



# Cure and survival of sporadic medullary thyroid carcinoma following systematic preoperative calcitonin screening

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## Abstract

**Background** The improvement in outcome of sporadic medullary thyroid carcinoma (MTC) during the last decades remains controversial, even if a trend toward a better prognosis has been recently proposed. This study was aimed to determine the time trend cure and survival rates in sporadic MTC according to the use of systematic preoperative calcitonin screening.

**Methods** Retrospective analysis of 178 sporadic MTC patients operated between 1980 and 2017 was performed. The impact of prognostic factors on cure and survival following the introduction of routine preoperative calcitonin screening in 2001 was evaluated according to the year of surgery.

**Results** Since 2001, a significant decline of node-positive tumors (from 56.1 to 34.7%) and advanced stage at diagnosis (stage III/IV from 56.1 to 34.7%) occurred, with a concomitant significant increase in cure rate (64.5% vs 38.6%;  $p = 0.0012$ ) and survival ( $p < 0.05$ ). At univariate analysis, the cure was achieved more frequently in more recently operated patients (64.5% vs 38.6%;  $p = 0.0012$ ), in disease staging I/II (86.5% vs 13.5%;  $p < 0.0001$ ), in patients undergoing preoperative calcitonin screening (63.8% vs 23.5%;  $p < 0.0001$ ) and in the absence of lymph node metastases (86.5% vs 13.5%;  $p < 0.0001$ ). At multivariate analysis, only preoperative calcitonin screening and stage at diagnosis turned out to be significant independent prognostic factors for cure and survival.

**Conclusion** The outcome of sporadic MTC improved in the new millennium; diagnosis was achieved earlier, at a less advanced stage. Routine preoperative calcitonin screening may have contributed to improve cure and survival rates.

**Keywords** MTC · Outcome · Calcitonin screening · Prognosis

## Introduction

Medullary thyroid carcinoma (MTC) is a rare thyroid malignancy arising from parafollicular C cells and characterized by early spreading to cervical lymph nodes. It occurs mainly as sporadic tumor; in approximately 30% of cases, it may occur

as hereditary variant, transmitted by *RET* proto-oncogene germline mutations. Although MTC accounts for only 5% of thyroid cancers, it is responsible for approximately 13% of all thyroid cancer-related death [1]. In recent decades, the incidence of MTC has increased with a higher proportion of tumors less than 10 mm in diameter as a result of thyroid ultrasound and measurement of serum calcitonin in subjects with thyroid nodules [2–5]. The 2015 American Thyroid Association (ATA) Guidelines recommend that surgery for MTC should at least include a total thyroidectomy with bilateral central (level VI) neck dissection [1].

Prognosis of MTC is considered intermediate between differentiated thyroid neoplasms and anaplastic tumor, with a reported overall 5- and 10-year survival varying from 78 to 91% and 61 to 88%, respectively [6, 7]. The main MTC prognostic factor for cure and survival is the stage of disease, and it strictly depends on early diagnosis, when the tumor is still limited to the thyroid without nodal or distant metastases [7]. Furthermore, despite the relatively high survival rates, only

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about 34 to 44% of patients are biochemically cured by surgery [8].

In recent years, a significant improvement in the prognosis of MTC has been reported by several studies; however, most of these studies included also hereditary variants of MTC that can be early diagnosed following the systematic genetic screening of *RET* mutations in relatives of index cases [2, 5, 9, 10].

Conversely, the improvement of cure and survival rates in sporadic MTC in the last decades has not been delineated in depth.

Serum calcitonin is the most specific and sensitive marker of MTC [11–13]; thus, the systematic preoperative calcitonin screening in nodular thyroid disease aiming at early MTC detection has been suggested, but its routine use is not recommended in all countries [14, 15].

The aim of the present study was to determine the time trend for cure and survival and prognostic factors in sporadic MTC according to the use of preoperative calcitonin screening.

## Material and methods

The present study focused on a series of 178 consecutive patients undergoing initial surgery for sporadic MTC between 1980 and 2017 at the Endocrine Surgery Units of Padua University Hospital.

Sporadic MTC was defined according to the absence of germline *RET* mutations and/or coexistent pheochromocytoma or other features associated with hereditary MTC or first-degree relatives affected by MTC. Thus, patients with genetically or clinically suspected hereditary MTC, C cell hyperplasia without histologically confirmed MTC, and patients with incomplete outcome follow-up data (less than 6 months) were excluded.

*RET* gene was systematically analyzed, before surgery, in all MTC patients since 2001 by direct sequencing of exons 5, 8, 10, 11, 13, 14, 15, and 16; moreover, it was also retrospectively performed in all survived patients operated for MTC before 2001, in order to genetically exclude the presence of hereditary MTC. In patients who died before 2001, hereditary MTC was excluded on clinical basis (absence of coexistent pheochromocytoma and/or other associated features, absence of MTC and/or *RET* mutations in first-degree relatives).

In- and out-patient medical records were retrospectively examined to find out data about demographics (age, gender, year of surgery), preoperative work-up including radiological and biochemical findings (focusing on calcitonin measurements), extent of surgery, and pathology.

According to the preoperative work-up, a calcitonin screening was considered “performed” if serum calcitonin assay was

available before surgery, allowing preoperative suspicion of MTC.

Calcitonin measurement methods varied significantly during the study period; radioimmuno-metric and, more recently, immunochemiluminescent techniques were used. These methods were not comparable since they had a variable sensitivity, specificity, and different normal reference values. Subsequently, calcitonin serum levels were normalized and scored as a ratio (calcitonin value/upper limit of the normal range value of the method) [10].

The extent of surgery was categorized as thyroidectomy, thyroidectomy plus central lymph nodes dissection, and thyroidectomy plus central and lateral lymph node dissection.

Pathology report was revised according to the eighth edition of AJCC TNM Staging System classification [16]; lymph node status, distant metastases, and stage at diagnosis were assessed according to pathological and surgical reports or according to clinical and radiological findings.

Follow-up data included biochemical, clinical, and radiological evaluation; the postoperative outcomes and follow-up data were assessed according to the last available medical record and further verified by direct phone interview to the patient and/or to the general practitioners.

Patients were classified according to the year of surgery in group A (patients operated between 1980 and 2000) and group B (between 2001 and 2017), following the introduction of preoperative systematic calcitonin screening in 2001 at our Institution.

The end point of the study was the surgical outcome in terms of cure and survival rates according to the timing of surgery.

Cure was defined as a disease-free status (absence of postoperative clinical or radiological signs of disease and undetectable calcitonin levels); patients with biochemical/radiological evidence of disease (persistent or recurrent) were considered not cured. Mortality and survival were assessed according to the specific MTC-related death.

The study was approved by the Institution Review Board.

## Data analysis

Statistical analysis was performed using MedCalc (version 18.2.1). Data were expressed as absolute numbers, percentages, means and standard deviations, and median with range or interquartile range (IQR). Categorical and continuous data were tested with the chi-square or Fisher’s exact test and Student’s *t* test or the Mann–Whitney test, respectively. Tumor size was analyzed as categorical variables (microMTC, size  $\leq 10$  mm and macroMTC, size  $> 10$  mm). The year of surgery was analyzed as a categorical variable (intervals: 1980–2000; 2001–2017) and the  $\chi^2$  was calculated to evaluate temporal trends of categorical variables.

Survival was calculated as the time from surgery until death or the last available follow-up. For mortality rate analysis, only disease-specific causes of death were considered. Survival data were analyzed by the Kaplan–Meier methods; univariate and multivariate analysis of factors affecting survival were conducted by the Cox proportional hazards regression model. Multivariate analysis of factors affecting cure was conducted by logistic regression. The level of significance was set at  $< 0.05$ .

## Results

The clinico-pathological features of 178 patients undergoing surgery for sporadic MTC are shown in Table 1.

**Table 1** Clinico-pathological characteristics of 178 patients undergoing surgery for sporadic medullary thyroid carcinoma

Characteristic	<i>n</i>	(%)
Gender		
Female	106	59.6
Male	72	40.4
Year of surgery		
Group A	57	32
Group B	121	68
Preoperative calcitonin assay		
Performed	144	80.9
Not performed	34	19.1
Extent of surgery		
Thyroidectomy	34	19.1
Total thyroidectomy + central node dissection	69	38.8
Total thyroidectomy + central and lateral node dissection	75	42.1
Tumor size (mm)		
$\leq 10$	44	24.7
$> 10$	134	75.3
Lymph nodal status		
N0	104	58.4
N1	74	41.6
Pathologic TNM staging		
I	64	36
II	40	22.5
III	16	9
IVA-B	49	27.5
IVC	9	5.1
Cure		
Cured	100	56.2
Not cured	78	43.8

Group A, surgery performed between 1980 and 2000; Group B, surgery performed between 2001 and 2017; N0, absence of nodal metastases; N1, presence of nodal metastases

The mean age was  $56.18 \pm 13.89$ . The female to male ratio was 1.47. A preoperative serum calcitonin measurement was available in 80.9% of patients; in the remaining 19.1%, a calcitonin assay was not performed before surgery and MTC was diagnosed only at final pathology. The median preoperative calcitonin level ratio was 27.42 (IQR 7.74, 88.83).

The surgical treatment was a total thyroidectomy plus central lymph node dissection in 80.9% patients; 52% of these patients underwent also a lateral neck lymph node dissection; in 19.1% of patients, only thyroidectomy without nodal dissection was performed.

At final pathology, a microMTC was found in 24.7%, while the MTC size was larger than 1 cm in 75.3%; lymph node metastases were reported in 41.6% of cases. At TNM staging, 58.5% of patients had stages I and II disease; 41.6% were diagnosed at stages III and IV. Distant metastases at diagnosis were detected in 5.1% of patients.

## Sporadic MTC cure and survival

Cure was achieved in 56.2% of patients at an overall median follow-up of 98 months (272 months in group A and 79 months in group B), ranging between 7 and 441 months. At univariate analysis, cure was achieved more frequently in females (67.9% vs 38.8%;  $p = 0.0001$ ), in patients undergoing preoperative routine calcitonin measurements (63.8% vs 23.5%;  $p < 0.0001$ ), in patients undergoing surgery in more recent years (64.5% in group B vs 38.6% in group A;  $p = 0.0012$ ), in smaller tumors (microMTC 70.4% vs macroMTC 51.5%;  $p = 0.028$ ), in the absence of lymph node metastases (86.5% vs 13.5%;  $p < 0.0001$ ), in less advanced stage (86.5% in stage I/II vs 13.5% in stage III/IV;  $p < 0.0001$ ), and in patients undergoing total thyroidectomy plus central lymph node dissection (81.1% vs 58.8% of patients undergoing only thyroidectomy and 32% undergoing total thyroidectomy + central and lateral lymph node dissection;  $p < 0.0001$ ).

At multivariate analysis, only gender, preoperative calcitonin screening, and stage at diagnosis turned out to be significant independent prognostic factors for cure (Table 2).

MTC-related death occurred in 31 cases (17.3%). The overall 5- and 10-year survival was 87% and 80.6%, respectively. The 10-year survival was significantly influenced by gender (90% in female vs 72.6% in male;  $p = 0.014$ ), preoperative calcitonin screening (87% when performed vs 54% not performed;  $p < 0.0001$ ) (Fig. 1), year of surgery (88.6% for group B vs 73.7% for group A;  $p = 0.009$ ) (Fig. 2), size of tumor (97.7% for microMTC vs 78.1% for macroMTC;  $p = 0.016$ ), lymph nodal status (100% in N0 vs 59.4% in N1;  $p < 0.0001$ ), TNM staging (100% for stage I/II vs 93.8% for stage III vs 61% for stage IV A/B vs 10% for stage IVC;  $p < 0.0001$ ), extent of surgery (98.6% for patients undergoing total thyroidectomy plus central lymph node dissection vs

**Table 2** Univariate and multivariate analyses of prognostic factors for cure in 178 patients undergoing surgery for sporadic medullary thyroid carcinoma

Predictive factors (n)	Univariate analysis				Multivariate analysis			
	n (%)				p value	Odds ratio	95% CI	p value
	Cured n = 100 (56.2%)		Not cured n = 78 (43.8%)					
Gender					0.0001	2.49	1.01–6.14	0.03
Female	72	72.0%	34	43.6%				
Male	28	28.0%	44	56.4%				
Preoperative calcitonin assay					< 0.0001	4.77	1.47–15.49	0.009
Performed	92	92.0%	52	66.7%				
Not performed	8	8.0%	26	33.3%				
Year of surgery					0.0012	–	–	NS
Group A	22	22.0%	35	44.9%				
Group B	78	78.0%	43	55.1%				
Tumor size					0.028	–	–	NS
≤ 10 mm	31	31.0%	13	16.7%				
> 10 mm	69	69.0%	65	83.3%				
Lymph nodal status					< 0.0001	–	–	NS
N0	90	90.0%	14	17.9%				
N1	10	10.0%	64	82.1%				
Pathologic TNM staging					< 0.0001	34.90	14.03–86.79	< 0.0001
I	59	59.0%	5	6.4%				
II	31	31.0%	9	11.5%				
III	5	5.0%	11	14.1%				
IVA-B	5	5.0%	44	56.4%				
IVC	0	0.0%	9	11.5%				
Extent of surgery					< 0.0001	–	–	NS
Thyroidectomy	20	20.0%	14	17.9%				
Central lymph node dissection	56	56.0%	13	16.7%				
Lateral cervical lymph node dissection	24	24.0%	51	65.4%				

Group A, surgery performed between 1980 and 2000; Group B, surgery performed between 2001 and 2017; N0, absence of nodal metastases; N1, presence of nodal metastases

91.2% for thyroidectomy vs 67.4% for total thyroidectomy plus central and lateral neck dissection;  $p < 0.0001$ ). The results were further confirmed by Cox analysis (Table 3).

At multivariate analysis, only stage at diagnosis and routine preoperative calcitonin screening turned out to be significant independent prognostic factors for survival (adjusted hazard ratio 4.09 and 2.83;  $p < 0.0001$  and 0.02, respectively) (Table 3).

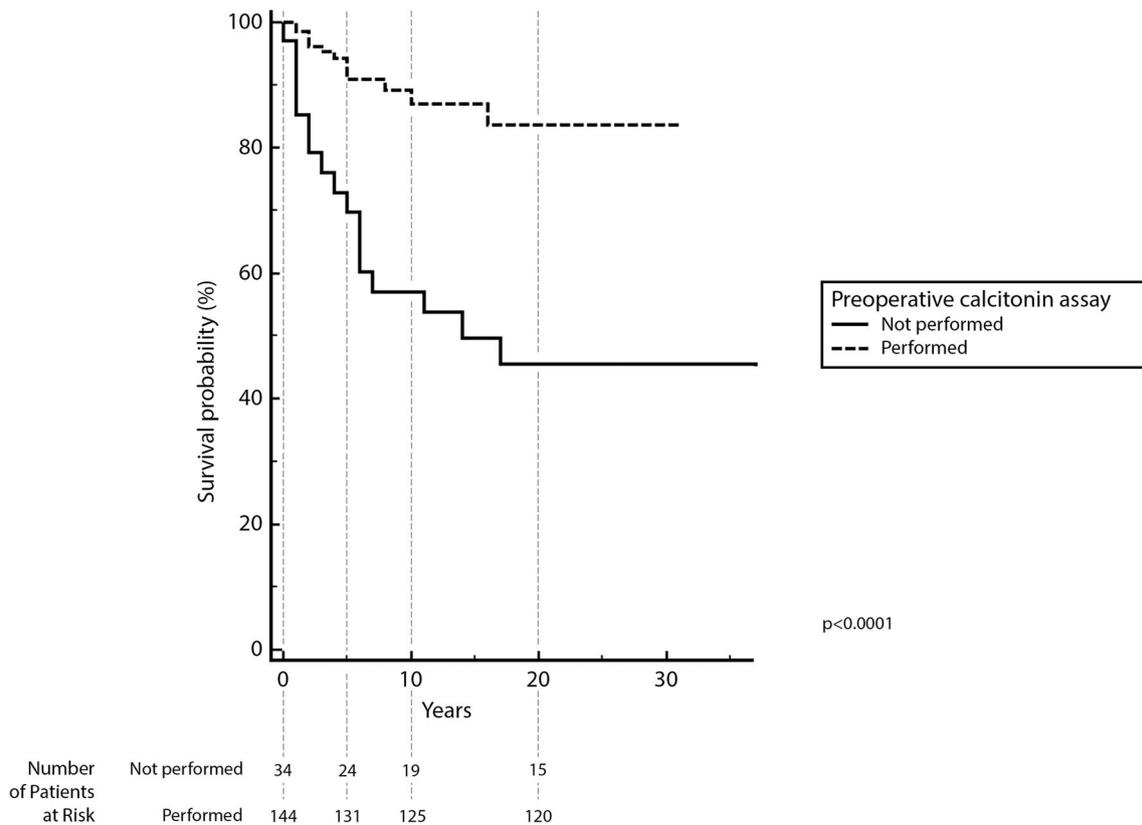
### Changing trends for sporadic MTC in the new millennium

Surgery for sporadic MTC was performed more frequently in patients operated after 2000 (68% in group B and 32% in

group A) (Table 4). No significant differences in age and sex were observed between the two groups.

A preoperative suspicion of MTC (according to calcitonin measurement) was available in 95% of patients within the group B and 50.9% in group A ( $p < 0.0001$ ). The median preoperative calcitonin level ratio was 12.43 (IQR 5.25, 46.94) in group A patients and 33.45 (IQR 9.18, 100.75) in group B ( $p = 0.12$ ).

Since 2001, a trend toward an increased prevalence of microMTC at pathology (28.9% in group B vs 15.8% in group A;  $p = 0.058$ ) and a significant declines of node-positive tumors (from 56.1% in group A to 34.7% in group B;  $p = 0.017$ ), advanced stages at diagnosis (from 56.1% of stage III/IV in group A vs 34.7% in group B;  $p = 0.0005$ ), and



**Fig. 1** Survival according to preoperative calcitonin screening in 178 sporadic medullary thyroid carcinomas

distant metastases (from 8.8% in group A to 3.3% in group B;  $p = 0.0005$ ) were observed.

Even if less extensive lymph nodal dissection was performed in more recently operated patients (lateral lymph node dissection in 66.7% of patients in group A vs 30.6% in group B;  $p = 0.005$ ), a concomitant increase in cure rate was observed (38.6% in group A vs 64.5% in group B;  $p = 0.0012$ ). MTC-related death occurred less frequently in group B (9% vs 35%;  $p < 0.0001$ ) that also showed a significantly increased survival ( $p < 0.05$ ) (Fig. 2).

## Discussion

Over the past few decades, medical advances have changed the landscape in which MTC is managed and contemporary series demonstrated that MTC has been better recognized and treated with a significant improvement in cure and survival. However, some series were biased by the inclusion of both sporadic and hereditary MTC that may have different prognosis [5, 10, 15].

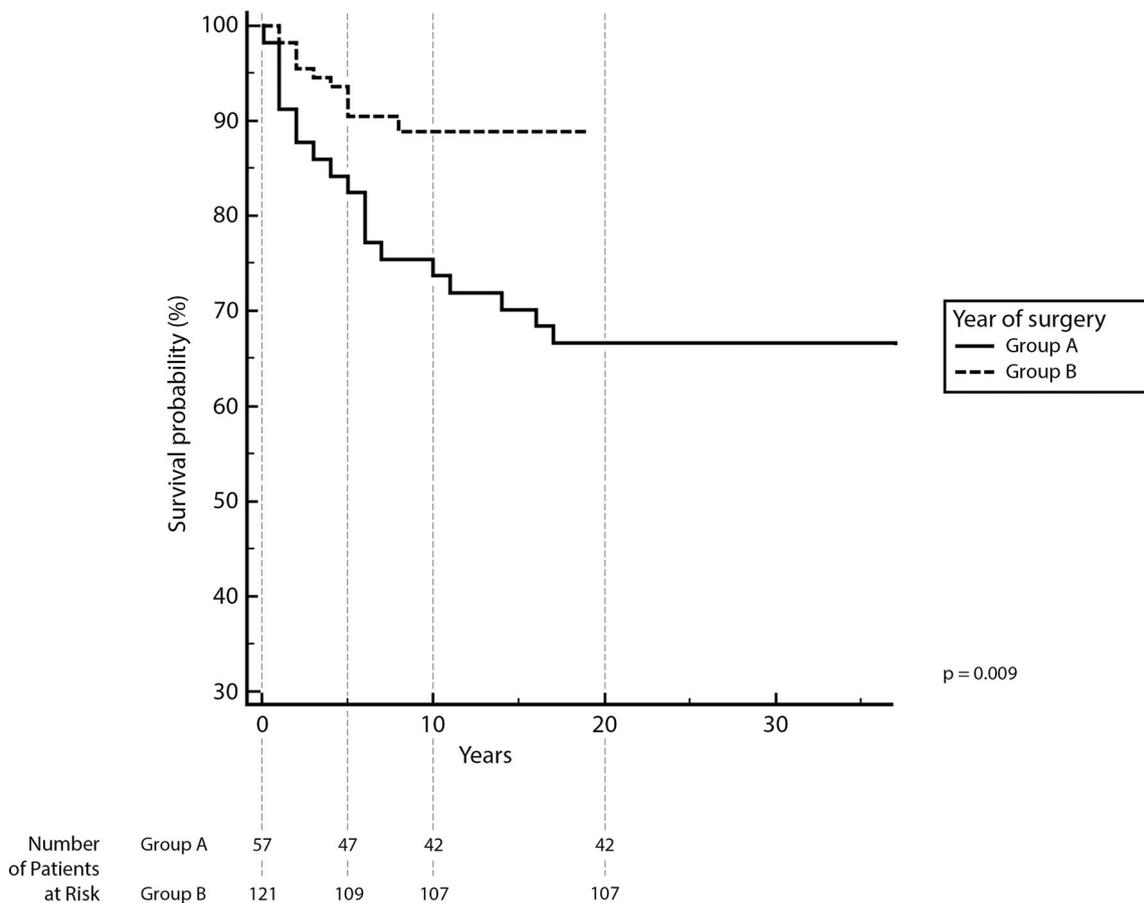
In fact, the discovery of *RET* mutations in hereditary MTC and the implementation of genetic screening in familial cases have certainly contributed to the identification of early stages of disease [10, 17], and, in many cases, even allowing a prophylactic surgery before the tumor growing [7, 18], with subsequent definitive cure.

To the contrary, the changes in disease onset and outcome improvement in patients undergoing surgery for sporadic MTC are still controversial. Some studies were not able to find any improvement in cure and survival rates [19]; more recent papers have found an increased rate of microMTC without nodal metastases and consequent better biochemical cure rate during recent decades [2, 5, 9, 10]. However, these studies are sometimes biased by the inclusion of hereditary cases that may have better outcomes when diagnosed early during a familial screening.

Thereby, the present study focused on sporadic MTC and aimed to determine prognostic factors and changing trends in cure and survival in 178 patients operated for sporadic MTC at the same Institution in two different eras (1980–2000; 2001–2017), according to the introduction of systematic routine preoperative calcitonin screening in the year 2001.

The improvement in clinical outcomes in terms of cure and survival observed in the present series in the last two decades was closely associated with the changes in the clinico-pathological features of MTC. Since 2001, a significant reduction in advanced stages of disease, regional and distant metastases, and a trend to increase microMTC was observed, reflecting a trend to early diagnosis.

Similar results were found also by Machens and Dralle in a retrospective analysis of 322 patients treated in a 21-year stretch; more localized and surgically cured sporadic MTCs



**Fig. 2** Survival according to the year of surgery in 178 sporadic medullary thyroid carcinomas; Group A, surgery performed between 1980 and 2000; Group B, surgery performed between 2001 and 2017

were found, probably reflecting a surge of microcarcinoma [3]. Other studies have confirmed that microMTC have higher cure rates and lower risk of metastases and death compared with larger tumors [2, 20, 21]. However, smaller tumors do not always equate to diagnosis at an earlier stage. In fact, Kazaure et al. reported that smaller diameter could be associated with a significant rate of poor prognostic characteristics, with lymph node metastases in about 30% of cases [22]. Moreover, a recent meta-analysis aimed to examine the clinico-

pathological features of microMTC in comparison with macroMTC confirmed that microMTC is as aggressive as macroMTC in multifocality and distant metastases and has a lower, but non-negligible, rate of extrathyroidal extension and cervical lymph node metastases [4]. Even if the present series confirmed the increasing number of microMTC in the last decades and the significant increase of cure and survival rates in tumors less than 1 cm, it clearly demonstrated that the size of the tumor alone was not an independent prognostic factor of

**Table 3** Univariate and multivariate analysis of factors affecting the overall survival in 178 patients undergoing surgery for medullary thyroid carcinoma

Variable	Univariate analysis			Multivariate analysis (stepwise cox)		
	UHR	95% CI	<i>p</i>	AHR	95% CI	<i>p</i>
Gender	2.4	1.15–4.98	0.019	–	–	–
Preoperative calcitonin assay	5.32	2.57–10.99	<0.0001	2.83	1.36 to 5.89	0.02
Year of surgery (group A vs group B)	2.64	1.23–5.69	0.013	–	–	–
Tumor size	4.82	1.15–20.26	0.031	–	–	–
TNM stage	4.68	2.36–9.25	<0.0001	4.09	2.08 to 8.02	<0.0001
Extent of surgery	3.87	1.90–7.90	0.0002	–	–	–

Group A, surgery performed between 1980 and 2000; Group B, surgery performed between 2001 and 2017; UHR, unadjusted hazard ratio; AHR, adjusted hazard ratio

**Table 4** Demographics, clinical, histological features, and cure rates in 178 patients undergoing surgery for medullary thyroid carcinoma according to the year of surgery

	Group A, <i>n</i> = 57 (32.0%)		Group B, <i>n</i> = 121 (68.0%)		<i>p</i> value
Gender					0.98
Female	34	59.6%	72	59.5%	
Male	23	40.4%	49	40.5%	
Preoperative calcitonin assay					< 0.0001
Yes	29	50.9%	115	95.0%	
No	28	49.1%	6	5.0%	
Tumor size (mm)					0.058
≤ 10	9	15.8%	35	28.9%	
> 10	48	84.2%	86	71.1%	
Lymph nodal status					0.017
N0	25	43.9%	79	65.3%	
N1	32	56.1%	42	34.7%	
Pathologic TNM staging					0.0005
I	11	19.3%	53	43.8%	
II	14	24.6%	26	21.5%	
III	2	3.5%	14	11.6%	
IVA-B	25	43.9%	24	19.8%	
IVC	5	8.8%	4	3.3%	
Extent of surgery					0.005
Thyroidectomy	12	21.1%	22	18.2%	
Central lymph node dissection	7	12.3%	62	51.2%	
Lateral cervical lymph node dissection	38	66.7%	37	30.6%	
Cure					0.0012
Yes	22	38.6%	78	64.5%	
No	35	61.4%	43	35.5%	

Group A, surgery performed between 1980 and 2000; Group B, surgery performed between 2001 and 2017; *N0*, absence of nodal metastases; *N1*, presence of nodal metastases

cure and survival in sporadic MTC. In fact, it confirmed the overwhelming prognostic role of stage at diagnosis, since patients at an earlier stage (I and II) had an approximately 35-fold increase chance of cure while patients with advanced tumor stage had a four-fold increase risk of death.

The increased number of early staged MTC in the last decades is probably due to early diagnosis, following calcitonin screening programs, although they are not practiced worldwide. A preoperative calcitonin screening in patients with nodular thyroid disease is performed almost routinely in Europe but not in the USA where the revised ATA guidelines do not recommend its routine use [1, 5]. In fact, despite some publications in the late 1990s demonstrating the higher diagnostic sensitivity and specificity of calcitonin compared with fine-needle aspiration findings, controversies remain concerning cost-effectiveness [10, 23]. Measurement of serum calcitonin in patients with thyroid nodules is done systematically at our Institution since 2001; in fact, a preoperative calcitonin measurement was available only in approximately half of cases of sporadic MTC before 2001 and in 95% after 2000. This strategy may have contributed to earlier diagnosis of

MTC; in fact, MTCs at stages I and II were detected more often in the recent years. Thus, the present study confirmed that the strongest independent prognostic factor for cure and survival in MTC remains stage of disease and, to a lesser extent, the availability of preoperative calcitonin screening. In fact, patients undergoing preoperative calcitonin screening had an approximately five-fold increase chance of cure and three-fold decreased risk of death.

Furthermore, the more likely chance to detect early stages by routine calcitonin screening was probably parallel to a more appropriate opportunity for an adequate extension of surgical treatment to improve prognosis. Interestingly, in the last decades, a more tailored surgery, according to the preoperative work-up, was performed at our Institution. In fact, even if it is difficult to assess the impact of surgical strategy in a retrospective setting, because the extent of surgery (especially regarding the nodal dissection) was not standardized and varied over time, in the first part of the present series, a more aggressive surgical strategy was adopted, with lateral nodal neck dissection in 66.7% of cases. In recent years, total thyroidectomy and central nodal neck dissection were

considered mandatory in all patients with a preoperative diagnosis of MTC, while lateral neck lymph nodal dissection was usually performed only in the presence of clinical or ultrasound evidence of metastases, independently from calcitonin levels. This strategy, even if less extended, allowed better results in terms of cure and survival. Moreover, patients undergoing more extensive surgery showed a worse prognosis compared with patients undergoing only central neck nodal dissection, probably because the former had a more advanced disease compared with the latter, in agreement with similar results recently reported by other authors [3]. However, in the present series, even if patients undergoing total thyroidectomy and central nodal neck dissection had the best chance of cure and survival, the extent of surgical treatment was not an independent prognostic factor either for cure or for survival.

The present study has some limitations that are common to retrospective studies. We subgrouped the periods as before and after 2000, according to the systematic introduction of calcitonin screening at our Institution; however, the improved outcome observed in more recent years could be explained by other factors including the widespread systematic use of high-resolution ultrasonography or the improved sensitivity of fine-needle aspiration and cytology. The widespread systematic use of high-resolution ultrasonography could contribute to the discovery of a greater number of smaller thyroid nodules, but without the calcitonin measurements, they could be misdiagnosed and treated later at a more advanced stage, with a lower probability to reach cure. Moreover, follow-up periods differed greatly between group A and group B, since distant cohorts were compared. By implication, the number of observations for group B could be more limited given the fact that patients operated in very recent years had less chance of completing a 10-year follow-up period. However, it should be considered that more than half (51%) of the more recent cohort (group B) were operated before 2007 and, therefore, they completed at least a 10-year follow-up.

## Conclusions

Biochemical cure and survival rates in patients undergoing surgery for sporadic MTC were consistently ameliorated in the last two decades, in parallel with a more likely chance to detect early staged tumors. In fact, early stage of disease at diagnosis and preoperatively performed calcitonin measurements remain the strongest predictive factor of postoperative cure and survival. This new landscape in sporadic MTC may reflect the increased use of systematic preoperative calcitonin screening.

**Authors' contributions** Francesca Torresan: study conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript. Caterina Mian:

study conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript. Elisabetta Cavedon: acquisition of data and Critical revision of the manuscript. Maurizio Iacobone: study conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** For this type of study (retrospective analysis), formal consent is not required. The study was approved by the Institution Review Board.

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