemical evidence that human nodular goiters grow by episodic replication of multiple clusters of thyroid follicular cells. *J Clin Endocrinol Metab* 1992;75:1151-1158.
13. Böttcher Y, Eszlinger M, Tönjes A, Paschke R. The genetics of euthyroid familial goiter. *Trends Endocrinol Metab* 2005;16:314-319.
14. Brix TH, Hegedüs L. Genetic and environmental factors in the aetiology of simple goitre. *Ann Med* 2000;32:153-156.
15. Bauer PS, Murray S, Clark N, et al. Unilateral thyroidectomy for the treatment of benign multinodular goiter. *J Surg Res* 2013;184:514-518.