

Type of Operation for Multinodular Goitre and Solitary Nodule

S. Lanitis, A. Kouloura, P. Zafiriadou, C. Karaliotas

Abstract

Many countries and medical associations have developed guidelines for the management of benign thyroid conditions, including the surgical management of multinodular goitre and the non-toxic solitary thyroid adenoma. It is clearly stated in most guidelines that the aim of the surgical procedure is the safe and definite management of the thyroid pathology. Our aim is to provide evidence to support or reject different kinds of surgical procedures used for the management of non-toxic thyroid conditions i.e. multinodular goitre and solitary nodule. Thyroid nodules are common in the general population. Only 4-8% are clinically detectable, but US has shown the incidence to be 13-67%. Many studies have reported that malignancy can be found in 5% of these nodules. The aim of this paper is to present the facts, the pros and cons of each operation used for the management of these thyroid conditions, and provide evidence concerning the ideal procedure that combines safety with the most definite results. Despite the fact that most authors, experts and relevant medical associations currently consider total thyroidectomy (TT) as the gold standard for the management of benign goitre, there is still debate in the literature. It seems that when compared to less radical operations, TT has a lower recurrence rate, and hence a lower risk for complications associated with a reoperation. Moreover, in expert hands, it is equally as safe as less radical procedures in terms of permanent complications (i.e hypoparathyroidism and recurrent laryngeal nerve injury). Nevertheless, subtotal thyroidectomy (ST) has been found to be safer in terms of temporary complications since lower rates have been recorded. The incidence of "occult thyroid cancers" ranges from 3% to 16.6% (level II-III); therefore, if initial surgery is anything less than TT or near-total thyroidectomy, a reoperation is indicated. Obviously, the high recurrence rate along with the significant rate of occult thyroid cancers increases the need for necessary reoperations after a ST; as a result, associated morbidity increases. The incidence of occult cancer in benign solitary non-toxic nodules is 5%, irrespective of the size of the nodule. The literature describes two acceptable surgical options, each with its pros and cons: an upfront TT or a total lobectomy, and in the case of an occult cancer, a completion total thyroidectomy. Both approaches are acceptable to the surgical community and are included in the national guidelines.

- For benign non-toxic solitary nodules, a total lobectomy or a total thyroidectomy can be performed after a thorough discussion with the patient, presentation of the current literature data, presentation of the pros and cons of each procedure, and acquisition of informed consent from the patient for the procedure chosen.
- For benign multinodular non-toxic goitre, total thyroidectomy is the procedure of choice since it may decrease the recurrence rate, it can decrease the reoperation rate, it can reduce the overall morbidity associated with a reoperation, and it can successfully manage "occult" thyroid cancers
- The operation should be performed by an experienced surgeon to ensure that the incidence of permanent complications (i.e. RLN palsy and hypoparathyroidism) is lower than 1-2%.

Key words: *Multinodular goitre; solitary nodule; thyroid surgery*

Introduction

Many countries and medical associations have developed guidelines for the management of benign thyroid conditions,

including the surgical management of multinodular goitre and non-toxic solitary thyroid adenoma. This paper was based on the following guidelines and sources: European society for medical Oncology (ESMO) 2012, American Association of clinical endocrinologists (AACE) 2010, National Comprehensive Cancer Network (NCCN) 2013, German Association of Endocrine Surgeons (GAES) 2011, 2013, American Thyroid Association (ATA) 2009, British Thyroid Association and Royal college of physicians (BTA)

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2007, AACE/AME/ETA 2010, European Thyroid Association (ETA). Moreover, in an attempt to provide the best possible evidence, data from randomized control trials (RCT) and meta-analyses were also used.

As clearly stated in most guidelines, the aim of the surgical procedure is the safe and definite management of the thyroid pathology [1]. Our aim is to provide evidence to support or reject different kinds of procedures used for the management of non-toxic thyroid conditions i.e. multinodular goitre and solitary nodule.

It is well known that thyroid nodules are common in the general population. Despite the fact that only 4-8% are clinically detectable, the percentage can be higher with the US reporting a range between 13 and 67 per cent. Moreover, thyroid nodules in postmortem specimens have been recorded in about 50% of the population [2]. Many studies have shown that malignancy can be found in 5% of these nodules irrespective of their size [3].

For the evaluation and management of thyroid nodules, the proposed algorithm in the NCCN guidelines Version 2, 2013 recommends starting the assessment with a thyroid-stimulating hormone (TSH) and neck ultrasonography (US) assessing in addition to the thyroid, the central and lateral cervical compartments for suspicious lymph nodes. If the TSH is normal or elevated, the diagnosis of a non-toxic solitary nodule or a benign multinodular goitre is suspected. Based on the clinical and sonographic features, a fine needle aspiration (FNA) of the suspicious nodes is recommended to exclude malignancy. For nodules not meeting criteria for FNA or for nodules with benign FNA, surveillance with US is recommended every six to twelve months. For nodules suspicious for malignancy, a different algorithm is followed which is not within the scope of this paper. As concerns the management of the remaining patients, one option is surgery. The aim of this paper is to present the facts, the pros and cons of each procedure and provide evidence regarding the ideal operation that combines safety with the most definite results.

Methods

First of all, we need to keep in mind that we are dealing with a benign condition; hence, three major questions need to be answered in order to decide on the most appropriate procedure: (a) what is the recurrence rate for each operation? (b) what is the incidence of occult thyroid cancer in these patients? and (c) is there a need for reoperation? If yes, in which cases and at what subsequent "cost"?

When choosing the appropriate surgery, we further need to consider the associated problems following each procedure - mainly, morbidity. And when we talk about morbidity in thyroid surgery, we mainly refer to temporary or permanent

recurrent laryngeal palsy and hypoparathyroidism. This raises yet another question: what is the safety of each procedure?

In an attempt to fulfill the aforementioned criteria and mainly to avoid serious complications, many different procedures have been adopted in the past for the management of thyroid nodules; some are still used by many authors. These range from a simple lobectomy to total thyroidectomy while in between, there are less radical operations such as subtotal thyroidectomy, near total thyroidectomy and the Hartley-Dunhill procedure.

Nowadays, there is a trend to perform total or near total thyroidectomy for most thyroid pathologies. In order to support this practice and decide on the most appropriate operation, we need to answer two important questions: (a) is total thyroidectomy necessary for the management of a benign disease such as multinodular goitre and benign solitary nodule? and (b) is TT a safe operation when performed by experts?

In order to answer the first question, we must take into account the recurrence rate after each type of operation and the associated sequelae. Moreover, it is important to know the incidence of occult thyroid cancer among these patients; ultimately, we also need to estimate the need for reoperation and the associated risk for complications.

When it comes to the safety of the operation, the major concern is the incidence of temporary or permanent hypoparathyroidism and the incidence of recurrent laryngeal nerve palsy. Of course, there also other minor issues with morbidity that have to be taken into account but since they have nothing to do with the extent of the thyroid resection per se, they are similar for the different operations.

Despite the fact that most authors, experts and relevant medical associations currently consider total thyroidectomy as the gold standard for the management of benign goitre, there is still considerable debate in the literature [4].

Those in favour of TT support that there is a lower risk for recurrence and subsequently, a lower need for reoperation. Consequently, this lowers the risk for postoperative complications since it is widely accepted that thyroid reoperations are associated with a higher risk of permanent hypoparathyroidism and recurrent laryngeal nerve damage.

It is also supported that TT is the proper operation and most likely adequate for the management of occult thyroid carcinoma, saving the patient an unnecessary reoperation. On the other hand, those in favour of a less radical operation, such as subtotal thyroidectomy, mainly support that the risk of major complication is lower with these operations [4]. Two major reviews have addressed this issue up to now [5,6]. The main conclusion was that subtotal thyroidectomy is indeed associated with a high risk of recurrence ranging from 0-50% [5]. However, the studies on which this sys-

tematic review was based were retrospective and there was heterogeneity in the follow-up time and the terminology of “recurrence”, hence the wide range in reported incidence. Nevertheless, in most studies the recurrence rate after ST was higher than 10% and the recommendation of the study was to offer TT as the appropriate procedure for the BMNG (B recommendation) [5]. Moreover, Moalem et al. also analyzed the complication rate after thyroid reoperations and found that there is a significantly higher incidence of morbidity in reoperations. The incidence of hypoparathyroidism ranges from 0-22% in reoperations as opposed to 0-4% after the first operation, while the incidence of recurrent laryngeal nerve palsy ranges from 0-13% in reoperations as opposed to 0-4% after the first operation [5,6]. It is obvious that following subtotal thyroidectomy a high recurrence rate is anticipated and the need for reoperation will be higher than TT, thereby increasing the possible overall morbidity for those patients that eventually will need to undergo a second operation. In conclusion, ST is not as definite an

operation as TT and overall, it is not as safe as TT.

This, however, is only an indirect conclusion. What we actually need is direct evidence from the comparison of TT vs. ST for the management of non-toxic multinodular goitre.

Results

Unfortunately, only four RCTs and no meta-analyses have addressed this issue. In consequence, we performed a meta-analysis of the RCT in an attempt to provide a good level of evidence for the effectiveness and the safety of the different surgical procedures used.

Overall, four RCTs on this subject fulfilled the criteria and had comparative data that could be included in a meta-analysis [4,7-9]. In total, 701 cases underwent either a ST (N=385), a TT (N=260) or a DO (N=316) with a follow-up ranging from 3.6 years to 14.5 years. Three studies compared DO with ST [4,7,8], two studies compared TT with ST [8,9] while only one paper compared DO with TT (Table 1) [8].

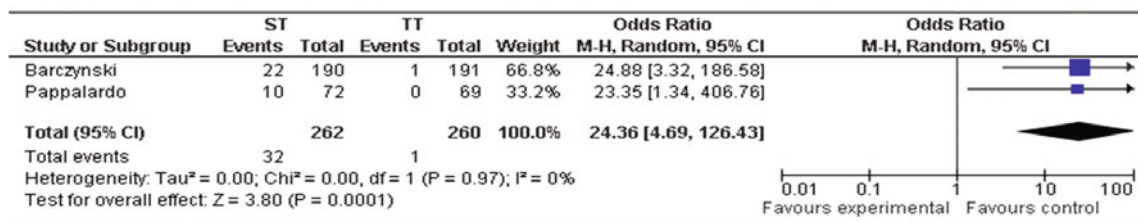
Table 1. RCT comparing various surgical procedures for the management of BMNG (DO=Dunhill operation, ST= Subtotal thyroidectomy, TT= total thyroidectomy, FU= follow up)

	DO	ST	TT	FU
Raves (2013)	6/100	8/100	-	11.3 years
Andaker (1992)	0/27	1/23	-	3.6 years
Pappalardo (1998)	-	10/72	0/69	14.5 years
Barczynski (2010)	9/189	22/190	1/191	5 years

The following results concerning recurrence rate are presented in table 2.

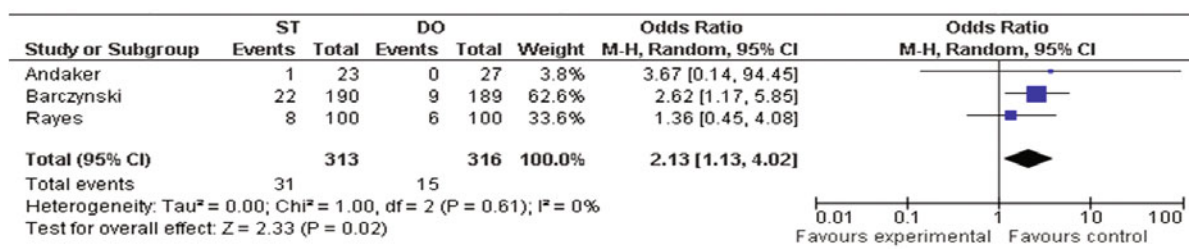
Table 2. Recurrence rate

2A. Subtotal versus Total Thyroidectomy (N=522)



The cumulative recurrence rate for ST was 12% while for TT was 0.38% and this was statistically very significant (p=0.0001).

2B. Subtotal versus Dunhill operation (N=629)



The cumulative recurrence rate for ST was 9.9% while for DO was 4.74% and this was statistically significant (p=0.02).

2C. TT vs. DO (N=380)

Only one study provided comparative data for these two operations [8]. The recurrence rate for DO was 4.76% while for TT was 0.52% and this was statistically significant ($p=0.01$).

Discussion (concerning recurrence rate)

Based on these results, it is obvious that ST is the least definite operation while TT is the most definite operation leading to the least recurrence rate which should be $<1\%$ in any case (level of evidence 2B) (See Table 2).

But why do we really need a definite operation for a benign disease when there is no evidence from the preoperative workup that there is a malignancy?

It is now well known that the size of the nodules is not a good indicator of malignancy and is no longer considered the principal criterion for performing an FNA from a nodule. Moreover, the incidence of occult cancers seems to be equal between solitary non-toxic nodules and multinodular non-toxic goitre [2]. The indication for performing an FNA is nowadays based on the US characteristics of the nodules such as the type of blood supply, the composition of the nodules and the presence of microcalcifications. Nonetheless, even after this workup, occult cancers can be found in thyroidectomy specimens; according to all guidelines, a

total thyroidectomy is the treatment of choice in such cases.

The incidence of these “occult thyroid cancers” ranges from 3% to 16.6% (level II-III) [5]; hence, if initial surgery is anything less than TT or near total thyroidectomy, a reoperation is indicated (B recommendation). Obviously, the high recurrence rate along with the significant rate of occult thyroid cancers increases the need for necessary reoperations after ST and, as a result, increases the associated morbidity.

Safety of the procedure

However, although TT is recommended to achieve more definite results and reduce the rate of reoperations, there is concern about the relative safety of this approach and whether the benefit outweighs the risk of this practice.

A major review in 2008 showed that the rate of permanent RLN palsy and hypoparathyroidism was not different between ST and TT and concluded that this rate was 1-2% when the operations were performed by a well-trained endocrine surgeon (Level II-IV) [5]. Nevertheless, ST was found to be safer in terms of temporary complications since lower rates were recorded.

Our meta-analysis of the RCT concerning the safety of the procedures about the complication of hypoparathyroidism showed the following: (Table 3)

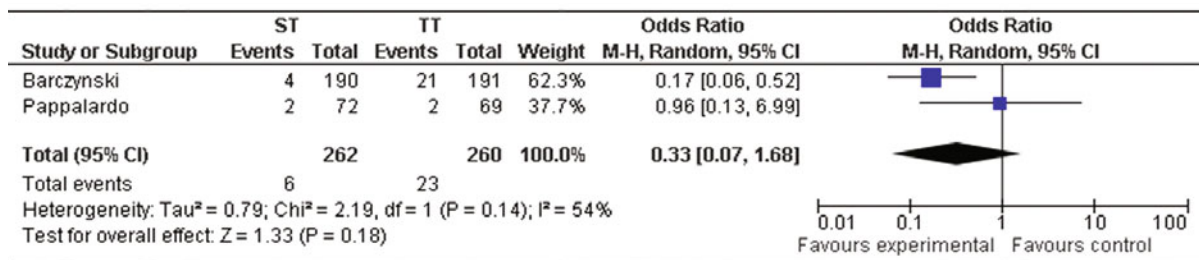
Table 3. Hypoparathyroidism

RCT comparing the various procedures for the management of the BMNG concerning major complications. (DO=Dunhill operation, ST= Subtotal thyroidectomy, TT= total thyroidectomy, FU= follow-up, *=permanent)

	DO	ST	TT	FU
Rayes (2013)	6/100 1/100*	6/100 0/100*	-	11.3 years
Andaker (1992)	2/27 0/27 *	4/23 0/23*	-	3.6 years
Pappalardo (1998)	-	2/72 1/72*	2/69 2/69*	14.5 years
Barczynski (2010)	8/189 0/189*	4/190 0/190*	21/191 1/191*	5 years

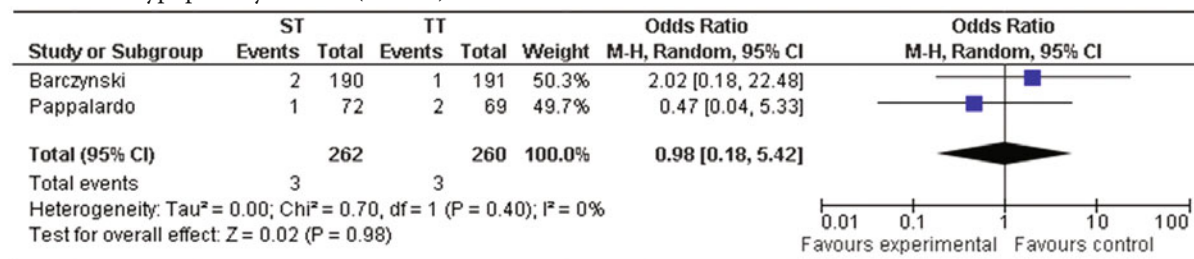
3A. Total versus subtotal thyroidectomy

Temporary hypoparathyroidism (N=322)



The incidence of temporary hypoparathyroidism was 2.29% after ST and 8.84% after TT, but this difference was not found to be significantly different in this meta-analysis compared with previous studies ($p=0.18$).

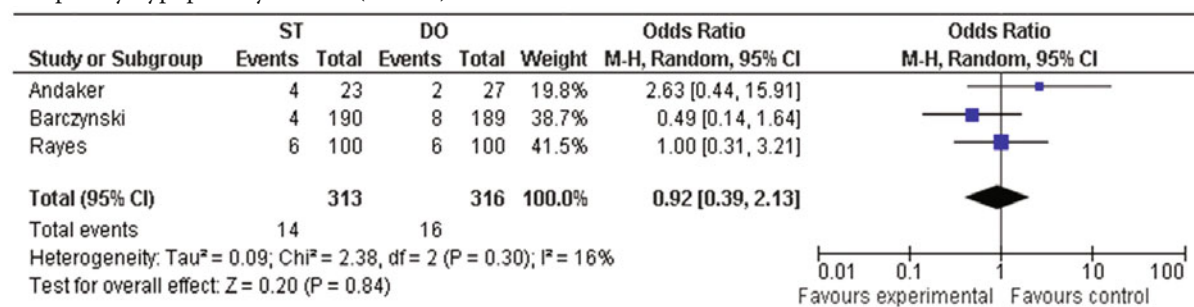
Permanent hypoparathyroidism (N=322)



The incidence of permanent hypoparathyroidism was 1.14% after ST and 1.15% after TT but this difference was not found to be significantly different in this meta analysis in accordance with previous studies (p=0.98).

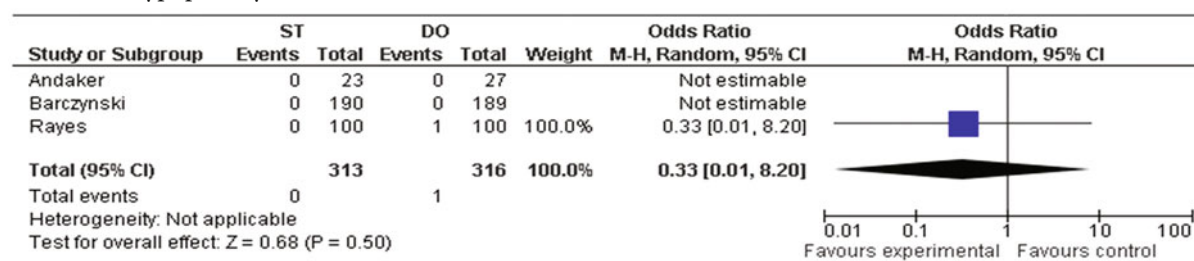
3B. Dunhill operation versus subtotal thyroidectomy

Temporary hypoparathyroidism (N=629)



The incidence of temporary hypoparathyroidism was 4.47% after ST and 5.06% after DO but this difference was not found to be significantly different in this meta analysis (p=0.84).

Permanent hypoparathyroidism (N=629)



The incidence of permanent hypoparathyroidism was 0% after ST and 0.31% after DO but this difference was not found to be significantly different in this meta analysis (p=0.5).

3C. Dunhill operation versus total thyroidectomy (N=380)

The results of the one RCT showed that the incidence of temporary hypoparathyroidism was 4.23% after DO and 10.99% after TT and this difference was significant

(p=0.007).

On the other hand, there were no permanent injuries after ST (0%) while there was only one injury after DO (0.52%) and there was no significant difference in this case (p>0.05)

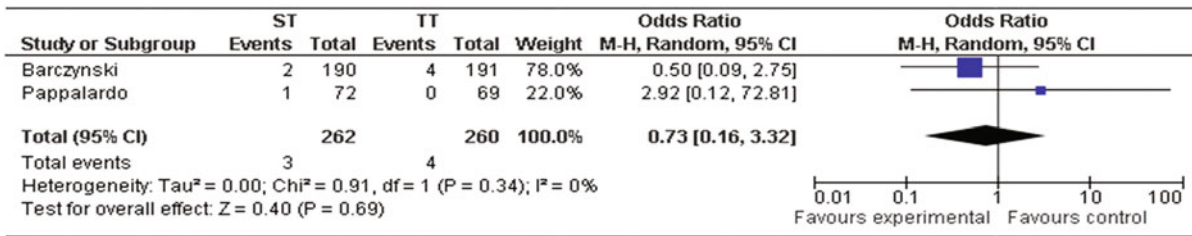
Regarding to recurrent laryngeal nerve injury the results were as follow (Table 4):

Table 4. Recurrent laryngeal nerve palsy

RCT comparing the various procedures for the management of the BMNG concerning major complications. (DO=Dunhill operation, ST= Subtotal thyroidectomy, TT= total thyroidectomy, FU= follow-up)

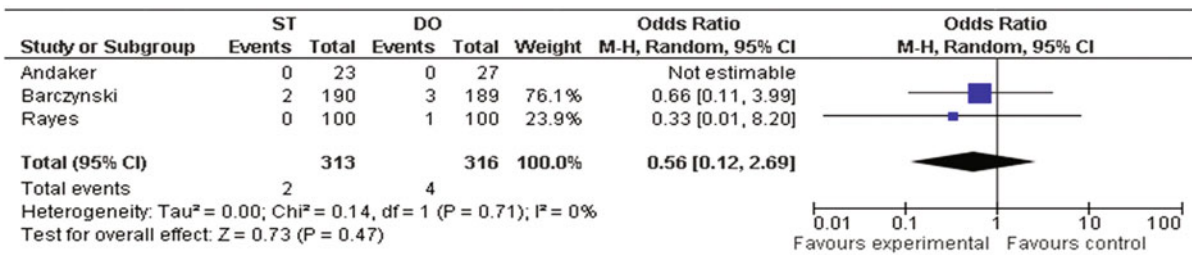
	DO	ST	TT	FU
Rayes (2013)	1/100	0/100	-	11.3 years
Andaker (1992)	0/27	0/23	-	3.6 years
Pappalardo (1998)	-	1/72	0/69	14.5 years
Barczynski (2010)	3/189	2/190	4/191	5 years

4A. Subtotal thyroidectomy versus total (N=522)



The incidence of RLN injury was 1.14% after ST and 1.53% after TT but this difference was not found to be significantly different in this meta analysis in accordance with previous studies ($p=0.69$).

4B. Subtotal versus dunhill operation (N=629)



The incidence of RLN injury was 0.63% after ST and 1.26% after DO but this difference was not found to be significantly different in this meta analysis ($p=0.47$).

4C. Dunhill operation versus total (N=380)

The results of the one RCT showed that the incidence of RLN injury was 1.59% after DO and 2.09% after TT and this difference was not significant ($p>0.05$)

In conclusion (management of BMNG)

- The operation needs to be as definite as possible to contain the recurrence rate and manage the occult thyroid cancer successfully. In this way, the reoperation rate is lower as is the subsequent morbidity rate. Total thyroidectomy is the best procedure to achieve this.
- The operation needs to be safe when performed by experts. It seems that the rate of both permanent as well as temporary complications is not higher when performing TT rather than ST, although there is a higher possibility for temporary hypoparathyroidism.

Hence, the benefit/risk ratio is better for TT when compared to less radical operations such as ST, and should be the preferred procedure. (Level of evidence 1a, 1b).

Surgical management of Benign Solitary non-toxic nodule

As already mentioned, the incidence of occult cancer in benign solitary non-toxic nodule is 5% irrespective of the size of the nodule [2]. The literature refers to two acceptable surgical options, each with their pros and cons: an upfront

TT or total lobectomy, and in the case of an occult cancer, completion total thyroidectomy [2]. Both approaches are acceptable by the surgical community and are included in the national guidelines.

Supporters of total lobectomy claim that hypothyroidism occurs in only 10.9% to 48.8%; hence, in a high percentage of patients, there is no need for the medical substitution of thyroid hormones. Moreover, the relative risk of a major complication is higher for TT when compared to total lobectomy: i.e. temporary hypoparathyroidism RR= 10.67 (5.75-19.31), permanent hypoparathyroidism RR= 3.17 (1.72-5.83), temporary RLN palsy RR=1.69 (1.30-2.20), permanent RLP palsy RR=1.85 (1.28-2.69), bleeding RR=2.58 (1.69-3.93) (10). Moreover, a systematic review including 32 studies showed that the pooled incidence of hypothyroidism after hemithyroidectomy was 22% [11]. Based on the fact that a reoperation in cases of occult thyroid cancer found during the total lobectomy is not a true reoperation since the surgical plane has not been previously explored, most national guidelines recommend total lobectomy for solitary non-toxic nodules which are not suspicious for malignancy. The same approach is recommended for nodules suspicious for malignancy. In cases where an occult thyroid cancer is found, the recommendation is to proceed with a completion total thyroidectomy. If there are multiple nodules bilaterally, the guidelines recommend upfront total thyroidectomy [1].

Nevertheless, in Greek reality, there are issues to be

taken in account when managing these patients. We need to consider the stress of the patient who will undergo a reoperation and the risks associated with the anaesthesia, as well as with the operation itself. We also need to take into account the risk of developing a nodule in the remaining lobe in the future, which is highly possible. Moreover, there is a question regarding the true percentage of patients who will eventually not need thyroid hormone supplements. Although these arguments are the opinions of experts as expressed at the meeting for the development of Greek national guidelines, we still need to keep them in mind when managing a solitary nodule. The rationale is to perform TT in such cases so as to reduce the recurrence rate, reoperation rate and associated morbidity. Moreover, in this way we can manage occult cancer successfully in one setting. Moreover, if the operation is performed by an expert endocrine surgeon, there will be a low percentage of permanent complications, making it a safe and definite procedure.

In conclusion (Management of non-toxic solitary nodule)

- a. For a benign non-toxic solitary nodule, a total lobectomy or a total thyroidectomy can be performed after a thorough discussion with the patient, presenting the current literature data and explaining the pros and cons of each procedure, and having obtained the patient's informed consent to the procedure chosen.
- b. For a benign multinodular non toxic goitre, total thyroidectomy is the procedure of choice since it can decrease the recurrence rate, the reoperation rate, and overall morbidity associated with a reoperation, and also successfully manage "occult" cancers
- c. The operation should be performed by an experienced surgeon so as to minimise permanent complications (i.e. RLN palsy and hypoparathyroidism) which should be less than 1-2%.

References

1. Musholt TJ, Clerici T, Dralle H, et al. German Association of Endocrine Surgeons practice guidelines for the surgical treatment of benign thyroid disease. *Langenbecks Arch Surg* 2011;396:639-49.
2. Yeung MJ, Serpell JW. Management of the solitary thyroid nodule. *Oncologist* 2008;13:105-12.
3. Bahn RS, Castro MR. Approach to the patient with nontoxic multinodular goiter. *J Clin Endocrinol Metab* 2011;96:1202-12.
4. Rayes N, Steinmuller T, Schroder S, et al. Bilateral subtotal thyroidectomy versus hemithyroidectomy plus subtotal resection (Dunhill procedure) for benign goiter: long-term results of a prospective, randomized study. *World J Surg* 2012;37:84-90.
5. Agarwal G, Aggarwal V. Is total thyroidectomy the surgical procedure of choice for benign multinodular goiter? An evidence-based review. *World J Surg* 2008;32:1313-24.
6. 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;32:1301-12.
7. Andaker L, Johansson K, Smeds S, et al. Surgery for hyperthyroidism: hemithyroidectomy plus contralateral resection or bilateral resection? A prospective randomized study of postoperative complications and long-term results. *World J Surg* 1992;16:765-9.
8. Barczynski M, Konturek A, Hubalewska-Dydejczyk A, et al. Five-year follow-up of a randomized clinical trial of total thyroidectomy versus Dunhill operation versus bilateral subtotal thyroidectomy for multinodular nontoxic goiter. *World J Surg* 2010;34:1203-13.
9. 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;164:501-6.
10. Kandil E, Krishnan B, Noureldine SI, et al. Hemithyroidectomy: a meta-analysis of postoperative need for hormone replacement and complications. *ORL J Otorhinolaryngol Relat Spec* 2015;75:6-17.
11. Verloop H, Louwerens M, Schoones JW, et al. Risk of hypothyroidism following hemithyroidectomy: systematic review and meta-analysis of prognostic studies. *J Clin Endocrinol Metab* 2012;97:2243-55.