

RESEARCH

Changing the paradigm: lobectomy for sporadic medullary thyroid cancer

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Abstract

Objectives: Total thyroidectomy is the treatment of choice for medullary thyroid cancer (MTC), although the sporadic forms are usually monocentric. Aim of the present study was to evaluate i) the performance of calcitonin (Ct) levels, ultrasound scans (US) and cytology in the preoperative identification of MTC and ii) the number of total thyroidectomies that could have been avoided being the location of the MTC diagnosed preoperatively.

Materials and methods: We retrospectively analyzed 89 *RET* germline negative patients diagnosed with MTC in the past 30 years, treated with total thyroidectomy ± lymphadenectomy, and followed in our Tertiary Care Center. In a subgroup of 55 patients, divided in those with a mono- or bi-lateral goiter, we applied ex-post criteria for the presurgical identification of the lobe holding the MTC nodule.

Results: Only 2/89 patients (2.2%) had a bilateral MTC at histology. A strongly significant correlation was found between preoperative basal Ct levels and MTC size. According to the ex-post identification criteria, the 84.4 and 56.5% of the nodules would have been identified preoperatively as MTC in monolateral and bilateral goiters, respectively.

Conclusions: This is the first European study that aims to evaluate the feasibility of lobectomy as first-line therapy for MTC based on the evaluation of thyroid US and serum Ct levels. These tools have been shown to have a good accuracy in detecting the affected lobe and strongly support the possibility to perform a more conservative surgery to treat *RET*-negative patients with suspicious MTC and nodular goiter.

Keywords: medullary thyroid cancer; lobectomy; sporadic medullary thyroid cancer; RET

Introduction

Medullary thyroid carcinoma (MTC) is a neuroendocrine tumor originating from the C-cells of the thyroid gland. Approximately, 25% of cases are familial and caused by an oncogenic germline mutation of the *RET* proto-oncogene, while the remaining 75% are sporadic. While familial forms are typically multicentric and associated

with C-cell hyperplasia (CCH), the risk of multifocality is lower than 5% in patients with sporadic disease (1, 2). Nevertheless, although for differentiated thyroid cancers, the trend to reduce overtreatments, treatment-related adverse events and costs is greatly increasing in the past decade, the recommendations for total thyroidectomy as

the best option for MTC (3, 4) seem to remain unchanged, even for *RET* germline negative patients with a single thyroid nodule and even if similar survival outcomes have been reported in patients treated with either lobectomy or total thyroidectomy (5, 6, 7, 8).

Since the late 1990s, some Japanese and Chinese studies reported data on sporadic monolateral MTCs treated by lobectomy, and showed the absence of recurrence in the contralateral lobe and a similar rate of biochemical cure compared to patients submitted to total thyroidectomy (2, 6, 7, 8, 9, 10, 11, 12). Based on those data, Japanese guidelines were the first and are still the only to suggest lobectomy, possibly associated to lymphadenectomy, as initial treatment in *RET*-negative patients with monolateral thyroid involvement (13).

In Europe, the possibility to perform lobectomy in patients with hypercalcitoninemia and desmoplasia-negative MTC was reported only by the Dralle's group, with a 100% rate of biochemical cure and no need for further treatments (14). We speculate that the main reasons why lobectomy has not entered into the clinical practice for *RET*-negative patients is related to the difficulties found to preoperatively diagnose both a monolateral MTC, especially in the context of a multinodular goiter, and the possible presence of suspicious lymph nodes in the contralateral central compartment. Indeed, both ultrasound (US) and cytology have a low specificity in the preoperative identification of this rare tumor (15, 16), and the central compartment is difficult to explore in the presence of the thyroid gland. Thus, the diagnosis is often based just on the finding of both basal and stimulated calcitonin (Ct) levels above the cut-offs of reference (17, 18, 19). Nonetheless, in many cases, an integrated evaluation of preoperative US, fine-needle aspiration cytology (FNAC) results and preoperative serum Ct levels could reliably both identify the MTC nodule and predict the possible lymph node involvement, thus allowing to select *RET*-negative patients suitable for a more conservative surgery.

Therefore, one of the aims of the present study was to evaluate the prevalence of bilaterality in our series of sporadic MTCs. Moreover, in a subgroup of patients for whom US and clinical data were available, we evaluated the performance of Ct levels, US and FNAC in the preoperative identification of MTC and the number of total thyroidectomies that could have been avoided being the location of the MTC diagnosed preoperatively.

Materials and methods

Study participants and medullary thyroid cancer diagnosis

In this retrospective study, we analyzed patients diagnosed with medullary thyroid cancer (MTC) in the

past 30 years and followed at our Tertiary Care Hospital. All patients were treated with total thyroidectomy alone or associated with central compartment and/or lateral neck dissection, had a definite diagnosis of MTC made by histopathological assessment after surgery, had a *RET*-negative germline genetic testing and a minimum 6-month follow-up. Laryngeal nerve monitoring was used in all patients operated since 2009, regardless of the disease extent.

Clinical, genetical, histopathological and biochemical data were extracted from medical records. Results of FNAC were reported according to the Bethesda classification (20). TNM classification was done according to the 8th edition of the American Joint Committee on Cancer/Union for International Cancer Control TNM staging system of thyroid cancer (21). In 28 patients, a calcium test was performed upon the finding of Ct levels above the normal range in ≥ 2 measurements, and the results interpreted were as previously reported (thresholds >79 for females and >466 pg/mL for males) (19). Patients' clinical status at last follow-up was classified as follows: i) remission if basal Ct and neck ultrasound were negative, ii) biochemical persistence if there were basal Ct levels detectable and no evidence of recurrence at ultrasound/radiological assessment, and iii) structural persistence if definite recurrence has been identified by ultrasound or other radiological exams. We defined permanent hypoparathyroidism as that documented at 6 months post-surgery and dysphonia due to recurrent nerve injury as that corresponding to a vocal cord paralysis on fiberoptic laryngoscopy.

The whole series including 89 patients was studied with the main aim to evaluate the prevalence of MTC bilaterality, while a subgroup of 55 patients with available ultrasound, cytology and Ct levels was used to find the best parameters to preoperatively identify the lobe holding the MTC nodule.

Identification of the lobe containing the MTC nodule

The ex-post presurgical identification of the lobe holding the MTC nodule was based on at least one of the following criteria: 0) no suspicious nodules were identified at US, cytology was not suspicious and Ct was not consistent with the nodule/s volume; A) the nodule was the only nodule in the thyroid, possibly characterized by US suspicious features, serum Ct levels were consistent with the nodule volume and the stimulated Ct (if obtained) was above the cut-off limits; B) the nodule was the only nodule in the thyroid, possibly with US suspicious features, and cytological evaluation was positive or suspicious for MTC or malignancy, and/or Ct measurement on the fine-needle washout fluid was positive; C) there were more than one nodule, but only one nodule had US suspicious features and/or a volume

consistent with Ct serum levels, and the stimulated Ct (if obtained) was above the cut-off limits; and D) there were more than one nodule, but only one nodule had a cytology positive or suspicious for MTC or malignancy and/or Ct measurement on the fine-needle washout fluid was positive. The 55 patients with all data available were included in one of these groups. The ex-post evaluation was done by two authors (ML and GS) who were not aware of the histopathologic description of the size and location of the MTC. The matching between ex-post analysis and the histological report was done by other two authors (CM and GG).

Statistical analysis

Statistical analyses were performed using the RStudio (version 4.2.2; R Project for Statistical Computing). The difference between values was considered significant when $P < 0.05$. The Shapiro–Wilk test was used to test the normality of the distributions of all analyzed variables.

Student's *t*-test or Wilcoxon rank sum test was used as appropriate to compare continuous variables among groups, while chi-square test or Fisher exact test were used, as appropriate, for categorical variables. The correlation between MTC size and basal Ct was computed with Spearman correlation test considering that data were not normally distributed.

The study was performed according to the ethical standards of the Institutional Research Committee and to the Declaration of Helsinki. All patients were enrolled in a protocol approved by the ethical committee of the Istituto Auxologico Italiano IRCCS and provided informed consent to the use of their anonymized clinical data for research purposes (study code approval: 2022_03_08_03).

Results

The main characteristics of the whole series are reported in Table 1. Among the 89 patients with a sporadic MTC and available histology, 72% were females, the median age at diagnosis was 62 years (range: 25–83 years) and the median preoperative basal Ct levels were 150 pg/mL (mean \pm SD: 1,573.2 \pm 7,608.1 pg/mL, range: 2–61,249 pg/mL). Cytology was positive or suspicious for MTC or malignancy in 31/39 (79.5%) nodules later diagnosed as MTC at histology. On the other hand, Bethesda I, II or III/IV cytologies were recorded in 10.3, 5.1 and 5.1% cases, respectively. The selection of the nodule to be submitted to FNAC was done based on the US features, which were suspicious (mildly or marked hypoechoic and/or with microcalcifications, irregular shape and irregular margins) (22) in most cases, although in a minority of patients FNAC was done even though the nodule was isoechoic with a hypoechoic halo or even spongiform. All patients underwent total

Table 1 Baseline characteristics of study participants. Data are presented as *n* (%), mean \pm SD or as median (range).

Baseline characteristics	Values
Total <i>n</i>	89*
Age (years)	
Median (range)	62 (25–83)
Mean \pm SD	59.4 \pm 13.0
Sex	
Female	64 (71.9)
Male	25 (28.1)
Basal preoperative Ct (pg/mL), <i>n</i> = 65	
Median (range)	150.0 (2.0–61,249.0)
Mean \pm SD	1,573.2 \pm 7,608.1
FNAC [†] , <i>n</i> = 39	
I	4 (10.3)
II	2 (5.1)
III or IV	2 (5.1)
V	3 (7.7)
VI or suspicious for MTC	28 (71.8)
Lymphadenectomy, <i>n</i> = 63	
Central compartment alone, <i>n</i>	61
Monolateral	21 (33.3)
Bilateral	24 (38.1)
Unspecified	18 (28.6)
Central + lateral neck, <i>n</i>	22
Monolateral	20 (90.9)
Bilateral	2 (9.1)
Histology	
Monolateral MTC	87 (97.8)
+ CCH	7
+ Ipsilateral microPTC	4
+ Contralateral microPTC	4
Bilateral MTC	2 (2.2)
+ CCH	1
MTC size (mm)	
Median (range)	11 (2–50)
Mean \pm SD	14.7 \pm 10.5
pTNM	
T1a	37 (41.6)
T1b	30 (33.7)
T2	16 (17.9)
T3a	3 (3.4)
T3b	1 (1.1)
T4a	2 (2.3)
N0/Nx	63 (70.8)
N1a	12 (13.5)
N1b	14 (15.7)
Surgical complications, <i>n</i> = 75	
Transient dysphonia	12 (16)
Permanent dysphonia	3 (4)
Transient hypoparathyroidism	19 (25.3)
Permanent hypoparathyroidism	5 (6.7)
Outcome at last follow-up, <i>n</i> = 80	
Remission	50 (58.2)
Biochemical persistence	15 (17.4)
Structural persistence	21 (24.4)

Ct, serum levels of calcitonin; FNAC, fine-needle aspiration cytology; MTC, medullary thyroid cancer; CCH, C-cell hyperplasia; PTC, papillary thyroid cancer.

*If *n* different from the total, it was specified for each feature. [†]FNAC on the nodule found to be MTC at histology.

thyroidectomy ± central neck compartment (CC) dissection and ± lateral neck compartment (LC) dissection. In particular, lymphadenectomy was performed in 63/89 patients (70.8%), limited to CC in 61/89 (68.5%), including the LC in 22/89 (24.7%) cases. The dissection of the CC was ipsilateral in 21/63 (33.3%) and bilateral in 24/63 (38.1%) cases (in 18 patients, no data on laterality were available), while the LC dissection was ipsilateral in 20/22 (90.9%) and bilateral in 2/22 (9.1%) cases. At histology, 6/89 patients (6.7%) had a multifocal MTC, which was bilateral in only two cases (2.2%). CCH was found in 8/89 (9%) patients (focal or peritumoral CCH was not included). One patient had both CCH and bilateral foci of MTC. Moreover, 8/89 (9%) patients had an incidental diagnosis of papillary thyroid cancer (PTC), mainly <1 cm, along with the MTC. The median MTC size was 11 mm (mean ± SD: 14.7 ± 10.5 mm, range: 2–50 mm). There was a significant correlation between MTC size at histology and both Ct preoperative levels and MTC size at US (rho = 0.62, *P*-value = 0.00000003; rho = 0.80, *P*-value = 0.000000006) (Fig. 1).

At the pathological TNM classification, 75.3% of patients had an MTC ≤2 cm and limited to the thyroid gland (pT1a or pT1b), 17.9% had an intrathyroid MTC >2 ≤4 cm (pT2), 3.4% had an MTC >4 cm limited to the thyroid (pT3a) and only 3/89 patients had an MTC involving thyroid-surrounding structures (pT3b/pT4a). Most patients (70.8%) had no or unknown lymph node involvement (N0a or N0b or Nx), while 13.5% had CC metastatic lymph nodes (pN1a) and 15.7% had LC involvement (pN1b). Considering patients with available data on post-surgical side effects (*n* = 75), transient hypoparathyroidism was diagnosed in 25.3% of patients, permanent hypoparathyroidism in 6.7% of them, while 20% had dysphonia (transient in 80% of cases). Finally, after a median follow-up of 27 months

(range: 6–255 months, mean ± SD: 57.7 ± 60.7 months), 58.2% of patients were biochemically cured, while 17.4% had biochemical persistence and 24.4% a structural persistence (Table 1). To note, among the 37 patients with basal preoperative Ct levels ≤250 pg/mL, 32 (86.5%) had a complete remission and five had biochemical persistence. On the other hand, the 21 patients in structural persistence had a basal preoperative Ct levels ranging 652–4,384 pg/mL (data not shown). Tumor size, Ct basal levels and pTNM, but not age and sex, were significantly associated with outcome (either comparing excellent response and biochemical persistence vs structural disease or excellent response vs biochemical and structural persistence, *P* < 0.0001) (data not shown).

In Table 2, the clinical characteristics of the 21 patients with structural persistent disease are shown. They were 16 females, the median age at D was 62 years (mean ± SD: 59.24 ± 14.77, range: 25–83), the median MTC size was 21 mm (mean ± SD: 22.1 ± 11.8, range: 7–38) and the median preoperative Ct levels were 1,181.25 pg/mL (mean ± SD: 1,499.72 ± 1,160.02, range: 8–4,384). One patient (#4) had a Ct non-secreting tumor, and he was followed-up with Ca 19.9 and carcinoembryonic antigen (CEA) as tumor markers. In 11 patients, the primitive tumor tissue was available for the genetic analysis, which showed the presence of the following mutations: *RET* M918T in six cases, *RET* C634R in one case, *HRAS* Q61R in one case and *HRAS* Q61L in one case, with two patients wild-type for mutations in the *RET* and *RAS* genes. Eleven of them underwent total thyroidectomy and bilateral dissection of the whole central neck compartment (CC) and of the ipsilateral LC, in six cases thyroidectomy was associated to the whole CC dissection, in one case both CC and LC were bilateral, in one case the CC was just ipsilateral and in two cases no neck dissection was done. Lymph node metastases were diagnosed at histology in all but five of the cases treated with any kind of lymph node dissection. As per the last follow-up data, the structural persistence was in the ipsilateral CC in seven cases (associated with distant metastases in two) and in the ipsilateral LC ± CC compartment in seven cases (associated with distant metastases in one). In five patients, the structural persistence was in the CC ± LC contralateral compartments (associated with distant metastases in three), and in two patients, only distant metastases were detected.

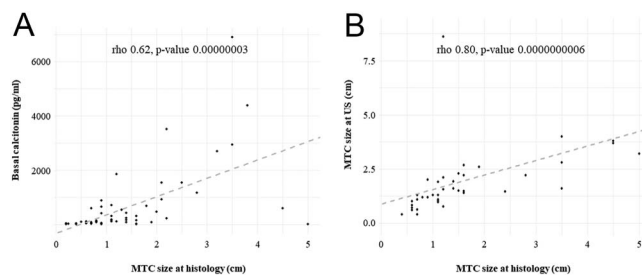


Figure 1

Panel A, Scatter plot of MTC histological size and basal serum levels of calcitonin; the dashed gray line represents the direction of the correlation. Spearman correlation test showed a significant association of moderate power between the two variables: rho = 0.62, *P*-value = 0.00000003. Panel B, Scatter plot of MTC histological size and MTC size measured during thyroid ultrasound evaluation; the dashed gray line represents the direction of the correlation. Spearman correlation test showed a significant strong association between the two variables: rho = 0.80, *P*-value = 0.000000006.

Subanalysis and ex-post MTC identification in 55 patients

We performed a subanalysis on 55 patients for whom a presurgical thyroid US report was available, thus allowing us to separate them into a group with monolateral (uni- or multi-nodular) goiter and another group with bilateral multinodular goiter (Table 3). Monolateral nodular goiter was present in 32/55

Table 2 Summary of main characteristics of patients with structural persistence (all patients underwent total thyroidectomy + lymphadenectomy).

Pt #	Sex	Age at Dx	MTC size (mm)	Preop Ct, pg/mL	Lymph node dissection	pN	Somatic mutation	Location + laterality of neck LN persistence	Location of distant metastasis
1	F	83	9	875	Bilateral CC	N1a	NA	Ipsilateral CC + LC	No
2	M	63	38	4,384	Bilateral CC + bilateral LC	N1b	NA	-	Skin*
3	F	77	32	2,693	Bilateral CC + ipsilateral LC	N1b	NA	Ipsilateral CC	No
4 [†]	M	45	50	8	Bilateral CC + ipsilateral LC	N1b	WT	Bilateral CC + supra-clavicular + contralateral LC	No
5	F	48	7	600	Bilateral CC + ipsilateral LC	N1b	NA	Ipsilateral LC	No
6	F	67	21	1,542	Bilateral CC + ipsilateral LC	N0a	RET M918T	Ipsilateral CC*	Cranial bone
7	F	46	10	NA	Bilateral CC	N0a	WT	Ipsilateral LC + CC*	No
8	F	64	12	1,854	Bilateral CC + ipsilateral LC	N1b	HRAS Q61R	Ipsilateral CC	No
9	F	53	8	NA	Bilateral CC	N0a	RET C634R	Ipsilateral CC	No
10	F	51	20	NA	Bilateral CC + ipsilateral LC	N0a	NA	Ipsilateral LC	No
11	F	71	35	2,938	Ipsilateral CC	N0a	HRAS Q61L	Contralateral CC	Liver
12	F	56	21	922.5	Bilateral CC	N1a	RET M918T	Contralateral CC	Bone
13	F	62	25	1,540	Bilateral CC + ipsilateral LC	N1b	NA	Ipsilateral LC	Lung
14	F	77	30	NA	No	N0b	NA	Ipsilateral CC	Skin
15	M	51	18	677.8	Bilateral CC + ipsilateral LC	N1b	RET M918T	Contralateral LC	Liver, peritoneum, adrenal glands
16	F	70	23	NA	No	N0b	NA	Ipsilateral CC	No
17	F	72	30	NA	Bilateral CC + ipsilateral LC	N1b	RET M918T	-	Lung
18	M	25	9	652	Bilateral CC	N1a	RET M918T	Ipsilateral LC*	Bone
19	F	69	35	870	Bilateral CC + ipsilateral LC	N1b	RET M918T	Bilateral CC + right anterior mediastinum	No
20	F	33	10	NA	Bilateral CC	N1a	NA	Ipsilateral CC + LC	No
21	M	61	21	1,440	Bilateral CC + ipsilateral LC	N1b	NA	Ipsilateral CC	No

*Patients submitted to surgical dissection of the indicated metastases (none of them cured after this intervention). [†]This patient had a calcitonin non-secreting tumor and was followed up by Ca 19.9 and CEA levels; F, female; M, male; Dx, diagnosis; Preop, preoperative; CC, central neck compartment; LC, lateral neck compartment; LN, lymph node; NA, not available; Pt, patient; pN, pathological N from TNM classification (8th edition).

(58.2%), while 23/55 cases had a bilateral nodular goiter (41.8%), without statistically significant differences as far as sex and basal Ct levels between the two groups, while age was significantly lower in the monolateral goiter group ($P = 0.016$). The rate of suspicious nodules by FNA (Bethesda classes V and VI) was higher in the monolateral goiter group, although not reaching the statistical significance (86.5 vs 69.2%, $P = 0.428$). To note, in the monolateral group, one case was non-diagnostic, one had a benign cytology and one had a Bethesda III diagnosis (data not shown). The extent of lymphadenectomy was not significantly different among the two groups. In the monolateral goiter cases, histology confirmed in all cases the presence of a monolateral MTC, even though in three patients a CCH was diagnosed (9.3%), being ipsilateral to the MTC in two cases and contralateral in one patient. Patients with bilateral nodules had a unifocal MTC in 22 cases (95.7%), a bilateral MTC in one case, with CCH in three cases. MTC size was not significantly different among the two groups. The TNM distribution was similar to that observed in the whole series and was not different among the two groups. In particular, an MTC ≥ 1 cm was found in 59.4% of monolateral goiter patients and in 52.2% of bilateral goiter cases, a preoperative Ct level ≥ 200 or ≥ 300 pg/mL was detected in 34.6 and 30.7% of

monolateral and 31.8 and 31.8% of bilateral cases, respectively (data not shown).

As far as post-surgical complications concerns, transient hypoparathyroidism was found in 27.6 and 20%, permanent hypoparathyroidism in 6.9 and 10%, and dysphonia in 20.7 and 25% of patients with monolateral and bilateral nodules, respectively.

The outcome at the last follow-up did not differ among the patients with monolateral or bilateral goiter, with remission in 62.5 and 73.9% of patients, biochemical persistence in 21.9 and 17.4% and structural persistence in 15.6 and 8.7% of cases, respectively (Table 3).

According to the ex-post identification criteria reported in the Methods section, in monolateral goiters, a suspicious nodule would have been identified in 28/32 (87.5%) patients (five cases criteria A, 17 cases criteria B, three cases criteria C and three cases criteria D); in bilateral goiters, a suspicious nodule would have been identified in 15/23 (65.2%) patients (three cases criteria C and 12 cases criteria D) (Fig. 2). The ex-post preoperative suspicion matched with the histological finding in 27/28 and 13/15 cases, being the rate of identification of 27/32 (84.4%) and 13/23 (56.5%), in monolateral and bilateral goiters, respectively (data not shown).

Table 3 Baseline characteristics of patients with available thyroid ultrasound evaluation ($n = 55$). Data are presented as n (%) or as specified.

Baseline characteristics	Monolateral (uni/multi-nodular)		Bilateral (multinodular)		P-value
	n	Value	n	Value	
Total n^*	32		23		
Age (years)	32		23		0.016
Median (range)		57.5 (27–83)		65 (47–77)	
Mean \pm SD		57.6 \pm 12.7		64.5 \pm 7.8	
Sex	32		23		0.431
Female		24 (75.0)		15 (65.2)	
Male		8 (25.0)		8 (34.8)	
Basal Ct (pg/mL)	26		22		0.804
Median (range)		105.5 (8–61,249)		91.5 (13.4–2,693)	
Mean \pm SD		2,823.7 \pm 11,990.9		414.9 \pm 691.1	
FNAC on MTC nodule	22		13		0.428
I		1 (4.5)		3 (23.1)	
II		1 (4.5)		0 (0)	
III/IV		1 (4.5)		1 (7.7)	
V		2 (9.1)		0 (0)	
VI/suspicious For MTC		17 (77.4)		9 (69.2)	
Lymphadenectomy	31		22		
Central compartment		22 (71.0)		13 (59.1)	0.391
Monolateral		8 (36.4)		6 (46.1)	0.351 [†]
Bilateral		7 (31.8)		2 (15.4)	
Unspecified		7 (31.8)		5 (36.4)	
Lateral neck		5 (16.1)		5 (22.7)	0.562
Monolateral		5 (100)		4 (80.0)	0.693 [‡]
Bilateral		0		1 (20.0)	
Histology	32		23		0.791
Single MTC focus		32 (100)		22 (95.7)	
Bilateral MTC foci		0 (0)		1 (4.3)	
CCH		3 (9.3)		3 (13.0)	
MTC size (mm)	32		25		0.308
Median (range)		11 (2.5–50)		11 (2–35)	
Mean \pm SD		15.4 \pm 12.4		12.5 \pm 8.9	
pTNM	32		23		
T					1.000
T1a		13 (40.6)		11 (47.8)	
T1b		12 (37.5)		9 (39.1)	
T2		3 (9.4)		2 (8.7)	
T3a		2 (6.3)		1 (4.4)	
T3b		1 (3.1)		0	
T4a		1 (3.1)		0 (0.0)	
N					1.000
N0/Nx		24 (75.0)		17 (73.9)	
N1a		5 (15.6)		4 (17.4)	
N1b		3 (9.4)		2 (8.7)	
Surgical complications	29		20		
Transient dysphonia		4 (13.8)		5 (25.0)	0.154
Permanent dysphonia		2 (6.9)		0	0.154
Transient HPT		8 (27.6)		4 (20.0)	0.604
Permanent HPT		2 (6.9)		2 (10.0)	0.604
Outcome at last follow-up	32		23		0.839
Remission		20 (62.5)		17 (73.9)	
Biochemical persistence		7 (21.9)		4 (17.4)	
Structural persistence		5 (15.6)		2 (8.7)	

Ct, serum levels of calcitonin; FNAC, fine-needle aspiration cytology; HPT, hypoparathyroidism; MTC, medullary thyroid cancer, CCH, C-cell hyperplasia.

*The number of cases with available data is reported for each characteristic. [†]Compares monolateral, bilateral and unspecified. [‡]Compares monolateral and bilateral.

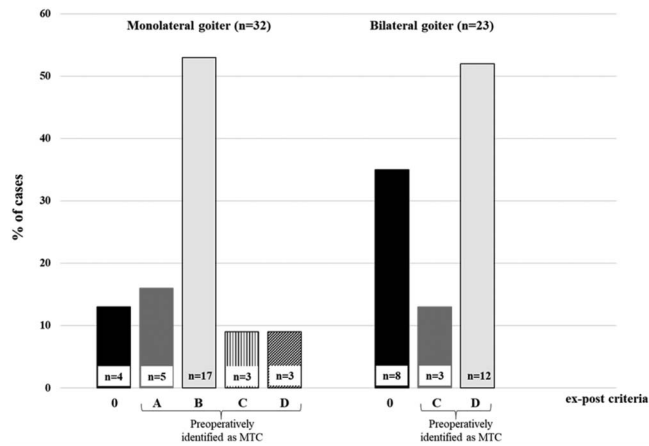


Figure 2

Monolateral and bilateral goiter patients whose MTC nodule would have been identified according to the ex-post criteria. 0) No suspicious nodules were identified at US, cytology was not suspicious and Ct was not consistent with the nodule/s volume; A) the nodule was the only nodule in the thyroid, possibly characterized by US suspicious features, serum Ct levels were consistent with the nodule volume and the stimulated Ct (if obtained) was above the cut-off limits; B) the nodule was the only nodule in the thyroid, possibly with US suspicious features, and cytological evaluation was positive or suspicious for MTC or malignancy and/or calcitonin measurement on the fine-needle washout fluid was positive; C) there were more than one nodule, but only one nodule had US suspicious features and/or volume consistent with Ct serum levels, and the stimulated Ct (if obtained) was above the cut-off limits; and D) there were more than one nodule, but only one nodule had a cytology positive or suspicious for MTC or malignancy and/or calcitonin measurement on the fine-needle washout fluid was positive.

Discussion

In the context of a growing interest in reducing health-related costs and overtreatments, surgical approaches for thyroid cancer are becoming increasingly more conservative, although this trend seems to be limited to the treatment of differentiated follicular-cell-derived thyroid cancer. To date, the recommendation for a conservative approach for *RET* germline negative monocentric MTC is included in guidelines only in Asia, even though it has been shown that a conservative approach is not different from total thyroidectomy in terms of survival and locoregional persistence/recurrence (6, 7, 8, 9, 10, 11, 12, 13). In our cohort of *RET*-negative patients, all submitted to total thyroidectomy ± lymphadenectomy, 97.6% had a single neoplastic focus, confirming that sporadic MTC is typically monocentric, in line with previous studies (1, 10).

According to the ex-post criteria that we defined, the vast majority of the patients with a monolateral goiter and around half of those with a bilateral goiter would have had the MTC nodule correctly identified preoperatively. Hence, those patients could have been submitted as first-line treatment to lobectomy and ipsilateral central neck

dissection ± lateral compartment in the absence of additional indications for total thyroidectomy or more extended procedures (i.e., large bilateral nodules and/or clinical suspicion of bilateral neck lymph nodes involvement), thus reducing the number of permanent and transient hypoparathyroidisms.

The extent of surgery should be driven by US findings and Ct levels, as suggested by ATA guidelines (3). Indeed, for basal Ct levels <200 pg/mL, no contralateral lateral neck involvement is usually found and central neck involvement occurs in <5% of cases. For Ct levels >200 and <500 pg/mL, the contralateral central neck compartment is involved in 10% of cases and the lateral neck in 14% (23). In the present series, the median preoperative Ct levels were 150 pg/mL and the median tumor histological size was 11 mm, with node metastases found at histology in 29% of cases. Basal Ct levels, MTC size and pTNM strongly correlated with the final outcome. The finding of a highly significant correlation between MTC size at histology and both basal preoperative Ct levels and US size further support the high predictivity of these two diagnostic tools and their value in the indication of the best surgical approach. Most of our cases can be thus considered as low risk cases, as previously suggested for MTC ≤2.5 cm and/or basal Ct ≤ 250 pg/mL (24). Indeed, we had a remission rate of 58.2%, rising to 86.5%, if we consider only cases with a basal Ct level ≤250 pg/mL. For these cases, lobectomy and ipsilateral CC dissection could be a viable and effective treatment, as also suggested by data of a large US series where no difference in survival was found based on surgical intervention in patients with tumor size ≤2 cm without distant metastases (25). On the other hand, the 21 patients with structural persistence had a basal preoperative Ct levels ranging 652–4,384 pg/mL. These persistent cases were mostly treated by bilateral central neck and ipsilateral lateral neck compartments dissection and were found to be persistent in the same compartments or in the contralateral lateral compartment. The presence of MTC nodules >2.5 cm with basal Ct levels >200–250 pg/mL indicates the need for a bilateral CC dissection associated with ipsilateral or bilateral LC dissection, depending on Ct levels (8, 10, 24). Nevertheless, lobectomy and ipsilateral CC dissection ± LC dissection could be suggested in selected cases, where the risks of an extensive procedure outweigh the risk of a persistent disease. Indeed, the probability to have an occult contralateral MTC focus is extremely low (no cases in the present and in a previous study (10), and 5% in another series (2)), and the node metastases possibly present in the contralateral compartment are infrequent (10% for Ct < 500 pg/mL, as reported above) and rarely likely to affect the survival of the patient. Moreover, it should be underlined that conservative surgery does not preclude the possibility of a reintervention in the case of progression and allows in some patients to avoid transient/permanent hypoparathyroidism and life-long L-thyroxine treatment.

Another insight which can be derived from the present study relates to the impact on early diagnosis of the routine evaluation of Ct in nodular goiter. The utility of this diagnostic tool is further confirmed in this series by the finding of low median basal Ct levels and small MTC size at histology, which are similar to those found in Germany where the Ct screening is applied (14), and lower than those reported in a US study in which the diagnosis is not based on the routine screening (2). Thus, the use of the routine Ct measurement is particularly useful for the implementation of less aggressive surgical approaches.

Finally, in our cohort, roughly 10% of patients also had a papillary thyroid cancer, in accordance with the already reported prevalence of this incidental finding in nodular goiter (26). We speculate that this finding should have no impact on the indication for lobectomy in MTC due to the indolent behavior of incidental PTCs.

According to the findings of the present study, we propose the algorithm reported in Fig. 3 to be followed in patients with uni- or multi-nodular goiter with Ct basal levels above the normal reference value. In particular, in patients with two basal Ct measurements above the reference range and a positive calcium stimulation test, we recommend to perform both a germline *RET* evaluation and a neck US to identify suspicious nodules. If a nodule with suspicious features and Ct levels consistent with the nodule size is found, we recommend performing lobectomy, potentially associated with ipsilateral lymph node dissection of the central compartment (based on Ct and US findings) for unilateral nodules. For bilateral

nodules or in the absence of suspicious nodules, the suggestion is to perform cytology with Ct measurement in the FNA washout, choosing lobectomy if a suspicious MTC can be identified (in the absence of specific requirements for total thyroidectomy). If no cytological diagnosis is obtained or if no nodules are identifiable on US, perform a total thyroidectomy, potentially associated to ipsi- or bilateral lymph node dissection of the central ± lateral compartments (based on Ct levels and US findings). In some cases, the extent of surgery can also be based on CEA levels, on CT findings and on functional imaging, i.e. DOPA and/or Ga68 DOTATOC PET. Although the presence of a bilateral MTC is extremely rare, patients treated with lobectomy should be followed-up by the evaluation of the trend of basal Ct, if detectable, and neck US.

The main limitation of our results is that they have been collected in a retrospective study setting, with an ex-post evaluation of the suspicious nodule, and the data might be different if the diagnosis would have been done ex-ante. On the other hand, the retrospective design of the study allowed us to collect a quite large cohort, increasing the power of the study. A future study based on prospective data may ensure stronger data. Another aspect to consider is the availability of genetic analysis. To plan a lobectomy in cases where MTC is identified preoperatively, it is essential to have germline *RET* analysis available within a reasonable timeframe to avoid excessive delays in surgical intervention. Nevertheless, we should consider that *RET* germline mutations can be reliably identified by PCR amplification and Sanger sequencing of 5/6 exons, a

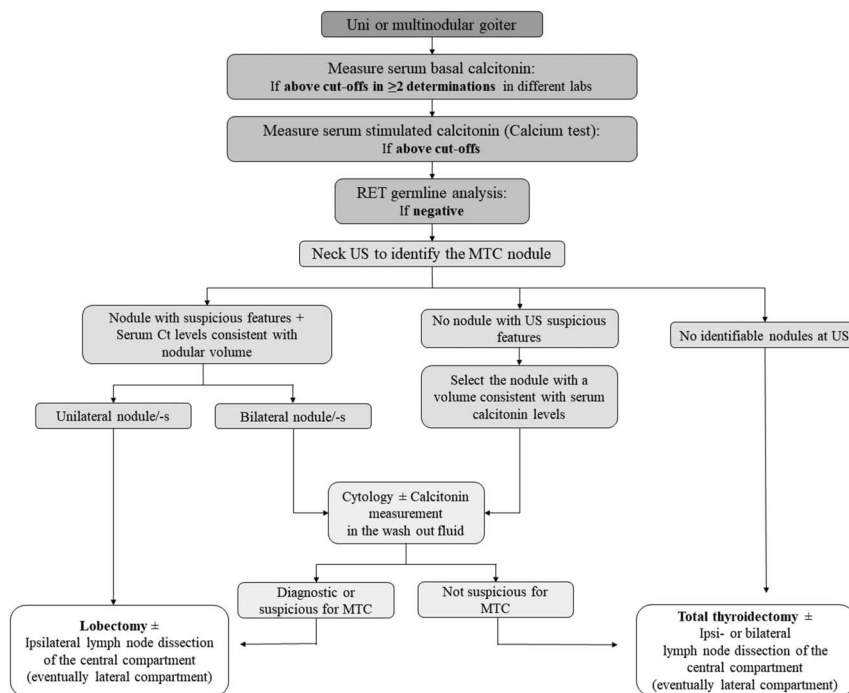


Figure 3
 Suggested algorithm to be followed in patients with mono- or bi-lateral goiter, with Ct basal levels above the normal reference value. US, ultrasound; Ct, calcitonin; MTC, medullary thyroid cancer.

methodology with a low cost and largely available. We should also underlie that the preoperative identification of the MTC nodule and thus the eligibility for lobectomy can be done in most monolateral goiters, but in only a part of bilateral goiters (half in this series). Finally, in some cases (15% in the present series), even if the tumor is small and the Ct levels are low, lymph node micrometastases can be present in the contralateral central compartment, which is hardly explorable when the thyroid is *in situ*, and not routinely dissected if the surgical procedure is lobectomy. Thus, patients should be informed about the possible structural persistence related to a limited surgery. On the other hand, if Ct levels are in the low range, nodal metastases not detected at preoperative US are usually micrometastases, with a very low or null impact on prognosis, while if Ct levels are in the high range, nodal metastases can be visualized by an US done by expert hands or by a CT scan, and surgery modulated upon those findings.

In conclusion, this is the first European study that aims to evaluate the feasibility of lobectomy as first-line therapy for MTC, based on the presurgical evaluation of thyroid US and serum Ct. Our data showed that these diagnostic tools have a good accuracy in detecting the affected lobe, cytology possibly associated with Ct on FNA washout being an adequate confirmatory analysis. Therefore, the results support the feasibility of a more conservative surgical approach for treating *RET*-negative patients with suspicious MTC, particularly but not exclusively in monolateral goiters.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the work reported.

Funding

This study was funded by the Italian Ministry of Health-Ricerca Corrente.

Author contribution statement

ML and LF designed the study, analyzed the data and wrote the manuscript. ML, CM, and GS collected the data. ML and GS performed the ex-post evaluation. CM and GG performed the matching between ex-post analysis and the histological report. LF followed the patients and performed ultrasonographic examinations. GD performed surgical treatments. GG performed the histological examination. All the authors revised the manuscript and approved its final version.

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