

ROMANIAN ACADEMY

Acta Endocrinologica

The International Journal of the Romanian Society of Endocrinology

(Registered in 1938)

New series

Vol. V, No. 4, October-December 2009

Endocrine Care

Is subtotal thyroidectomy an obsolete indication for the management of benign multinodular goiter?

V. Muntean, I. Domsa, C. Ghervan, A. Valea, O. Fabian

ACTA ENDOCRINOLOGICA continues the former **Romanian Journal of Endocrinology**



EDITURA ACADEMIEI ROMÂNE

IS SUBTOTAL THYROIDECTOMY AN OBSOLETE INDICATION FOR THE MANAGEMENT OF BENIGN MULTINODULAR GOITER?

V. Muntean¹, I. Domsa², C. Ghervan³, A. Valea³, O. Fabian¹.

*Railway Clinical Hospital, Department of Surgery¹, Department of Pathology²,
Emergency Clinical County Hospital, Department of Endocrinology³, "Iuliu
Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, Romania.*

Abstract

Introduction. In our department the standard surgical procedure for multinodular goiter used to be subtotal resection. Over the years, total thyroidectomy has progressively replaced subtotal resections and is performed in most of our patients at present.

Patients and Methods. In a prospective cohort, observational study, we assessed the immediate surgical outcome in 742 consecutive patients with multinodular goiter (MNG), admitted for surgery and operated in our hospital. Of all patients, 664 were women (89.5%) and 78 men (11.5%), aged 15 to 85 years, mean (\pm SD) of 48 ± 13.8 years. Pathology was done on frozen and permanent sections. The complications directly related to surgery in subtotal thyroidectomy (STT) were compared to total thyroidectomy (TT) or near-total thyroidectomy (NTT) patients: temporary hypoparathyroidism, temporary RLN injury, permanent hypoparathyroidism and permanent RLN injury. The χ^2 test (95% confidence interval) was used and values of $p < 0.05$ were considered significant.

Results. There were no significant differences among the patients with SST for MNG, NTT or TT, and TT for recurrent MNG or completion thyroidectomy, with respect to temporary and permanent RLN injury. Significant differences were found for temporary hypoparathyroidism in STT for MNG (9 out of 361 patients, 2.45%) and NTT or TT for MNG (21 out of 266 cases, 7.89%) ($p < 0.01$) and between STT for MNG (9 out of 361 cases, 2.45%) and TT for recurrent MNG for completion thyroidectomy (8 out of 45 cases, 17.77%) ($p < 0.01$) and no difference between NTT or TT for MNG (21 out of 266 cases, 7.89%) and TT for recurrent MNG or completion thyroidectomy (8 out of 45 cases, 17.77%) ($p = 0.11$). We registered no permanent hypoparathyroidism in our patients.

Conclusions. Total thyroidectomy is now the preferred option for the management of patients with bilateral benign MNG. However, TT is associated with a considerable rate of complications, higher than of STT. In patients with bilateral MNG and no malignancy, STT remains in our opinion, a valuable option.

Key words: multinodular goiter, subtotal thyroidectomy, total thyroidectomy.

^Correspondence to: V. Muntean, CF Clinical Hospital, Republicii Rd.18, 400015, Cluj-Napoca, Romania Tel: +40-722704401; Fax: +40264-450394; e-mail: valentin.muntean@gmail.com

Acta Endocrinologica (Buc), vol.V no. 4, p. 471-488, 2009

INTRODUCTION

Until recently, despite numerous studies, the surgical treatment of multinodular goiter was a matter of debate and controversy. The majority of recent papers (1-3) recommend total thyroidectomy as the procedure of choice. The main arguments in favour of total thyroid resection for multinodular goiter are the low morbidity of the procedure in recent series and the higher operative risk of completion thyroidectomy when recurrent goiter or incidental carcinoma after partial resections. The risk of goiter recurrence after subtotal resection, the necessary supplementary hormone therapy in many patients and inadequate resection when incidental carcinoma is found on the operative specimen are other inconveniences.

In our department the standard surgical procedure for multinodular goiter used to be subtotal resection. Starting with year 1998, inspired and encouraged by the increasing published series, we have initiated total thyroid resection in benign multinodular goiter. Over the years total thyroidectomy has progressively replaced subtotal resections and at present it is preferred in most of our patients. In order to clarify the pros and cons for total thyroidectomy (TT) or near-total thyroidectomy (NTT) versus partial resection / subtotal thyroidectomy (STT), five years ago we initiated a prospective study of diagnosis, operative indications, pathology results and immediate outcomes in our patients with thyroid surgery for benign multinodular goiter.

PATIENTS AND METHODS

In a prospective, cohort, observational study, we assessed the immediate surgical outcome in 742 consecutive patients with multinodular goiter, admitted for surgery and operated at a tertiary referral hospital, between July 2003 and June 2008. Of the 742 patients, 664 were women (89.5%) and 78 men (11.5%), aged 15 to 85 years, with a mean (\pm SD) of 48 years (\pm 13.8). All the patients were sent to our hospital by endocrinologists. The study protocol was approved by the Ethics Committee of the "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca.

The patients underwent outpatient functional and imagistic thyroid evaluation, medical treatment and follow-up for variable periods of time, under close supervision of endocrinologists. In 18 patients (2.54%) the goiter was recurrent after a previous thyroidectomy. The surgery was indicated for: symptomatic goiter (dyspnea, dysphagia, voice changes or venous compression) or enlarging; cosmetic reasons; autonomous nodules or dominant nodules in multinodular goiter, suspicion of malignancy; on patient request, because of uncertainty of whether the nodules could represent a malignancy. All the patients included in the study were rendered euthyroid before admission for surgery. Of the 742 patients, 120 had a dominant nodule and underwent preoperative fine needle aspiration cytology (FNAC) under ultrasonographic guidance, with a benign (4,5) / non-neoplastic aspect or THY2 (6). All patients had preoperative calcium measurements and indirect laryngoscopy.

The surgical procedures performed were: subtotal thyroidectomy (STT), partial lobectomy (PL), lobectomy (L), near-total thyroidectomy (NTT) and total thyroidectomy (TT). The standard for L or TT was complete removal of one or both lobes, respectively, while identifying the recurrent laryngeal nerves (RLN) and the parathyroid glands. We systematically performed autotransplantation of parathyroid glands resected or devascularized during thyroidectomy. Patients with NTT underwent the same surgical procedure, with less than 1 g of thyroid tissue left on one side, at the point where RLN enters below the cricothyroid muscle. The surgical procedure for PL or STT was partial removal of one or respectively both lobes, preservation of parathyroid glands *in situ* and autotransplantation of parathyroid glands resected or devascularized, leaving 2-3 g of thyroid tissue along the posterior aspect of the lobes.

The resected thyroid specimen was immediately sectioned and, if there was any suspicion of malignancy, sent for frozen sections. Frozen sections were systematically performed in multinodular goiters with a dominant nodule or nodules suspicious for malignancy on clinical examination, ultrasound or radionuclide scanning. Permanent sections were performed in all patients. Serum calcium was measured in the morning of the day after surgical procedure, when most of the patients were discharged. At that time, any changes of voice or clinical signs of hypocalcemia were noticed. Calcium and Vitamin D3 were routinely given on discharge to patients with TT or NTT.

On the 5th day after surgical procedure the patients were admitted for clinical examination and removal of sutures (when permanent). Serum calcium was measured if it decreased in the day after operation or if there are any signs of hypocalcemia on clinical examination. Indirect laryngoscopy was selectively performed in patients with persistent voice changes. RLN injury and hypoparathyroidism were noticed when present. In patients with cancer on permanent sections a completion total thyroidectomy was performed. If there was no malignancy on permanent sections, the patients were put on L-thyroxine 100 µg/day and scheduled for clinical, serum calcium FT4 and TSH outpatient follow-up at the endocrinologist office, three weeks later. Permanent hypoparathyroidism and permanent RLN injury were diagnosed if persistent after a six months follow-up.

We analyzed the pathology results on frozen and permanent sections. The complications directly related to surgery in STT patients were compared to TT or NTT patients: temporary hypoparathyroidism, temporary RLN injury, permanent hypoparathyroidism and permanent RLN injury. The *y* test (95% confidence interval) was used and values of $p < 0.05$ were considered significant.

RESULTS

Of the 742 patients, 34 (4.58%) with multinodular goiter (two with dominant nodule) did not follow the study protocol or were lost to follow-up and were excluded from the final analysis.

708 patients with multinodular goiter: Surgical procedure, frozen and permanent sections and final diagnosis

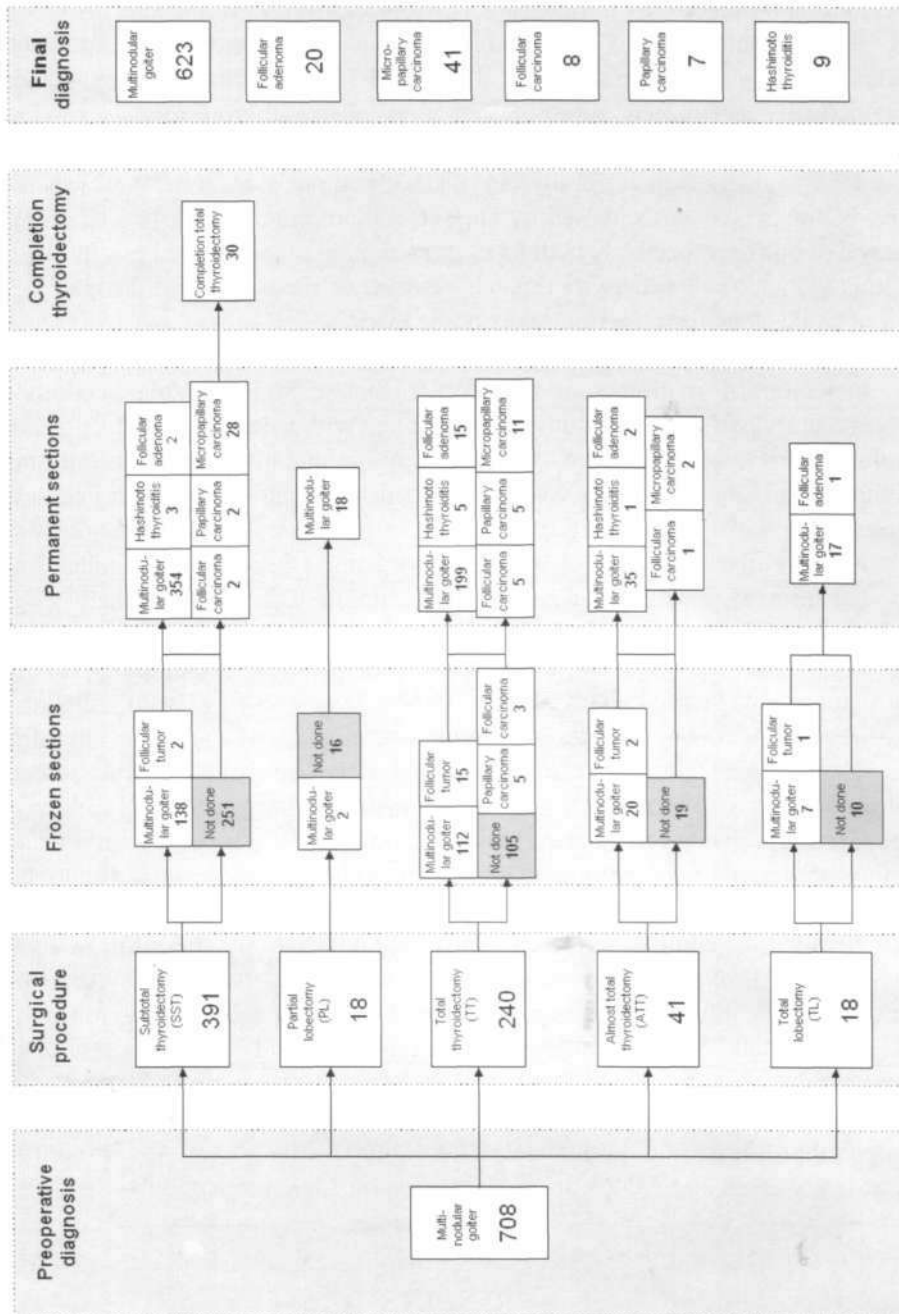


Figure 1. Surgical procedure, pathology report, frozen, and permanent sections, additional surgery/completion thyroidectomy and final diagnosis in 708 patients with multinodular goiter

Table 1 lists the surgical procedures performed in the 708 patients with multinodular goiter, in the five years studied. Subtotal thyroidectomy (STT) was performed in 391 patients (55.2%) and total (TT) and near-total thyroidectomy (NTT) in 240 (33.9%) and 41 (5.8%) patients, respectively (TT and NTT 281 patients, 39.7%, altogether). There was no operative mortality in this group and three patients required urgent re-exploration for compressive haematoma, all after STT. We also recorded subcutaneous haematoma in nine patients and two had postoperative infection of the surgical wound.

The pathology report on frozen and permanent sections, for the five different surgical procedures, is depicted in Fig.1. In the 391 STT patients frozen sections were performed in 140 cases (35.8%), and revealed follicular tumor in two patients. On permanent sections 32 patients had malignancy, 2 papillary, 2 follicular and 28 papillary microcarcinoma, and 30 patients (7.67%) underwent completion total thyroidectomy (Table 2). Five patients with completion thyroidectomy, all of them with multicentric papillary microcarcinoma, were found to have microcarcinoma on the thyroid remnant. In patients with TT, frozen section was performed in 135 of 240 patients (56.25%) and revealed 5 papillary carcinoma, 2 follicular carcinoma and follicular tumors in 15 patients. On permanent sections 36 of the 240 TT patients (15%) had cancer. 5 papillary carcinoma, 5 follicular carcinoma and 11 papillary microcarcinoma. In the 41 NTT patients. 22 frozen sections (53.6%) revealed two follicular tumors. Malignancy was found on permanent sections in 3 patients, one follicular carcinoma and 2 papillary microcarcinoma. In the 708 patients with preoperative diagnosis of multinodular goiter 56 had cancer on permanent sections (7.90%): papillary carcinoma 7, follicular carcinoma 8 and micropapillary carcinoma 41.

Of the 708 patients with multinodular goiter 118 had a dominant nodule with a benign cytology on FNAC. All the patients underwent TT or NTT with frozen sections (Fig.2). Frozen sections revealed cancer in 7 patients, 4 papillary

Table 1. Patients with multinodular goiter: Number of patients and surgical procedures / study year

	Number of patients No. (%)	Subtotal thyroidectomy No. (%)	P a r t i a l Lobectomy No. (%)	Lobectomy No. (%)	Almost total thyroidectomy No. (%)	Total thyroid ectomy No. (%)
07.2003-06.2004	98	81(81%)	2(2%)	1(1%)	2(2%)	12(12%)
07.2004-06.2005	122	90(74%)	2(1.5%)	2(1.50%)	4(3%)	24(20%)
07.2005-06.2006	135	91(67%)	5(4%)	4(3%)	7(5%)	28(21%)
07.2006-06.2007	155	88(57%)	4(3%)	5(3%)	8(5%)	50(32%)
07.2007-06.2008	198	41(20%)	5(3%)	6(3%)	20(10%)	126(64%)
07.2004-06.2008	708	391(55.2%)	18(2.5%)	18(2.5%)	41(5.8%)	240(33.9%)

Table 2. Patients with recurrent multinodular goiter after previous surgery and with completion thyroidectomy: Number of patients / study year and surgical procedures

Period	Number of patients No.(%)	Recurrent after previous surgery No.(%)	Completion TT No.(%)
07.2003-06.2004	~ 9 8 ~	" 2(2%)	~4(4%)~
07.2004-06.2005	122	2(2%)	6(5%)
07.2005-06.2006	135	4(3%)	8(6%)
07.2006-06.2007	155	4(3%)	8(5%)
07.2007-06.2008	198	6(3%)	4(2%)
07.2004-06.2008	708	18(2.54%)	30(3.75%)
Number of patients with total lobectomy (TL)		3(0.42%)	
Number of patients with total thyroidectomy (TT)		15(2.12%)	30(3.75%)

118 patients with multinodular goiter and dominant nodule, benign on FNAC: Frozen and permanent sections

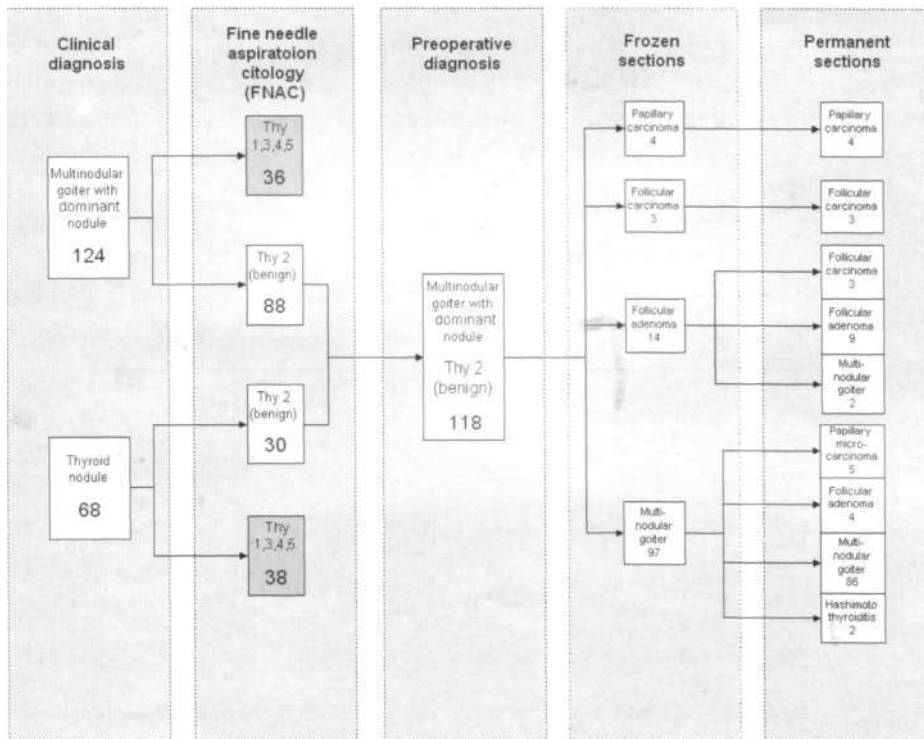


Figure 2. Pathology report, frozen and permanent sections in 118 patients with multinodular goiter and dominant nodule, benign on FNAC

Table 3. Complications in patients with subtotal thyroidectomy (STT), near-total (NTT) and total thyroidectomy (TT)

Complications	361 patients with subtotal thyroidectomy (STT) Number (%)	266 patients with near-total and total thyroidectomy (NTT and TT) Number (%)	45 patients with total thyroidectomy for recurrent goiter or completion (TT) Number (%)
Temporary RLN injury *	5(1.38%)	2(0.75%)	KZ22%)
Permanent RLN injury **	2(0.55%)	1(0.38%)	-
Temporary hypoparathyroidism	9(2.45%)	21(7.89%)	8(17.77%)
Permanent hypoparathyroidism	-	-	-

*Data based on the indirect laryngoscopy performed in patients with vocal changes.

and 3 follicular carcinoma, and permanent sections found other 8 malignancies, 3 follicular carcinoma and 5 papillary microcarcinoma. On permanent sections 15 of 118 patients with multinodular goiter and dominant nodule had cancer (12.71%).

Table 3 depicts the complications related to surgery in 361 patients with STT for multinodular goiter (391 minus the 30 patients with cancer on frozen sections who underwent completion thyroidectomy), 266 patients with NTT or TT for multinodular goiter (281 minus the 15 patients with recurrent goiter) and 45 patients with TT for recurrent multinodular goiter (15 patients) or completion thyroidectomy after initial subtotal resection (30 patients). There were no statistically significant differences among the patients with SST for multinodular goiter, NTT or TT for multinodular goiter, and TT for recurrent multinodular goiter or completion thyroidectomy, with respect to temporary and permanent RLN injury. We found a statistically significant difference with respect to temporary hypoparathyroidism between STT for multinodular goiter (9 out of 361 patients, 2.45%) and NTT or TT for multinodular goiter (21 out of 266 patients, 7.89%), $p < 0.01$ and between STT for multinodular goiter (9 out of 361 patients, 2.45%) and TT for recurrent multinodular goiter or completion thyroidectomy (8 out of 45 patients, 17.77%), $p < 0.01$ and no difference between NTT or TT for multinodular goiter (21 out of 266 patients, 7.89%) and TT for recurrent multinodular goiter or completion thyroidectomy, (8 out of 45 patients, 17.77%), $p = 0.11$. We registered no permanent hypoparathyroidism in our patients.

DISCUSSION

Total excision of the thyroid in the treatment of benign lesions has been surrounded by even more controversy than its role in cancer treatment (7). Traditionally, in benign cases surgery has generally evolved to be as organ preserving as possible (8) and STT has been the standard surgical procedure for multinodular goiter. However, a more radical extent of resection seems justified in order to ensure

that the risk of recurrence is as low as possible, even if its safety was documented in large series for more than thirty years (9,10). TT for benign multinodular goiter was largely embraced by thyroid surgeons only after 1990 (11). Many surgeons perform TT in all patients (12), others recommend this procedure only when both thyroid lobes are involved and when the risk of recurrence is significant (13). Because of lower operative complications, some authors are in favour of NTT. In the following discussion we will consider some of the pros and cons for TT or NTT as an alternative for STT in patients with benign multinodular goiter.

Operative risks

There are a few clinical situations in which the operative risk is the main factor when considering the best therapy. For both benign and malignant thyroid pathology, high surgery rates of complications are not acceptable. In many series, total thyroidectomy TT has been performed with a definitive complication rate of 1% or less for the two main complications, RNL injury and hypoparathyroidism (14,15). Meticulous operative technique and experience in performing thyroid operations are essential for the best outcome with the fewest complications. The widespread adoption of TT for benign thyroid pathology during the last decade was followed by an increased number of complications in some series, mainly permanent hypoparathyroidism (Table 4). In a recent study of 1648 TTs performed in 26 Scandinavian departments, hypocalcemia persistent 6 months after surgery was recorded in 4.4% of patients (16).

The complications of total thyroidectomy can be minimized with increasing experience (7,24). The operative risk is higher in hospitals with an operative volume of less than 150 procedures annually (25). In terms of individual surgeon experience, surgical risk is increased up to the 50th operation, with an exponential decrease to under 1% after other 130 operations (26). Residents can perform TT safely and effectively under the direct supervision of a senior surgeon, with results similar to those of experienced surgeons (26-28).

Careful dissection of the recurrent laryngeal nerve (RLN) represents perhaps the most critical component of thyroidectomy. It long has been established that routine identification of the nerve reduces the risk of iatrogenic injury. In recent years, much NTT attention has been paid to the role that functional monitoring plays in identification and preservation of the RLN (29), and as an adjunct to visual identification of the nerves in minimal-access thyroid surgery (30). Most authors (31,32) agree that neuromonitoring of the RLN during thyroid surgery cannot be demonstrated to reduce RLN injury significantly, compared with the adoption of routine RLN identification. However, its application can be considered for selected high-risk thyroidectomies, in particular if the anatomic situation is complicated by prior surgery, large tissue masses or aberrant nerve course (33,34). Preservation of parathyroid function has moved from the time-consuming technique of dissection of a vascularised pedicle in all cases, to initially selective, and then routine, parathyroid autotransplantation (35).

Table 4. Published data on complications after TT

Author, year	Number of patients with TT	Temporary RLN injury	Permanent RLN injury	Temporary hypoparathyroidism	Permanent hypoparathyroidism
Bergenfelz, 2008(16)	1,648	4.1%	0.97%	9.9%	4.4%
Serpell, 2007 (17)	336		0.3%	13.4%	1.8%
Bron, 2004(13)	834	2.3%	1.1%	14.4%	2.4%
Chiang, 2004(18)	521	5.1%	0.9%		
Jamski, 2004(19)	2323	8.9%	1.9%		
Friguglietti, 2003(20)	370	1.88%	0.35%	12.27%	1.61%
Bellantone, 2002(21)	526		0.4%		3.4%
Rosato, 2002(22)	9,599	4.3%	1.3%	14%	2.2%
Mishra, 2001(23)	127		0.8%		1.6%

Recent technological innovations are facilitating new approaches to surgery of the thyroid gland. Endoscopic surgical techniques allow improved visualization and permit thyroidectomy to be performed through small incisions, often less than 3 cm, which may improve cosmetic outcomes. Finally, surgical robotics, with the promise of further enhanced visualization and surgical dexterity better than that possible with traditional endoscopic approaches, may have future applications to thyroid surgery (36). The only real advantage of new haemostatic technologies, bipolar coagulation, ligature vessel sealing system and harmonic scalpel, has been a shorter operation time (37).

In many series, TT in patients with thyroid hyperfunction and specifically Graves disease resulted in increased risk for complications (38,39) when compared with euthyroid goiters. TT in large goiters (40,41) and retrosternal goiters (42,43) have also resulted in an increased operative risk. Most of the published series (25,44-48), with few exceptions (3,12,49), report the increase of operative risks with the extent of resection (Table 5). With few exceptions (53), in most of the published studies, there is no statistical difference of RLN palsy among primary STT, NTT and TT. Systematic exposure of the nerve during operation reduces the risk of RLN lesions (58). On the contrary, temporary and permanent hypoparathyroidism is much more common in patients with TT when compared with STT patients. Some authors recommend NTT as an alternative to TT, because of lower incidence of postoperative hypoparathyroidism and no increase risk of recurrence (52,57,59,61).

Most of the authors (44,45,58,62) did not notice, but few (54,56) noticed an

Table 5. Comparative published data on complications after STT, ATT, TT

Author, year	No of patients	Surgical procedure	Temporary RLN injury	Permanent RLN injury	Temporary hypopara thyroidism	Permanent hypopara thyroidism
Tezelman, 2008(12)	2906	STT NTT/TT			1.42% 8.4%	
Vaiman, 2008(3)	6223	STT NTT TT		1.2% 1.1% 1.4%		1.9% 2% 2%
Rafferty, 2007(50)	350	TT Completion TT	3.3% 2%	0 0.5%		3.3% 2.5%
Sevim, 2007(51)	290	TT Completion TT	5% 7%	3% 3%		
Erbil, 2006(52)	216	NTT TT			9.8% 26%	
Ozbas, 2005(49)	750	STT NTT TT	2.4% 0.6% 1.9%	0.6% 0 0	8.2% 12.2% 30%	0 0.4%
Aytac, 2005(46)	418	STT TT Completion TT	2% 13.6% 13%	0.03% 9% 8.7%		
Thomusch, 2003(53)	5195	STT NTT TT		0.8% 1.4% 2.3%		1.5% 2.8% 12.5%
Erdem, 2003(54)	141	Completion TT		3.5%		4.2%
Varcus, 2002(55)	1411	STT TT		1.0% 3.0%		0 0.6%
Mishra, 2002(56)	42	Completion TT	4%	0	17%	05
Steinmuller, 2001(57)	2235	STT NTT			15.9% 22.6%	
Muller, 2001(58)	949	Completion TT	5%	3%	2%	0.5
Zaraca, 2000(59)	202	STT NTT TT			2.2% 15.4% 37.7%	
Makeieff, 2000(60)	25	Completion TT	12%	4%	20%	4%

increased operative risk for completion thyroidectomy (Table 5). To reduce the risk, the completion thyroidectomy should be performed by specialized centres (56), either within 7 days of the primary operation or after a minimum of 3 months (62,63).

Incidental carcinoma or microcarcinoma

A strong argument in favor of TT or NTT in multinodular goiter is the common scenario of the incidental finding of cancer in patients operated for benign thyroid conditions (64,65). When less than TT or NTT resection has been performed, completion thyroidectomy is often indicated by the oncology team, with all the inconveniences of a second surgery, psychological and increased operative risks. The reported incidence of carcinoma following thyroidectomy for a presumably benign thyroid disease varies in large limits: 3.4% (microcarcinoma) (66); 7.1% (microcarcinoma) (67); 13.7%(68); 14.07% (microcarcinoma) (69); 21.6% (70).

The reported incidence of cancer in cytologically-benign solitary or dominant cystic nodules in multinodular goiter that have recurred after aspiration was 8.8% (71). The carcinoma incidence was found lower in toxic multinodular goiter - 9.09% and Graves disease - 5.73% when compared to nontoxic multinodular goiter 16.62% (20). In other two studies cancer was found in 7.3% and 8.2% patients with toxic multinodular goiter and 6% and 8.7% in patients with Graves disease (72,73). Tumours are multicentric in 19.8% of the patients (73); 40.7% (67).

With available diagnostic tools (ultrasonography and FNAC) the preoperative diagnosis of malignancy in multinodular goiter is impossible in many cases. Frozen section is unhelpful in the management of thyroid nodules with cytologically proven malignant or on benign aspirates. Selective use of frozen section complements fine needle aspiration cytology findings of suspicious or follicular lesions, especially in the subset with papillary cancer, sometimes allow one-stage total thyroidectomy (74). With follicular lesions it is very difficult to distinguish between benign disease and malignancy, since the diagnosis of malignancy depends on capsular and/or blood vessel invasion (75).

The majority of incidental carcinoma on thyroidectomy specimens is represented by microcarcinomas. Papillary microcarcinoma of the thyroid (PTMC) is defined as a papillary thyroid carcinoma measuring less than 10 mm in the greatest dimension. PTMC is often multifocal and found with increasing incidence with more accurate histopathology examination of surgical specimens (76). The ideal therapeutic approach in PTMC patients remains a subject of debate among endocrinologists and surgeons. Most of the authors are in favour of total thyroidectomy when a pre-operative diagnosis of PTMC is reached (66,67).

It is even more controversial what should be done in patients with incidental PTMC after STT. Some authors recommend that the treatment of patients with PMC should be not different from the treatment of patients with PTMC, and recommend systematic completion thyroidectomy followed by radioiodine and suppressive therapy (67,70,76). Other authors consider that further surgery, such as completion total thyroidectomy or lymph node dissection is not necessary unless gross nodal metastases (64,77), extracapsular invasion (78,79) or multicentricity (80,81) are present.

Postoperative follow-up

Hormonal replacement and the risk of recurrence

In theory, STT in patients with multinodular goiter is a conservative treatment for a benign condition, specifically addressing patient complaints, compression, hyperfunction or esthetic, and leaving a functional thyroid remnant and the patient independent of hormonal replacement. In practice, many of the patients become hypothyroid and dependent on hormonal replacement (49,82). STT leaves a diseased remnant gland. Attempts to suppress nodular recurrence by thyroxin treatment is not always successful. After STT for multinodular goiter, rates of up to 40% are reported for recurrent goiter in the long-term follow-up (53) and in the range of 15-30% it is common in many series (3). The incidence of recurrent goiter in our patients was 2.54% (18 of 708 patients - Table 2), similar to other reports (49). The risk depends on the quality of the remnant gland, on how much thyroid tissue is left in place and the effect of hormonal suppression of thyroid enlargement. There is also considerable variance among endocrinologists on how recurrence is defined, when and the reasons for addressing the patient for further resection.

TT precludes patients from requiring further surgery for recurrent diseases. The patient remains dependent on hormonal replacement and should have the psychological and economic capacity for a permanent medical follow-up and substitutive therapy (55).

Doctor's and patient's preference

Whom and when to operate ?

In what patients do the endocrinologists recommend surgery? There are no clear recommendations or criteria for operating multinodular goiter, and in an endemic area, with high prevalence of goiter, decisions are even more difficult. Depending on their experience and preferences, suspicion of malignancy, difficulties in controlling hyperfunction or thyroid progressive enlargement, some endocrinologists send small goiters for surgery, others continue conservative treatment until late in the evolution of disease, when compression becomes serious or malignancy is proven/obvious.

There are certain situations in which we operate small goiters and/or with minor changes on patients that cannot tolerate the uncertainty of whether the nodule could represent a malignancy, despite extensive discussions with the physician. Other patients request neck ultrasound and thyroid removal after having relatives operated for goiter or thyroid cancer. For patients with minimal unilateral changes, a minimally invasive TL/isthmusectomy under local anesthesia via a very small incision, or via an endoscopic approach for cosmetic purposes, may be the optimal solution (83). Intra-operative frozen sections might sometimes be helpful when we decide less than total thyroidectomy. When both lobes are involved in the pathology process, and this is often the case in an endemic area, TT or NTT remain the alternatives to STT. In these situations, someone may consider that too much has been done for such a small problem.

What surgery?

Many of our patients are now well informed when addressing to the surgeon and some of them have strong opinions regarding the surgery they wish. Because of fear of cancer, some patients request total removal of the gland. Other patients wish to remain independent of hormonal substitution and prefer subtotal resection, whenever possible. It is the endocrinologist's and surgeon's task to inform the patient and to recommend what they consider to be the optimal treatment, and afterwards to adjust therapy to the patient's wish.

Endocrine function after STT is difficult to predict, so that most endocrinologists would recommend TT for toxic goiters. Patients undergoing STT warrant long-term follow-up because of the inability to accurately predict postoperative function. Failure from hypothyroidism develops early; recurrent hyperthyroidism increases with the number of years of follow-up (84).

The endocrinologists' opinion

Long term thyroxin replacement therapy has no inconvenience. Doses are adjusted in the first months of treatment in order to maintain TSH levels in the normal range (0.4 - 4.2 mU/L, optimal around 1 mU/L), therefore the patient needs no further follow-up. The exception concerns pregnant women for whom replacement doses must be increased during pregnancy with a mean of 45% (85). In consequence, TSH surveillance is needed every two months in order to maintain an appropriate level of thyroid hormones. This is quite different from patients with STT, who need at least one annual visit and hormonal assay in order to adjust the replacement therapy and to identify a possible recurrence of the previous pathology. Even appropriate replacement therapy is not able to prevent recurrences (86).

Calcitonin deficiency post thyroidectomy has no impact on plasmatic calcium levels or on bone density, not even in children with prophylactic total thyroidectomy at a very young age (87).

The surgeons' opinion

Because total thyroidectomy is associated with increased operative risks, subtotal thyroid resection based on the morphologic changes in the thyroid gland is still recommended by some surgeons as the standard treatment regimen for multinodular goiter. Serious complications, permanent RLN injury and permanent hypoparathyroidism are difficult to treat and to explain to the patient, mainly when operated for minor complaints. STT is a standard surgical procedure, with its own philosophy, and not a salvage solution, when total lobe removal is not possible or too risky because of inability to visualise the parathyroid glands or RLN. In many modern books of surgery STT is not described and it is probable that some residents who learn surgery in departments in which the standard surgical procedure is TT, never see STT at all. In such a case it is expected to have similar or even higher operative risks for STT when compared to TT or NTT.

Other surgeons with experience in thyroid surgery would prefer TT or NTT because of similar operative risks in their experience and increased risks of completion thyroidectomy, when necessary. Actually, some completion

thyroidectomy, mainly after more than 5 days from initial surgery, might be a nightmare for the surgeon, who wishes he/she had never performed it and waits anxiously in the postoperative period for voice changes or clinical signs of hypocalcemia. Moreover, completion is often perceived as a failure by the patients and often doctors involved in patient's care.

Conclusion

In patients with bilateral multinodular goiter and no distinct or suspect for malignancy nodule, STT remains, in our opinion, a valuable option. When performed as a standardized surgical procedure, the operative risk of STT is lower than for TT. With an adequate amount of thyroid remnant, most of the patients remain independent of hormonal substitution and the recurrence rate is low. When necessary, completion surgery performed by experienced surgeons should not have a higher complication rate than TT.

References

1. 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(7): 1301-1312.
2. Agarwal G, Aggarwal V. Is total thyroidectomy the surgical procedure of choice for benign multinodular goiter? An evidence-based review. *World J Surg* 2008; 32(7): 1313-1324.
3. Vaiman M, Nagibin A, Hagag P, Buyankin A, Olevson J, Shlamkovich N. Subtotal and near total versus total thyroidectomy for the management of multinodular goiter. *World J Surg* 2008; 32(7): 1546-1551.
4. Gharib H, Goellner JR. Fine-needle aspiration biopsy of the thyroid: an appraisal. *Ann Intern Med* 1993; 118(4):282-289.
5. Layfield LJ, Abrams J, Cochand-Priollet B, Evans D, Gharib H, Greenspan F, Henry M, LiVolsi V, Merino M, Michael CW, Wang H, Wells SA. Post-thyroid FNA testing and treatment options: a synopsis of the National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Conference. *Diagn Cytopathol* 2008; 36(6):442-448.
6. Watkinson JC. The British Thyroid Association guidelines for the management of thyroid cancer in adults. *Nucl Med Commun* 2004; 25(9):897-900.
7. Kotan C, Kosem M, Algun E, Ayakta H, Sonmez R, Soylemez O. Influence of the refinement of surgical technique and surgeon's experience on the rate of complications after total thyroidectomy for benign thyroid disease. *Acta Chir Belg* 2003; 103(3):278-281.
8. Gimm O, Brauckhoff M, Thanh PN, Sekulla C, Dralle H. An update on thyroid surgery. *Eur J Nucl Med Mol Imaging* 2002; 29 Suppl 2:S447-52. Epub; 2002 Jul 11.:S447-S452.
9. Perzik S. The place of total thyroidectomy in the management of 909 patients with thyroid disease. *Am J Surg* 1976; 132(4):480-483.
10. Katz AD, Bronson D. Total thyroidectomy. The indications and results of 630 cases. *Am J Surg* 1978; 136(4):450-454.
11. Sellar CA, Schafer M, Buchler MW. [Surgery of the goiter]. *Ther Umsch* 1999; 56(7):380-384.
12. Tezelman S, Borucu I, Senyurek GY, Tunca F, Terzioglu T. The change in surgical practice from subtotal to near-total or total thyroidectomy in the treatment of patients with benign multinodular Goiter. *World J Surg* 2009; 33(3): 400-405.

Surgical management of benign multinodular goiter

- 13 Bron LP, O'Brien CJ. Total thyroidectomy for clinically benign disease of the thyroid gland. *Br J Surg* 2004; 91 (5):569-574.
- 14 Zarnegar R, Brunaud L, Clark OH. Prevention, evaluation, and management of complications following thyroidectomy for thyroid carcinoma. *Endocrinol Metab Clin North Am* 2003; 32(2):483-502.
- 15 Zambudio AR, Rodriguez J, Riquelme J, Soria T, Canteras M, Parrilla P. Prospective study of postoperative complications after total thyroidectomy for multinodular goiters by surgeons with experience in endocrine surgery. *Ann Surg* 2004; 240(1): 18-25.
- 16 Bergenfelz A, Jansson S, Kristoffersson A, Martensson H, Reihner E, Wallin G, Lausen I. Complications to thyroid surgery: results as reported in a database from a multicenter audit comprising 3,660 patients. *Langenbecks Arch Surg* 2008; 393(5):667-673.
- 17 Serpell JW, Phan D. Safety of total thyroidectomy. *ANZ J Surg* 2007; 77(1-2): 15-19.
- 18 Chiang FY, Lee KW, Huang YF, Wang LF, Kuo WR. Risk of vocal palsy after thyroidectomy with identification of the recurrent laryngeal nerve. *Kaohsiung J Med Sci* 2004; 20(9): 431-436.
- 19 Jamski J, Jamska A, Graca M, Barczynski M, Wlodyka J. [Recurrent laryngeal nerve injury following thyroid surgery]. *Przegl Lek* 2004; 61(1):13-16.
- 20 Friguglietti CU, Lin CS, Kulcsar MA. Total thyroidectomy for benign thyroid disease. *Laryngoscope* 2003; 113(10): 1820-1826.
- 21 Bellantone R, Lombardi CP, Bossola M, Boscherini M, De Crea C, Alesina P, Traini E, Princi P, Raffaelli M. Total thyroidectomy for management of benign thyroid disease: review of 526 cases. *World J Surg* 2002; 26(12): 1468-1471.
- 22 Rosato L, Avenia N, De Palma M, Gulino G, Nasi PG, Pezzullo L. [Complications of total thyroidectomy: incidence, prevention and treatment]. *Chir Ital* 2002; 54(5):635-642.
- 23 Mishra A, Agarwal A, Agarwal G, Mishra SK. Total thyroidectomy for benign thyroid disorders in an endemic region. *World J Surg* 2001; 25(3):307-310.
- 24 Dralle H, Sekulla C. [Thyroid surgery: generalist or specialist?]. *Zentralbl Chir* 2005; 130(5):428-432.
- 25 Thomusch O, Machens A, Sekulla C, Ukkat J, Lippert H, Gastinger I, Dralle H. Multivariate analysis of risk factors for postoperative complications in benign goiter surgery: prospective multicenter study in Germany. *World J Surg* 2000; 24(11): 1335-1341.
- 26 Lamade W, Renz K, Willeke F, Klar E, Herfarth C. Effect of training on the incidence of nerve damage in thyroid surgery. *Br J Surg* 1999; 86(3):388-391.
- 27 Acun Z, Cihan A, Ulukent SC, Comert M, Ucan B, Cakmak GK, Cesur A. A randomized prospective study of complications between general surgery residents and attending surgeons in near-total thyroidectomies. *Surg Today* 2004; 34(12):997-1001.
- 28 Emre AU, Cakmak GK, Tascilar O, Ucan BH, Irkorucu O, Karakaya K, Balbaloglu H, Dibeklioglu S, Gul M, Ankarali H, Comert M. Complications of total thyroidectomy performed by surgical residents versus specialist surgeons. *Surg Today* 2008; 38(10):879-885.
- 29 Miller MC, Spiegel JR. Identification and monitoring of the recurrent laryngeal nerve during thyroidectomy. *Surg Oncol Clin N Am* 2008; 17(1): 121-144.
- 30 Terris DJ, Anderson SK, Watts TL, Chin E. Laryngeal nerve monitoring and minimally invasive thyroid surgery: complementary technologies. *Arch Otolaryngol Head Neck Surg* 2007; 133(12): 1254-1257.
- 31 Netto IP, Vartarian JG, Ferraz PR, Salgado P, Azevedo JB, Toledo RN, Testa JR, Carrara-de-Angelis E, Kowalski LP. Vocal fold immobility after thyroidectomy with intraoperative recurrent laryngeal nerve monitoring. *Sao Paulo Med J* 2007; 125(3): 186-190.

32. Shindo M, Chheda NN. Incidence of vocal cord paralysis with and without recurrent laryngeal nerve monitoring during thyroidectomy. *Arch Otolaryngol Head Neck Surg* 2007; 133(5):481-485.
33. Hermann M, Hellebart C, Freissmuth M. Neuromonitoring in thyroid surgery: prospective evaluation of intraoperative electrophysiological responses for the prediction of recurrent laryngeal nerve injury. *Ann Surg* 2004; 240(1):9-17.
34. Chan WF, Lang BH, Lo CY. The role of intraoperative neuromonitoring of recurrent laryngeal nerve during thyroidectomy: a comparative study on 1000 nerves at risk. *Surgery* 2006; 140(6):866-872.
35. Delbridge L. Total thyroidectomy: the evolution of surgical technique. *ANZ J Surg* 2003; 73(9):761-768.
36. Becker AM, Gourin CG. New technologies in thyroid surgery. *Surg Oncol Clin N Am* 2008; 17(1):233-248.
37. Sartori PV, De Fina S, Colombo G, Pugliese F, Romano F, Cesana G, Uggeri F. Ligasure versus Ultracision(R) in thyroid surgery: a prospective randomized study. *Langenbecks Arch Surg* 2008; 393(5):655-658.
38. Pelizzo MR, Bernante P, Toniato A, Piotto A, Grigoletto R. [Hypoparathyroidism after thyroidectomy. Analysis of a consecutive, recent series]. *Minerva Chir* 1998; 53(4):239-244.
39. Chiang FY, Lin JC, Wu CW, Lee KW, Lu SP, Kuo WR, Wang LF. Morbidity after total thyroidectomy for benign thyroid disease: comparison of Graves' disease and non-Graves' disease. *Kaohsiung J Med Sci* 2006; 22(11):554-559.
40. Chaudhary IA, Samiullah, Masood R, Majrooh MA, Mallhi AA. Recurrent laryngeal nerve injury: an experience with 310 thyroidectomies. *J Ayub Med Coll Abbottabad* 2007; 19(3):46-50.
41. Runkel N, Riede E, Mann B, Buhr HJ. Surgical training and vocal-cord paralysis in benign thyroid disease. *Langenbecks Arch Surg* 1998; 383(3-4):240-242.
42. Chauhan A, Serpell JW. Thyroidectomy is safe and effective for retrosternal goitre. *ANZ J Surg* 2006; 76(4):238-242.
43. Chow TL, Chan TT, Suen DT, Chu DW, Lam SH. Surgical management of substernal goitre: local experience. *Hong Kong Med J* 2005; 11(5):360-365.
44. Sandonato L, Graceffa G, Cipolla C, Fricano S, Acquaro P, Latteri F, Latteri MA. [Benign diseases of the thyroid: indications for surgical treatment and the current role of total thyroidectomy]. *Chir Ital* 2003; 55(2): 179-187.
45. Testini M, Nacchiero M, Portincasa P, Miniello S, Piccinni G, Di Venere B, Campanile L, Lissidini G, Bonomo GM. Risk factors of morbidity in thyroid surgery: analysis of the last 5 years of experience in a general surgery unit. *Int Surg* 2004; 89(3): 125-130.
46. Aytac B, Karamercan A. Recurrent laryngeal nerve injury and preservation in thyroidectomy. *Saudi Med J* 2005; 26(11): 1746-1749.
47. Gaujoux S, Leenhardt L, Tresallet C, Rouxel A, Hoang C, Jublanc C, Chigot JP, Menegaux F. Extensive thyroidectomy in Graves' disease. *J Am Coll Surg* 2006; 202(6):868-873.
48. Erbil Y, Barbaras U, Issever H, Borucu I, Salmalioglu A, Mete O, Bozboru A, Ozarmagan S. Predictive factors for recurrent laryngeal nerve palsy and hypoparathyroidism after thyroid surgery. *Clin Otolaryngol* 2007; 32(1):32-37.
49. Ozbas S, Kocak S, Aydintug S, Cakmak A, Demirkiran MA, Wishart GC. Comparison of the complications of subtotal, near total and total thyroidectomy in the surgical management of multinodular goitre. *Endocr J* 2005; 52(2): 199-205.
50. Rafferty MA, Goldstein DP, Rotstein L, Asa SL, Panzarella T, Gullane P, Gilbert RW, Brown DH, Irish JC. Completion thyroidectomy versus total thyroidectomy: is there a difference in complication rates? An analysis of 350 patients. *J Am Coll Surg* 2007; 205(4):602-607.
51. Sevim T. Risk factors for permanent laryngeal nerve paralysis in patients with thyroid carcinoma.

Clin Otolaryngol 2007; 32(5):378-383.

52. Erbil Y, Barbaras U, Salmaslioglu A, Yanik BT, Bozbora A, Ozarmagan S. The advantage of near-total thyroidectomy to avoid postoperative hypoparathyroidism in benign multinodular goiter. *Langenbecks Arch Surg* 2006; 391(6):567-573.

53. Thomusch O, Sekulla C, Dralle H. [Is primary total thyroidectomy justified in benign multinodular goiter? Results of a prospective quality assurance study of 45 hospitals offering different levels of care]. *Chirurg* 2003; 74(5):437-443.

54. Erdem E, Gulcelik MA, Kuru B, Alagol H. Comparison of completion thyroidectomy and primary surgery for differentiated thyroid carcinoma. *Eur J Surg Oncol* 2003; 29(9):747-749.

55. Varcus F, Bordos D, Peix JL, Caloghera C, Lazar F. [Surgical treatment of thyroid nodules. The immediate results after different thyroidectomy methods]. *Chirurgia (Bucur)* 2002; 97(5):433-440.

56. Mishra A, Mishra SK. Total thyroidectomy for differentiated thyroid cancer: primary compared with completion thyroidectomy. *Eur J Surg* 2002; 168(5):283-287.

57. Steinmuller T, Ulrich F, Rayes N, Lang M, Seehofer D, Tullius SG, Jonas S, Neuhaus P. [Surgical procedures and risk factors in therapy of benign multinodular goiter. A statistical comparison of the incidence of complications]. *Chirurg* 2001; 72(12):1453-1457.

58. Muller PE, Jakoby R, Heinert G, Spelsberg F. Surgery for recurrent goitre: its complications and their risk factors. *Eur J Surg* 2001; 167(11):816-821.

59. Zaraca F, Di Paola M, Gossetti F, Proposito D, Filippoussis P, Montemurro L, Mancini B, Gallina S, Talarico E, Talarico C, Lazzaro M, Mulieri G, Flati D, Flati G, Carboni M. [Benign thyroid disease: 20-year experience in surgical therapy]. *Chir Ital* 2000; 52(1):41-47.

60. Makeieff M, Marlier F, Khudjadze M, Garrel R, Crampe L, Guerrier B. [Substernal goiter. Report of 212 cases]. *Ann Chir* 2000; 125(1):18-25.

61. Acun Z, Comert M, Cihan A, Ulukent SC, Ucan B, Cakmak GK. Near-total thyroidectomy could be the best treatment for thyroid disease in endemic regions. *Arch Surg* 2004; 139(4):444-447.

62. Walgenbach S, Junginger T. [Is the timing of completion thyroidectomy for differentiated thyroid carcinoma prognostic significant?]. *Zentralbl Chir* 2002; 127(5):435-438.

63. Erbil Y, Bozbora A, Ademoglu E, Salmaslioglu A, Ozarmagan S. Is timing important in thyroid reoperation? *J Otolaryngol* 2008; 37(1):56-64.

64. Ito Y, Higashiyama T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Kuma K, Miyauchi A. Prognosis of patients with benign thyroid diseases accompanied by incidental papillary carcinoma undetectable on preoperative imaging tests. *World J Surg* 2007; 31(8):1672-1676.

65. Sakorafas GH, Giotakis J, Stafyla V. Papillary thyroid microcarcinoma: a surgical perspective. *Cancer Treat Rev* 2005; 31(6):423-438.

66. Pisello F, Geraci G, Sciume C, Li VF, Modica G. [Total thyroidectomy of choice in papillary microcarcinoma]. *G Chir* 2007; 28(1-2):13-19.

67. Sakorafas GH, Stafyla V, Kolettis T, Tolumis G, Kassaras G, Peros G. Microscopic papillary thyroid cancer as an incidental finding in patients treated surgically for presumably benign thyroid disease. *J Postgrad Med* 2007; 53(1):23-26.

68. Taneri F, Kurukahvecioglu O, Ege B, Yilmaz U, Tekin E, Cifter C, Onuk E. Prospective analysis of 518 cases with thyroidectomy in Turkey. *Endocr Regul* 2005; 39(3):85-90.

69. Sacco R, Aversa S, Innaro N, Carpino A, Bolognini S, Amorosi A. [Thyroid microcarcinoma and multinodular struma. Personal experience and considerations regarding surgical therapy]. *Chir Ital* 2006; 58(1):69-75.

70. Carlini M, Giovannini C, Mercadante E, Castaldi F, Dell'Avanzato R, Zazza S. [Incidental thyroid microcarcinoma in benign thyroid disease. Incidence in a total of 100 consecutive thyroidectomies]. *ChirItal* 2006; 58(4):441-447.
71. Pla-Marti V, Fernandez-Martinez C, Pallas-Regueira A, Rodriguez-Carrillo R, Ibanez-Arias A, Flors-Alandi C, Roig-Vila JV. [Approach to cytologically-benign recurrent thyroid cysts]. *Cir Esp* 2005; 77(5):267-270.
72. Cakir M, Arici C, Alakus H, Altunbas H, Balci MK, Karayalcin U. Incidental thyroid carcinoma in thyrotoxic patients treated by surgery. *Horm Res* 2007; 67(2):96-99.
73. Miccoli P, Minuto MN, Galleri D, D'Agostino J, Basolo F, Antonangeli L, Aghini-Lombardi F, Berti P. Incidental thyroid carcinoma in a large series of consecutive patients operated on for benign thyroid disease. *ANZ J Surg* 2006; 76(3): 123-126.
74. Cheng MS, Morgan JL, Serpell JW. Does frozen section have a role in the intraoperative management of thyroid nodules? *ANZ J Surg* 2002; 72(8):570-572.
75. Giuliani D, Willemsen P, Verhelst J, Kockx M, Vanderveken M. Frozen section in thyroid surgery. *Acta Chir Belg* 2006; 106(2): 199-201.
76. Kucuk NO, Tari P, Tokmak E, Aras G. Treatment for microcarcinoma of the thyroid—clinical experience. *Clin Nucl Med* 2007; 32(4):279-281.
77. Noguchi S, Yamashita H, Murakami N, Nakayama I, Toda M, Kawamoto H. Small carcinomas of the thyroid. A long-term follow-up of 867 patients. *Arch Surg* 1996; 131 (2): 187-191.
78. Yamashita H, Noguchi S, Murakami N, Toda M, Uchino S, Watanabe S, Kawamoto H. Extracapsular invasion of lymph node metastasis. A good indicator of disease recurrence and poor prognosis in patients with thyroid microcarcinoma. *Cancer* 1999; 86(5):842-849.
79. Shulutko AM, Semikov VI, Griaznov VI, Chakvetadze NG, Popov SV. [Clinical value, diagnosis and treatment of thyroid differentiated microcarcinoma]. *Khirurgiia (Mosk)* 2007;(12):4-10.
80. Ardito G, Revelli L, Lucci C, Giacinto O, Praquin B. [Papillary microcarcinoma [correction of carcinoma] of the thyroid: clinical experience and prognosis factors]. *Ann Ital Chir* 2001; 72(3):261-265.
81. Pelizzo MR, Bosch IM, Toniato A, Pagetta C, Pioletto A, Bernante P, Casara D, Pennelli G, Rubello D. Natural history, diagnosis, treatment and outcome of papillary thyroid microcarcinoma (PTMC): a mono-institutional 12-year experience. *Nucl Med Commun* 2004; 25(6):547-552.
82. Peix JL, Van Box SP. [Role of total thyroidectomy in the treatment of benign thyroid diseases]. *Ann Endocrinol (Paris)* 1996; 57(6):502-507.
83. Mechanick JI, Carpi A. Thyroid cancer: the impact of emerging technologies on clinical practice guidelines. *Biomed Pharmacother* 2008; 62(8):554-558.
84. Sivanandan R, Ng LG, Khin LW, Lim TH, Soo KC. Postoperative endocrine function in patients with surgically treated thyrotoxicosis. *Head Neck* 2004; 26(4):331-337.
85. Mandel SJ, Larsen PR, Seely EW, Brent GA. Increased need for thyroxine during pregnancy in women with primary hypothyroidism. *N Engl J Med* 1990; 323(2):91-96.
86. Zelmanovitz T, Zelmanovitz F, Genro S, Gus P, de Azevedo MJ, Gross JL. [Analysis of the factors associated with recurrence of post-thyroidectomy goiter]. *Rev Assoc Med Bras* 1995; 41(2):86-90.
87. Niccoli-Sire P, Murat A, Baudin E, Henry JF, Proye C, Bigorgne JC, Bstandig B, Modigliani E, Morange S, Schlumberger M, Conte-Devolx B. Early or prophylactic thyroidectomy in MEN 2/ FMTC gene carriers: results in 71 thyroidectomized patients. The French Calcitonin Tumours Study Group (GETC). *Eur J Endocrinol* 1999; 141(5):468-474.