Clinico-pathologic and dynamic prognostic factors in sporadic and familial medullary thyroid carcinoma: an Israeli multi-center study

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Abstract

Objective: Multiple clinical, pathological and biochemical variables, including the response to initial treatment, are associated with medullary thyroid carcinoma (MTC) prognosis. Studies that include separate analyses of familial and sporadic MTC patients followed for long period are scarce. This study evaluated the association between baseline clinico-pathologic variables and response to initial treatment and short- and long-term disease outcomes in sporadic and familial MTC.

Methods: Patients treated for MTC at four tertiary medical centers were retrospectively analyzed. Clinical and pathological data were collected. The outcomes measured included disease persistence 1 year after diagnosis, disease persistence at last follow-up, disease-related mortality (DRM) and all-cause mortality.

Results: The study enrolled 193 patients (mean age: 48.9 ± 18.7 , 44.7% males), of whom 18.1% were familial cases. The mean follow-up period was 10.1 ± 9.4 years (8.5 ± 8.1 in sporadic and 16.9 ± 11.6 in familial MTC). Disease persistence 1-year after diagnosis and at last follow-up was detected in 56.1 and 60.4% patients, respectively. All-cause and DRM were 28.5 and 12.6%, respectively. Extra-thyroidal extension (ETE) and distant metastases (DM) were associated with disease persistence at last follow-up. ETE and DM were also significantly associated with DRM. Complete remission 1 year after diagnosis had high correlation with no evidence of disease at last follow-up (Cramer's V measure of association 0.884, $P < 0.001$) and with 100% disease-specific survival (Cramer's V measure of association 0.38, $P < 0.001$).

Conclusions: Apart from clinico-pathologic parameters, close correlation was found between 1-year status and long-term prognosis. These results underscore the importance of combining classical and dynamic factors for both sporadic and familial MTC prognostication and treatment decision making.

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Introduction

Medullary thyroid carcinoma (MTC), originating from para-follicular c-cells in the thyroid gland, is a rare malignancy diagnosed in up to 5% of thyroid cancer patients (1). While most MTC cases are sporadic, up to 30% are associated with a germline mutation in the *RET* proto-oncogene and considered familial MTC.

Several studies evaluated the association of clinico-pathologic variables and MTC outcomes, to identify prognostic factors that might aid in treatment decisions. Multiple variables were found to be associated with MTC prognosis, including older age at diagnosis, disease stage, disease form (hereditary vs sporadic), extrathyroidal extension (ETE), location and number of lymph node metastases (LNM) and postoperative residual disease (2, 3, 4, 5, 6, 7, 8, 9, 10, 11). Biochemical markers, including calcitonin and carcinoembryonic antigen (CEA) levels play important roles in MTC prognosis, as well (12, 13, 14, 15). A dynamic risk stratification method that includes response to the initial treatment has been suggested, similar to that used for non-medullary differentiated thyroid cancer (16, 17, 18, 19). However, many of the studies are confounded by including sporadic and familial MTC patients or even patients with C-cell hyperplasia who underwent prophylactic thyroidectomy. Data based on large cohorts with long-term follow-up are still limited.

This multicenter study identified prognostic variables, including response to initial treatment, associated with short- and long-term outcomes in a large cohort of MTC patients, grouped and divided according to sporadic and familial MTC.

Patients and methods

This study included patients with MTC who were diagnosed from 1963 through 2016 and were followed at four tertiary medical centers in Israel. The study protocol was approved by the Institutional Ethics Board at all four centers (Meir medical Center ethical committee, Rabin Medical Center ethical committee, Assaf Harofe Medical Center ethical committee and Hadassah Medical Center Ethical Committee). In accordance with Helsinki regulations regarding clinical studies based solely on review of charts, informed consent was waived by ethic committees of four institutes. Medical records were reviewed for demographic, pathological and clinical variables. Demographic data included gender and age at MTC diagnosis. Patients were defined as having familial

or sporadic MTC according to clinical criteria and/or *RET* proto-oncogene analysis results. *RET* mutation carriers who underwent prophylactic thyroidectomy and did not have a discrete tumor on pathology were not included. Pathologic information included the size of largest dimension of the primary tumor, focality (solitary or multifocal, unilateral or bilateral) and extension (intrathyroidal vs. extrathyroidal), LNM and distant metastases (DM).

Disease status 1-year after diagnosis and at last follow-up were recorded. Excellent response to treatment was defined as the absence of any biochemical or structural evidence of MTC. Calcitonin levels within the assay reference range were considered normal. Persistent/recurrent disease was defined in the presence of calcitonin level above the upper normal limit of the assay and/or detection of structural findings compatible with loco-regional or distant metastatic lesions. For patients who died during the follow-up period, the cause and date of death and any association with MTC were recorded.

Statistical analysis

Categorical variables are presented as numbers and percentages, and continuous variables are expressed as mean $\pm$ S.D. or median. Categorical comparisons were performed with χ^2 test, and continuous variables were compared using Student *t* test or one-way ANOVA, as appropriate. Fisher's exact test was used to test the correlations between categorical variables when low frequencies did not allow using the χ^2 test. Cramer's V-test was procured to measure the association between two nominal variables. The Kaplan–Meier method was used for univariate survival analyses, and the log-rank test was used to determine whether differences in survival were statistically significant. Cox regression was used for multivariate survival analysis, with bootstrapping estimation when the numeric estimation failed. Logistic regression was used to model binary outcomes. All analyses were performed using IBM SPSS Statistics for Windows v24.0.1 (IBM Corp.). A *P* value of <0.05 was considered statistically significant.

Results

Patient demographics and clinical characteristics

The cohort included 193 patients with MTC diagnosed from 1963 through 2016, of whom 35 (18.1%) had familial

type. Documented germline RET mutation analysis results were available for 94/193 subjects: 68.6% (24/35) of familial MTC and 44.3% (70/158) of sporadic MTC. Mean age at diagnosis was 48.9 ± 18.6 years (25.5 ± 11 familial vs. 54.4 ± 15 sporadic, $P < 0.001$). Male patients constituted 44.7% of the entire cohort. Baseline demographic and pathologic features of the cohort, stratified to sporadic vs familial MTC, are presented in Table 1.

Total thyroidectomy was performed in 166/183 (90.7%) patients, hemithyroidectomy in 12/183 (6.6%) and lymph node dissection in 126/161 (77.8%). Additional treatment was given to 71/181 (39.2%) including reoperation in 35/71 (49.3%) patients, radiotherapy in 26/71 (36.6%), chemotherapy in 8/71 (11/3%), tyrosine kinase inhibitors (TKIs) in 16/71 (22.5%), liver-targeted therapy in 7/71 (9.9%) patients, somatostatin analogs in 16/71 (22.5%) patients and peptide-related radiotherapy (PRRT) in 2/71 (2.8%). The extent of surgical intervention and the use of additional treatment were similar between the familial and sporadic groups (Table 1).

Short-term disease outcome

The short- and long-term disease outcomes for the total cohort and stratified into sporadic vs familial MTC are shown in Table 2.

One year after diagnosis, 43.9% (68/157) patients were disease-free (excellent response to treatment) while 56.1% (88/157) had biochemical and/or structural persistent disease; with no differences between familial

and sporadic disease, although structural incomplete response was more prevalent in familial cases and biochemical incomplete response was more prevalent in the sporadic group. On univariate analysis, male gender, tumor size ≥ 1 cm, ETE, multifocality, LNM and DM were significantly associated with disease persistence at 1 year. Following logistic regression analysis, only ETE, LNM and DM remained independent predictors of persistent disease with HR of 5.2 for ETE and 11.3 for LNM (Table 3).

Long-term disease outcome

At last follow-up, only 67/169 (39.6%) patients were disease-free, with 102/169 (60.4%) having some evidence of persistent/recurrent disease. Persistence was more prevalent in the familial group (58.7% in sporadic MTC vs 67.7% in familial MTC, $P = 0.06$; Fig. 2, panel A).

Variables associated with persistence at last visit were age > 45 years, familial type, female gender, ETE, LNM and DM. After multivariate logistic regression, only ETE and DM remained independent predictors of persistence, with hazard ratios of 1.89 ($P = 0.049$) and 2.38 ($P = 0.006$), respectively (Table 4).

Correlation between 1 year and last visit status

A high correlation (Cramer's V measure of association 0.884, $P < 0.001$) was found between 1-year status and last follow-up status (Fig. 1). During follow-up, only nine patients changed status. While 1 of 88 (1.13%) patients with persistent disease at 1 year restaged to cure, while 8 of

Table 1 Clinico-pathological characteristics of patients with medullary thyroid carcinoma.

Characteristics	Total	Sporadic	Familial	P value
n (%)	193	158 (82)	35 (18)	–
Age at diagnosis, mean $\pm$ s.d., years	48.9 ± 18.7	54.4 ± 15.2	25.5 ± 11.2	< 0.001
Male gender, n (%)	87/193 (44.7)	73/158 (46.2)	14/35 (40)	NS
Tumor size, mm, mean $\pm$ s.d.	24.9 ± 18	26.4 ± 18.3	17.9 ± 14.7	0.028
Extra-thyroidal extension, n (%)	50/145 (34.5)	46/123 (37.4)	4/22 (18.2)	NS
Multifocal tumor, n (%)	57/148 (38.5)	35/121 (28.9)	22/27 (81.5)	< 0.001
Bilateral tumor, n (%)	42/153 (27.5)	20/126 (15.9)	22/27 (81.5)	< 0.001
Lymph node metastases, n (%)	91/134 (67.9)	75/113 (66.4)	16/21 (76.2)	NS
Distant metastases, n (%)	34/162 (21)	29/137 (21.2)	5/25 (20)	NS
Stage 1–2	58/161 (36.0)	45/133 (33.8)	13/28 (46.4)	NS
Stage 3–4	103/161 (64)	88/133 (66.2)	15/28 (53.6)	NS
No operation	5/183 (2.7)	4/151 (2.6)	1/32 (3.1)	NS
Hemi-thyroidectomy	12/183 (6.6)	11/151 (7.3)	1/32 (3.1)	NS
Total thyroidectomy	166/183 (90.7)	136/151 (90.1)	30/32 (93.8)	NS
Lymph node dissection	126/161 (77.8)	106/135 (78.5)	20/27 (74.1)	NS
Radiotherapy	33/166 (19.9)	28/135 (20.7)	5/31 (16.1)	NS
Follow-up, years, mean $\pm$ s.d.	10.1 ± 9.4	8.5 ± 8.1	16.9 ± 11.6	< 0.001
Follow-up, years, median (range)	7.0 (0–42)	6.0 (0–42)	19 (0–43)	–

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Table 2 Short- and long-term disease outcomes of 193 patients with medullary thyroid carcinoma.

Outcomes	Total	Sporadic	Familial	P value
n (%)	193	158 (82)	35 (18)	–
Disease outcome at 1 year, n (%)				NS ^a
Excellent response at 1 year	68/157 (43.9)	59/129 (45.7)	10/28 (35.7)	
Persistent/recurrence at 1 year	88/157 (56.1)	70/129 (54.3)	18/28 (64.3)	
Evidence of disease				0.009
Biochemical	31/79 (39.2)	30/66 (45.5)	1/13 (7.7)	
Structural	48/79 (60.8)	36/66 (54.5)	12/13 (92.3)	
Disease outcome at last visit, n (%)				0.006 ^b
Excellent response at last visit	67/169 (39.6)	57/138 (41.3)	10/31 (32.2)	
Persistent/recurrence at last visit	102/169 (60.4)	81/138 (58.7)	21/31 (67.7)	
Evidence of disease				NS
Biochemical	24/98 (24.5)	18/80 (22.5)	6/18 (33.3)	
Structural	74/98 (75.5)	62/80 (77.5)	12/18 (66.7)	
Mortality, n (%)				
All-cause mortality	55/190 (28.9)	46/155 (29.7)	9/35 (25.7)	0.023 ^b
Disease-related mortality	24/177 (13.6)	19/142 (13.4)	5/35 (14.3)	NS ^b

^a χ^2 test; ^bKaplan–Meier survival analysis.

67 (11.9%) who were considered cured at 1 year restaged to recurrence/persistence disease at last visit. The change in disease status was observed in 1/18 (5.5%) and 8/129 (6.2%) of familial and sporadic cases, respectively. The

close correlation between 1-year status and last follow-up status was maintained in the sub-group analyses of both sporadic and familial MTC (0.873, $P < 0.001$ and 0.915, $P < 0.001$, respectively).

Table 3 Logistic regression analysis testing for variables associated with disease persistence 1 year after diagnosis in 193 patients with medullary thyroid carcinoma.

Variable	n (%)	Univariate OR (95% CI)	P value	Multivariate OR (95%CI)	P value
Age at diagnosis*		–	NS	–	–
≤45	37/59 (62.7)				
>45	47/93 (50.5)				
Disease form		–	NS	–	–
Familial	18/28 (64.3)				
Sporadic	70/129 (54.3)				
Gender			0.004	–	NS
Female	39/87 (45.3)	1			
Male	49/71 (69.0)	2.68 (1.39–5.18)			
Tumor size (cm)*			0.032	–	NS
<1	8/26 (30.8)	1			
≥1	58/106 (4.7)	2.72 (1.09–6.8)			
Extra-thyroid extension			<0.001		0.020
No	25/84 (29.8)	1		1	
Yes	40/45 (88.9)	18.9 (6.67–53.45)		4.67 (1.12–19.45)	
Multifocal tumor			0.001	–	NS
No	32/80 (40.0)	1			
Yes	35/50 (70.0)	3.50 (1.65–7.43)			
Bilateral tumor			0.014	–	NS
No	44/100 (44)	1			
Yes	24/35 (68.6)	2.78 (1.23–6.28)			
Lymph nodes metastases			<0.001		0.001
No	6/40 (15)	1		1	
Yes	60/78 (84.6)	31.2 (10.76–90.3)		9.53 (2.32–39.14)	
Distant metastases		**		**	
No	50/115 (43.5)		<0.001		0.002
Yes	31/31 (100)				

*Analysis of age at diagnosis and tumor size as continuous variables did not alter the results; **estimated using bootstrapping; accurate estimation of OR was impossible due to 0 counts.

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Table 4 Cox regression analysis for testing variables associated with disease persistence at last follow-up among 193 patients with medullary thyroid carcinoma.

Variable	n (%)	Univariate HR (95% CI)	P value	Multivariate HR (95% CI)	P value
Age at diagnosis (years)*			0.003	–	NS
≤45	48/70 (68.6)	1			
>45	51/94 (54.3)	1.93 (1.24–2.99)			
Disease form			0.001	–	NS
Familial	21/31 (67.7)	1.93 (1.17–3.17)			
Sporadic	81/138 (58.7)	1			
Gender			<0.001	–	NS
Male	52/72 (72.2)	0.42 (0.28–0.63)			
Female	50/97 (51.5)	1			
Tumor size (cm)*			NS	–	–
<1	9/28 (32.1)	–			
≥1	64/108 (9.3)	–			
Extra-thyroid extension			<0.001		0.049
No	31/86 (36.0)	1		1	
Yes	42/46 (91.3)	3.71 (2.32–5.95)		1.89 (1.00–3.58)	
Multifocal tumor			NS	–	–
No	37/84 (44.0)	–			
Yes	39/52 (75.0)	–			
Bilateral tumor			NS	–	–
No	49/102 (48.0)	–			
Yes	28/37 (75.7)	–			
Lymph node metastases			<0.001	–	NS
No	8/40 (20.0)	1			
Yes	71/81 (87.7)	3.21 (1.53–6.73)			
Distant metastases			<0.001		0.006
No	58/120 (48.3)	1		1	
Yes	31/31 (100)	4.20 (2.66–6.64)		2.38 (1.28–4.42)	
1-year status			<0.001	**	**
Persistent	80/81 (98.8)	1			
Cure	8/67 (11.9)	7.38 (3.55–15.33)			

*Analysis of age at diagnosis and tumor size as continuous variables did not alter the results; **1-year status was not included in the logistic regression due to statistical considerations.

Clinico-pathologic predictors of disease-related and overall mortality

During the follow-up period, 28.5% (55/190) patients died. Of these, 13.6% (24/190) were disease-related deaths (Table 2). Data regarding survival of three subjects who left the country were missing. While rates of disease-related mortality (DRM) were similar between familial and sporadic types, rates of overall mortality (OM) were higher in the sporadic group (29.7 vs 25.7%, $P=0.023$) yet. This difference lost significance on multivariate analysis (Table 5). These data are depicted as Kaplan-Meier curves in Fig. 2, panel B.

On logistic regression analysis (Table 5), the clinico-pathologic variables independently associated with DRM were ETE ($P=0.049$) and DM ($P<0.001$). This logistic regression excluded the response to initial treatment due to statistical considerations. Age at diagnosis ($P=0.029$) and DM ($P<0.001$) were independently associated with OM.

Complete remission 1 year after diagnosis (43.9%, 69/157) was associated with 100% disease-specific survival

Figure 1

Kaplan-Meier plot of the association between disease status at 1-year and persistence at last follow-up among 193 medullary thyroid cancer patients.

Table 5 Cox regression analysis testing the association between clinico-pathologic variables, disease-related mortality and all-cause mortality in patients with medullary thyroid carcinoma.

	Disease-related mortality (<i>n</i> = 24/177)			All-cause mortality (<i>n</i> = 55/190)		
	<i>n</i> (%)	Univariate HR (95% CI)	Multivariate HR (95% CI)	<i>n</i> (%)	Univariate HR (95% CI)	Multivariate HR (95% CI)
Age at diagnosis (years)*		NS	–		<i>P</i> = 0.002	<i>P</i> = 0.029
<45	11/72 (15.3)			18/74 (24.3)	1	1
≥45	12/95 (12.6)			32/104 (30.8)	2.73 (1.44–5.18)	2.42 (1.09–5.38)
Gender		NS	–		<i>P</i> = 0.008	NS
Male	12/67 (17.9)			31/84 (36.9)	2.13 (1.21–3.75)	
Female	8/81 (9.9)			24/106 (22.6)	1	
Disease form		NS	–		<i>P</i> = 0.046	NS
Familial	5/35 (14.3)			9/35 (25.7)	1	
Sporadic	19/142 (13.4)			46/155 (29.7)	0.49 (0.24–1.03)	
Tumor size (cm)*		NS	–		NS	–
<1	2/29 (6.9)			7/30 (23.3)		
≥1	15/107 (14.0)			34/117 (29.1)		
Extra-thyroid extension		<i>P</i> = 0.006	<i>P</i> = 0.049		NS	–
No	5/76 (6.6)	1	1	23/95 (24.2)		
Yes	9/44 (20.5)	4.18 (1.5–11.5)	3.26 (1.01–10.58)	16/47 (34.0)		
Multifocal tumor		NS	–		NS	–
No	9/84 (10.7)			22/90 (24.4)		
Yes	9/53 (17.0)			17/56 (30.4)		
Bilateral tumor		NS	–		NS	–
No	9/101 (8.9)			27/109 (24.8)		
Yes	8/39 (20.5)			14/41 (34.1)		
Lymph node metastases		NS	–		NS	–
No	3/37 (8.1)			10/42 (23.8)		
Yes	12/72 (16.7)			28/90 (31.1)		
Distant metastases		<i>P</i> < 0.001	<i>P</i> < 0.001		<i>P</i> < 0.001	<i>P</i> < 0.001
No	6/107 (5.6)	1	1	26/128 (20.3)	1	1
Yes	14/29 (48.3)	15.5 (5.9–40.4)	12.1 (4.07–39.1)	23/34 (67.6)	6.68 (3.7–12.46)	11.53 (5.63–23.6)
1-year status		<i>P</i> = 0.023	**		<i>P</i> = 0.026	NS
Cure	0/59 (0.0)	1		11/69 (15.9)	1	
Persistent	19/70 (27.1)	59.8 (1.8–2015.82)		35/88 (39.8)	2.21 (1.10–4.45)	

*Analysis of age at diagnosis and tumor size as continuous variables did not alter the results; **1-year status was not included in the logistic regression due to statistical considerations.

(Cramer's *V* measure of association 0.38, *P* < 0.001) as shown in Fig. 3 panel A. This close correlation was maintained in sub-group analysis of the sporadic MTC patients (Cramer's *V* measure of association 0.40, *P* < 0.001), but was not statistically significant among familial patients (Cramer's *V* measure of association 0.30, *P* = 0.265).

Predictors of disease outcome in the sporadic MTC group

To control for the large differences in age, tumor size and length of follow-up between familial and sporadic cases, we repeated the univariate and multivariate analyses considering sporadic cases only (*n* = 158). Following logistic regression analysis ETE (OR 8.90, 95% CI 1.69–46.91, *P* = 0.002), LNM (OR 17.21, 95% CI 2.63–112.49, *P* = 0.003) and DM (accurate estimation of OR was impossible) remained independent predictors

of persistent disease 1 year after diagnosis. The factors that were associated with disease persistence at the end of follow-up in multivariate analysis were DM (HR 2.36, 95% CI 1.19–4.71, *P* = 0.014) and 1-year status (due to the very high correlation of 1-year status and last follow-up status accurate estimation of OR was impossible). DM and 1-year status were also associated with DRM and OM in the sporadic MTC group.

Discussion

In the present study, we evaluated combination of clinico-demographic variables and response to initial treatment as predictors of MTC prognosis. This cohort included 193 MTC patients, of whom 35 (18%) were defined as familial. This rate of familial cases is similar to that reported in large series (3, 4, 8, 9, 12, 17, 18, 19, 20). As expected, subjects with familial MTC were diagnosed at younger ages and with smaller tumors. A higher portion of familial

MTC patients presented with multifocal and bilateral disease, probably because of the unique pathophysiology of C-cell hyperplasia preceding MTC development in these patients. The 1-year status and disease-related mortality were similar in the sporadic and familial MTC groups, while a higher OM and a higher rate of persistent/recurrent disease at the last follow-up were detected in the familial MTC. The follow-up period in this cohort was longer than that reported in other studies (3,4, 13, 15, 17, 18) and could have affected our results. Additionally,

the higher all-cause mortality that was observed among the sporadic MTC patients could be due to older age at diagnosis.

For many years, researchers have been trying to define prognostic tools to optimize the treatment of MTC patients. Traditional risk factors include clinico-demographic variables such as age at diagnosis, factors related to disease extension and disease form (sporadic vs hereditary) (2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15). Nevertheless, since the discriminatory ability of these prognostic factors was insufficient, attempts were made to define novel prognostic factors such as a nomogram combining several risk factors (12), alternative TNM scoring (21), tumor molecular profile (22, 23) and dynamic risk stratification (16, 17, 18, 19).

The present study evaluated a combination of clinico-demographic variables and response to initial treatment. Our analyses revealed some classical prognostic factors. ETE, LNM and DM were associated with 1-year persistence, while only DM remained an independent predictor of all long-term outcomes. Separate analysis of 158 sporadic cases revealed similar findings. These results are in accordance with previous studies (3, 4, 5, 7, 8, 9, 10, 11, 20). Moreover, the low DRM rate seen in our cohort (13%) confirms other reports of very favorable, long-term outcomes for most MTC patients.

At variance with previous studies, including the Surveillance Epidemiology and End Results (SEER) study (2, 3, 4, 5, 6), in our cohort younger age at diagnosis was

Figure 2

Kaplan-Meier survival plots on the differences between familial and sporadic medullary thyroid carcinoma at last follow-up. Panel A: disease-free survival. Panel B: overall survival.

Figure 3

Kaplan-Meier plot for the association between disease status at 1-year and disease-specific mortality in 193 patients with medullary thyroid carcinoma.

not significantly associated with disease persistence and DRM. This discordance may be the result of difference in number of familial cases included in each study, ranging from 22 to 43% (2,3). In the SEER study, the proportion of familial MTC was unknown (5,6). Furthermore, some studies included patients with C-cell hyperplasia diagnosed after prophylactic thyroidectomy among RET mutation carriers (4, 9).

In our study, 44% of patients achieved an excellent response 1-year after initial treatment, a rate that fits within the expected 30–55% reported by others. The previously reported risk of structural recurrence for this group was 1–8% (16). In our cohort, 11.9% of patients with excellent response at 1 year had some evidence of disease at follow-up, confirming a very close association between 1-year status and long-term outcomes. On the other hand, among patients who were not cured with initial therapy, 98.8% had biochemical and/or anatomic evidence of MTC at the last follow-up. The association of 1-year persistence and DRM was even stronger. None of the patients who were defined as disease free 1-year after initial therapy died from complications of MTC. This close association was also maintained in sub-group analyses of familial and sporadic disease. These results support dynamic risk assessment for MTC patients that includes response to initial therapy. This approach, which is already accepted for non-medullary differentiated thyroid cancer (24), was suggested for MTC and was shown to improve the prognostic ability of the TNM/AJCC staging system (16, 17, 18, 19, 25).

The current study has several strengths and limitations. The main strength is the relatively large size of the cohort in combination with long follow-up period and detailed clinical data, partially described earlier (26, 27). The cohort includes almost half of the MTC patients diagnosed in Israel during the study period (28), and consequently, reliably represents the clinical characteristics and management of MTC patients in the country. Additionally, patients' clinical and pathological data were comprehensively extracted from the medical records by experienced physicians. Thus, hereditary cases were accurately identified, and disease status and MTC-related mortality were well defined.

Yet, a main limitation of this study was the retrospective nature of data collection and the associated missing information. Although this is a relatively large cohort, the sample size was probably underpowered to detect small, but clinically important differences, especially regarding the smaller group of patients with

familial MTC. Moreover, since the data were collected from tertiary medical centers, a selection bias might exist.

Finally, although post-operative calcitonin levels may improve prognostic accuracy, we decided not to include calcitonin levels in the analysis due to the variety of analytic methods used during the follow-up period and among medical centers. Abnormal calcitonin levels were indirectly considered in the definition of recurrent/persistent disease.

In conclusion, in this large, multicenter MTC cohort, we found an association between several clinical and pathologic variables at presentation and short- and long-term prognosis. Furthermore, disease status 1 year after diagnosis, which reflects the response to initial treatment, was closely correlated with long-term prognosis in both familial and sporadic cases. In the current era of developing novel systemic therapies for advanced MTC, and considering the favorable long-term outcome observed for most cases, our findings might contribute to identifying high-risk patients who could benefit from more intense treatment.

Declaration of interest

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

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