



# Surgical treatment of multifocal, intermediate risk, differentiated thyroid cancer (DTC): single reference centre experience

Lucia Stella Curto<sup>1^</sup>, Rita Gervasi<sup>2^</sup>, Nadia Innaro<sup>2</sup>

<sup>1</sup>Department Surgery, Hospital of Soverato, Catanzaro, Italy; <sup>2</sup>Unit of Endocrine Surgery, A.O.U. Mater Domini, Catanzaro, Italy

**Contributions:** (I) Conception and design: All authors; (II) Administrative support: N Innaro; (III) Provision of study materials or patients: LS Curto; (IV) Collection and assembly of data: LS Curto, R Gervasi; (V) Data analysis and interpretation: LS Curto; (VI) Manuscript writing: All authors (VII) Final approval of manuscript: All authors.

**Correspondence to:** Lucia Stella Curto, MD. Department Surgery, Hospital of Soverato, 88068 Soverato, Catanzaro, Italy. Email: [luciestella15@gmail.com](mailto:luciestella15@gmail.com).

**Background:** Surgical treatment of multifocal intermediate risk differentiated thyroid cancer (DTC) is not well established such as the role of multifocality in DTC, that remains unclear. The ATA guidelines do not specifically report the risk of recurrence associated with multifocality in its risk stratification system.

**Methods:** The study was lead in the Endocrine Surgery Department of A.O.U. Mater Domini of Catanzaro. A total of 92 patients were selected from 2016 to 2021. Only patients with intermediate risk DTC were selected and divided into two groups: multifocal DTC (mDTC) and UNIfocal DTC (uDTC). Inside mDTC group, we consider patients with single lobe multifocal carcinoma (smDTC) and bilateral lobes multifocal DTC (bmDTC).

**Results:** There were no correlations in term of sex, histological type and complications between two groups; we found a strong correlation in term of age, fine needle aspiration cytology (FNAC), cancer node involvement, angioinvasion and extrathyroidal extension (ETE).

**Conclusions:** Both hemithyroidectomy (HT) and total thyroidectomy (TT) are correct procedures for the treatment of mDTC. According to our centre, surgical treatment must be tailored on case patient. HT could be sufficient in older patient without ETE, angioinvasion and N0. In other condition TT must be applied. Totalization procedure should be considered only for patients with risk factors, such as ETE and angioinvasion.

**Keywords:** Differentiated thyroid cancer (DTC); multifocal thyroid cancer; intermediate risk thyroid cancer

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## Introduction

In the last 20 years, differentiated thyroid cancer (DTC) had a marked increase, especially in high income countries, like Italy (1). This increase had a similar distribution in males and females, even if the incidence of DTCs, especially papillary ones, keeps higher in women (2).

Environmental factors and regional differences in access to the health system realize different incidence rates from region to region (3).

According to the ATA Risk Classification System, DTC are divided into low, intermediate and high risk. Low risk DTC are intrathyroidal cancer <1 cm without vascular invasion or microvascular invasion, N0 or micrometastases, intrathyroidal papillary microcarcinomas *BRAF* wild-type or *BRAF* mutated; intermediate risk cancer presents microscopic invasion of the tumour in perithyroidal tissue, aggressive biology or cN1 and multifocal papillary microcarcinoma with extrathyroidal extension (ETE).

<sup>^</sup> ORCID: Lucia Stella Curto, 0000-0002-6978-1357; Rita Gervasi, 0000-0003-4395-2039.

The high-risk category includes patients with macroscopic ETE, incomplete tumor resection, distant metastases (4). Each patient should be staged after surgery to define risk of persistence and recurrence of the disease.

The interest of our group is about a specific category of intermediate risk DTC; sometimes DTCs appear with different foci of cancer (multifocal DTC) inside thyroid parenchyma. These foci can be occurred into single or both lobes. There isn't a unique theory about multifocality origin. Probably it comes from intra-glandular spread of tumor cells from a primary focus, but some studies indicated an independent origin of single focus (5,6). Sometimes mDTC can be detected in both thyroid lobes, but often preoperative ultrasonography fails to reveal it: in fact, microscopic multifocality, which is very common, may go undetected.

The implication of multifocality in DTC remains unclear; some studies report an association with higher rates of disease recurrence and poorer prognosis when compared with unifocal disease, but others refuse this thesis (7,8).

Surgical management should be tailored, according to risk factors such as radiation exposure or family history, and after patient interview.

However, hemithyroidectomy (HT) should be performed for cancer <1 cm with healthy contralateral lobe, meanwhile for cancer with diameter between 1–4 cm, it could be indicated HT or total thyroidectomy (TT). The ATA guidelines find thyroid lobectomy alone to be an acceptable behaviour for unifocal, intrathyroidal carcinomas but do not specifically report the risk of recurrence associated with multifocality in its risk stratification system (9).

When it is possible, HT is favourite due to perioperative morbidity reduction; when TT is chosen, recurrence risk and persistence of the disease could be reduced.

The purpose of the study was to determine the most correct surgical management for patients with unilateral multifocal intermediate-risk DTC thyroid cancer.

Furthermore, we want to estimate the prevalence of TT and HT surgical treatment in patients with intermediate-risk multifocal DTC (1–4 cm in diameter) and the incidence of reoperation in patients that underwent HT [totalization (T)] in our centre.

We estimate the incidence of occult contralateral multifocal foci of carcinoma in patients undergoing TT.

At the end, we compare morbidity rates of TT *vs.* HT and T. We present the following article in accordance with the STROBE reporting checklist (available at <https://aot.amegroups.com/article/view/10.21037/aot-22-2/rc>).

## Methods

The retrospective study was conducted in the Department of Endocrine Surgery of A.O.U. Mater Domini in Catanzaro that SIUEC (Società Italiana Unitaria di Endocrinochirurgia) recognized as the Regional Reference Centre for Thyroid Pathology. It is considered a high-volume centre.

A total of 883 patients with thyroid disease were selected between January of 2016 and June of 2021. Of these, 92 patients (75 women and 17 men) were enrolled according to the inclusion criteria. Only patients with a diagnosis of intermediate risk DTC were recruited. We considered the intermediate risk definition declared in ATA guidelines (10).

The inclusion criteria were age >18 years, preoperative diagnosis or suspicion of unilateral thyroid cancer T1–T2 (1–4 cm) with fine needle aspiration cytology (FNAC) positive for TIR3A or TIR3B, TIR4, TIR5, cN0 (11).

Exclusion criteria were the presence of macroscopic nodules in contralateral lobe, autoimmune thyroiditis, familiar history of thyroid cancer or neck exposure to radiations.

TT or HT were performed. T is the surgical removal of remaining lobe after HT and it was performed in some cases. When aggressive features such as capsular invasion or perithyroidal tissue infiltration were identified in the definitive histological examination, patients underwent T.

On the basis of definitive histological examination, we divided the patients into two groups: multifocal DTC (mDTC) and unifocal DTC (uDTC); inside mDTC group we consider patients with single lobe multifocal carcinoma (smDTC) and bilateral lobes multifocal DTC (bmDTC).

Subgroup analysis was performed to compare gender, age, tumor size, lymph node metastasis, histological analysis, angioinvasion, ETE, capsule infiltration, clinical outcomes (complication rates, reoperation rate: HT followed by T).

We registered some cases of unexpected cancer lesions in the contralateral lobe. Based on histopathologic features we determined if HT or TT were appropriate and when totalization was necessary.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval was not required because this research was conducted in accordance with institutional regulations and did not involve clinical trials. No new surgical protocol has been tested. Furthermore, in accordance with Declaration

**Table 1** Characteristic of cohort

Items	Absolute value	Percentage value (%)
Age (median), years	44.63	
Gender		
Female	75	81.52
Male	17	18.48
Histological type		
Follicular	14	15.22
Papillar	78	84.78
FNAC		
TIR3	27	29.3
TIR4-5	43	46.7
Information not found	22	23.9
DTC (1–4 cm)		
Unifocal DTC	62	67.39
Multifocal DTC	30	32.61
Multifocal monolateral	11	36.67
Multifocal bilateral	19	63.33
Procedure		
Hemithyroidectomy	30	32.61
Total thyroidectomy	62	67.39
Totalization procedure	5	5.43
Complications		
Nerve paralysis	5	5.43
Hypocalcemia	4	4.26
Hemorrhage	0	0

FNAC, fine needle aspiration cytology; DTC, differentiated thyroid cancer.

of Helsinki, throughout the process we followed ethical guidelines and informed consent was taken from all individual participants. Data set was anonymous and not traceable to any patient.

### Statistical analysis

Data were collected in an XLS database (Microsoft office 2016; Microsoft Corporation, Redmond, WA, USA), and XLSTAT (Version 2012.6.06; New York, NY, USA), statistical software was used for statistical analysis.

Differences between groups were analysed with the Chi-square test. Univariate logistic regression was performed. Results were reported as odds ratio (OR) and 95% confidence intervals (95% CIs). P values less than 0.05 were considered significant.

### Results

The descriptive characteristics of the cohort are summarized in *Table 1*. Ninety-two data records from January of 2016 to June of 2021 were collected by Operative Unit of Endocrine Surgery of A.O.U Mater Domini of Catanzaro.

Among 92 DCT intermediate unilateral risk operated, Group mDTC consisted of 30 patients, 25 women and 5 men, mean age 44.25 years. Group uDTC consisted of 62 patients, 49 women and 13 men, mean age 44.83 years.

There were no significant differences in the number of male and female patients between the two groups (OR: 1.32,  $P=0.62$ ); but we found an association between age and multifocality in this cohort. Diagnosis of mDTC is more common in patients under 50 years old (OR 2.83,  $P=0.02$ ).

The mean tumor size was 2.10 mm for mDTC and 2.8 mm for uDTC.

Among histopathologic characteristics, 78 were considered papillary thyroid cancer (PTC) and 14 follicular thyroid cancer (FTC). There is correlation between multifocality and histological type (OR: 0.51,  $P=0.33$ ).

Forty-three patients were operated because of TIR4 or TIR5 lesions. Twenty-seven patients presented TIR3 lesions, in 22 cases the information was not available. Association between FNAC and multifocality was found ( $P=0.0087$ ).

Among mDTC group, 5 patients underwent HT while 25 underwent TT. T was performed in 4 patients because of the extrathyroidal tissue extension [2], large diameter [1] and patient and the endocrinologist preference [1]. Only one patient refused T.

Patients with bmDTC were 19 (63.4%), while in smDTC group were 11 (36.7%).

Among uDTC 25 patients underwent HT while 37 had TT. T was not necessary in this group.

No significant rates were found about 3 major post-operative complications: 11.2% in patients underwent TT vs. 6.6% in patient underwent HT (OR: 1.78,  $P=0.48$ ); in particular no cases of bleeding, nerve paralysis ( $P=0.71$ ), hypocalcaemia ( $P=0.74$ ). This result is probably due to the small amount of cohort.

There were 5 patients with cancer node involvement in

**Table 2** Difference between mDTC and uDTC groups

Items	mDTC group	uDTC group	P value
Gender			0.62
Female	25	49	
Male	5	13	
Age (years)			0.02**
<50	21	28	
>50	9	34	
Tumor size (mm)	2.1	2.8	
Histological type			0.33
FTC	3	11	
PTC	27	51	
FNAC			0.0087**
TIR4/5	20	20	
TIR3	7	28	
Procedure			
Hemithyroidectomy	5	25	
Total thyroidectomy	25	37	
Totalization procedure	4	0	
Complications			
Nerve paralysis	2	3	0.71
Hypocalcemia	1	3	0.74
Hemorrhage	0	0	0
Histological features			
Lymph node infiltration	5	2	0.039**
Angioinvasion	12	11	0.02**
Capsule infiltration	6	7	0.26
ETE	12	12	0.03**

\*\* , statistically significant. mDTC, multifocal differentiated thyroid cancer; uDTC, unifocal differentiated thyroid cancer; FTC, follicular thyroid cancer; PTC, papillary thyroid cancer; FNAC, fine needle aspiration cytology; ETE, extrathyroidal extension.

mDTC (16.6%), and 2 patients in uDTC (3.23%). There is a significant difference between these two groups (OR =6, P=0.039).

Angioinvasion (OR =3.09, P=0.02) and ETE (OR: 2.77, P=0.03) were significant different between the two groups. Capsule infiltration was not different (OR: 1.96, P=0.26).

Characteristics are summarized in *Table 2*.

According to univariate analysis, there is not association between gender and histological type with number of cancer foci.

## Discussion

In Italy, the incidence of DTC is on the increase, although there are interregional differences. Calabria is one of the Italian regions with the greatest incidence of thyroid cancer, even if 5-year survival rates are about 97% for woman and 95% for men (12).

Surgical debate is still open about intermediate-risk DTC, especially when the diameter is 1–4 cm. ATA Guidelines do not explain which procedure is the best when mDTC of 1–4 cm is present. Different studies were conducted with contrasting data about aggressive levels of treatment.

According to our data there is no association between gender, histological type and multifocality, but we saw that young people are more likely affect by mDTC than the older ones.

We recognized that patients with mDTC had a preoperative diagnosis with FNAC TIR4-TIR5, presented a smaller histological tumor diameter than uDTC, a higher probability of lymph node metastases (N1).

Our interest is focused on surgical management of multifocal intermediate risk DTC with diameter between 1–4 cm.

The prognostic role of multifocality DTC continues to generate debate. In recent years several papers and meta-analysis talked about this argument (13). Some studies concluded that multifocality can't be considered as a risk factor for the higher death rate, recurrence or tumor spread out of the neck. Therefore, a more aggressive treatment is not indicated, theoretically, for patients with multifocal PTC (14). On the other hand, some studies revealed that mDTCs were more likely to have node infiltration and advanced TNM stage when compared to uDTC (15).

The purpose of our study is to evaluate which is the best surgical approach to multifocal intermediate risk-DTC when it is not preoperatively diagnosed.

In our study, 67% of patients with DTC underwent TT, and 33% were subjected to HT.

The advantages of TT are a complete removal of cancer with no re-operations (reductions of hospitalization) and the ability to recognize bilateral occult cancers. The disadvantages are major complications risks, including, hypocalcaemia, bleeding, recurrent laryngeal nerve

injury and rare bilateral recurrent laryngeal nerve injury that requires a tracheostomy; furthermore, long hospitalization times, substitutive hormonal therapy. Refers to complications, many studies recognized the role of the surgeon and especially surgeon experience which likely influences the risks of thyroidectomy: it has been seen that higher volume surgeons have lower complication rates (16-18).

According to literature, high-volume surgeons and high-volume hospitals are able to reduce the increased disease-related risk of post-thyroidectomy complications, hospital stay and costs (19).

The advantages of HT, indeed, are lower complication rates, lower hospitalization time, no thyroid hormone replacement, while the disadvantages are the possibility of re-intervention, Tg evaluation can't be used during follow up, such as radioiodine therapy can't be performed (20).

In our study, 30 HT were performed, 25 for unifocal DTC and 5 for multifocal DTC. Each patient underwent HT for suspected single nodule in one lobe. Diagnosis of mDTC was made after histological examination. Four patients of 5 underwent totalization, 1 patient refused surgical intervention. Histological examination after totalization revealed multifocal microcarcinoma in macroscopic healthy lobe for 2 patients, while the other 2 patients do not have pathological conditions. ETE and angioinvasion were found in pathological examination before T in the two patients with bilateral cancer. Indeed, in the other 2 patients nor ETE or angioinvasion were found. Fifty percent of patients underwent HT had an occult cancer (<1 cm) in the contralateral lobe. Due to small sample statistical examination do not reach P value (P=0.55).

Some studies revealed that macroscopic PTC had a low risk of recurrence after TT and RAI. The outcome could be influenced from ETE and lymph node infiltration.

According to various studies, selected patients with multifocal disease without risk factors such as ETE, big nodules and angioinvasion could be managed with HT, with a rate of papillary thyroid carcinoma of the contralateral lobe, regional recurrence, and overall survival comparable to patients with unifocal disease. Therefore, multifocal disease should not be an indication for the completion of thyroidectomy (21).

Our work group believes that Totalization procedure must be considered only for patients with risk factors, such as ETE and angioinvasion, but additional studies are needed.

In reference to complications after TT and HT, we

recognized a different rate (HT 6.6% *vs.* TT 11.3%), even if statistical significance is not reached. Even if this point is favourable for TT, surgeon experience could reduce the risks of complication during thyroidectomy. This consideration should be consistent with other studies (22).

The limits of our studies are the small group of mDTC, smDTC, bmDTC, uDTC.

## Conclusions

In conclusion, HT and TT are two validate procedure in mDTC. According to our Centre, surgical treatment must be tailored to case patient. HT could be sufficient in older patients without ETE, angioinvasion and N0. In the other condition TT or T must be applied.

Further and bigger studies are needed to further clarify the extent of surgery for mDTC.

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## Footnote

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval was not required because this research was conducted in accordance with institutional regulations and did not involve clinical trials. No new surgical protocol has been tested. Furthermore,



in accordance with Declaration of Helsinki, throughout the process we followed ethical guidelines and informed consent was taken from all individual participants. Data set was anonymous and not traceable to any patient.

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