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Influence of Older Age on the Clinical Features and Prognosis of Sporadic Medullary Thyroid Carcinoma

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ABSTRACT

Sporadic medullary thyroid carcinoma (MTC) is a rare cancer with widely varying clinical outcomes, and the influence of age at diagnosis on prognosis remains unclear. We examined 432 patients with sporadic MTC, followed for a median of 7.4 years, and stratified them into two age-based groups: under 65 years (group A, n = 338, 78.2%) and 65 years or older (group B, n = 94, 21.8%). No notable differences in baseline characteristics were observed between the groups, though younger patients had a significantly longer median follow-up. During the study, 41 patients (9.5%) died from the disease, with similar mortality rates in both age groups. Nonetheless, survival analysis revealed that younger patients had a longer overall survival compared to older patients [HR 2.5, 95% CI: 1.27–4.94, $p < 0.01$]. Among those who died, disease severity at diagnosis and treatment strategies were comparable between age groups. These findings suggest that while age at diagnosis does not appear to influence clinical or pathological features of sporadic MTC, younger patients tend to have a longer survival despite similar rates of disease-related mortality.

Keywords: Death rate, Medullary thyroid carcinoma, Distant metastasis, Sporadic, Age

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Introduction

Medullary thyroid carcinoma (MTC) is an uncommon cancer [1] that can arise sporadically or as part of a hereditary syndrome. Its clinical behavior and outcomes are highly variable, influenced by multiple prognostic factors. Female patients [2] and those diagnosed at earlier stages [2, 3] generally show better outcomes, whereas adverse histologic characteristics—such as extra-thyroidal extension, lymph node metastases, and distant spread [4–6]—are associated with a worse prognosis. Similarly, elevated calcitonin (CT) levels [7] and the presence of aggressive RET gene mutations (e.g., M918T) [8] have been linked to unfavorable outcomes.

Although several studies have explored the role of age in MTC prognosis [3, 9, 10], findings remain inconsistent, partly because most analyses included both sporadic and hereditary cases, complicating interpretation.

The objective of this study was to investigate the clinical presentation and outcomes of sporadic MTC in older patients (≥65 years) [11] and to compare their epidemiological, clinical, and pathological characteristics with those of a younger cohort (<65 years).

Results and Discussion

A summary of the epidemiological, clinical, and pathological characteristics of the study cohort is presented in **Table 1**.

Table 1. Epidemiologic, clinical, and pathological characteristics of 432 patients with sporadic medullary thyroid carcinoma (MTC)

Feature	Category	n (%)
Sex	Male	188 (43.5)
	Female	244 (56.5)
Age (years)	Median (IQR)	54 (43–63)
	Range	16–83
Preoperative calcitonin (pg/mL) [a]	≤100	147 (41.1)
	>100	211 (58.9)
Tumor size (cm) [b]	Median (IQR)	1.5 (0.8–2.7)
	Range	0.1–9
Tumor size category	≤1	156 (36.1)
	1.1–4	239 (55.3)
	>4	28 (6.5)
Multifocality	Yes	69 (16)
	No	363 (84)
Minimal extrathyroidal extension (mETE)	Yes	86 (19.9)
	No	346 (80.1)
Histologic pattern [c]	Conventional	157 (59.5)
	Spindle cell	57 (21.6)
	Others [d]	50 (18.9)
T stage	T1a	147 (34)
	T1b	94 (21.8)
	T2	89 (20.6)
	T3	77 (17.8)
	T4	21 (4.9)
	Tx	4 (0.9)
Central compartment lymph node dissection	Yes	378 (87.5)
	No	54 (12.5)
Latero-cervical lymph node dissection	Yes	158 (36.6)
	No	274 (63.4)
N stage	N0	204 (47.2)
	N1a	66 (15.3)
	N1b	36 (8.3)
	N1a + N1b	93 (21.5)
	Nx	33 (7.6)
M stage	M0	22 (5.1)
	M1	48 (11.1)
	Mx	362 (83.8)
Somatic mutation testing [e]	Positive	94 (58.8)
	Negative	66 (41.3)
Somatic mutation type	RET M918T	63 (67)
	Other mutations	31 (33)
Follow-up duration (months)	Median (IQR)	88.5 (50–138.8)
	Range	25–247
Second neck surgery	Yes	48 (11.1)
	No	384 (88.9)
Local treatments [f]	Yes	44 (10.2)
	No	388 (89.8)
Systemic treatments	Yes	59 (13.7)

	No	373 (86.3)
Type of systemic therapy	Chemotherapy	5 (8.5)
	Tyrosine kinase inhibitors (TKI)	47 (79.7)
	Chemotherapy + TKI	5 (8.5)
	Somatostatin analogs	2 (3.4)
Clinical outcome	Excellent response	229 (53)
	Biochemical incomplete response	67 (15.5)
	Local metastatic disease	29 (6.7)
	Distant metastatic disease	107 (24.8)
Surgery site	Pisa	323 (74.8)
	Other centers	109 (25.2)

[a] available in 358/432—82.9%, [b] available in 423/432—97.9%, [c] available in 264/432—61.1%, [d] angiosarcoma, clear cell, follicular, mixed (papillary thyroid cancer/MTC), oncocytic, papillary, small cell, [e] available in 160/432—37%, [f] external beam radiotherapy (ERBT), trans-arterial chemioembolization (TACE), trans-arterial radioembolization (TARE).

Females accounted for the majority of cases (56.5%), and the median age at diagnosis was 54 years. Preoperative calcitonin (CT) values were available for 358 of 432 patients (82.9%), with most patients (58.9%) having levels above 100 pg/mL. In 74 patients, preoperative CT measurements were missing due to either surgery performed outside Pisa without a complete preoperative work-up or because the MTC diagnosis was incidental, identified only postoperatively.

Tumor size ranged between 1.1 and 4 cm in the majority of cases (55.3%), while microcarcinomas (≤1 cm) accounted for 36.1%, and tumors larger than 4 cm represented 6.6% of cases. Tumors were unifocal in 84% of patients, and minimal extrathyroidal extension (mETE) was observed in approximately 20% of cases. Central compartment lymph node dissection was performed in 87.5% of patients, while latero-cervical dissection was carried out in 36.6%. Among the 33 patients (7.6%) in whom lymph nodes were not removed (Nx), most of the remaining had no nodal involvement (N0, 47.2%), whereas 66 patients (15.3%) had central compartment metastases (N1a), 36 (8.3%) had latero-cervical metastases (N1b), and 93 (21.5%) exhibited metastases in both compartments (N1a + N1b).

Histologic subtypes were assessed in 264 patients (61.1%), with conventional MTC being the most common (59.5%), followed by spindle cell variants (21.6%). Somatic mutation analysis was performed in 160 patients (37%), with RET M918T identified as the predominant mutation.

During follow-up, 48 patients (11.1%) underwent a second neck surgery, 44 (10.2%) received local treatments, and 59 (13.7%) were treated with systemic therapy. After a median follow-up of 88.5 months (7.4 years), 229 patients (53%) achieved an excellent response, 67 (15.5%) had a biochemical incomplete response, and 136 (31.5%) developed metastatic disease, of which 29 (21.3%) were local and 107 (78.7%) were distant metastases.

Age-related differences in sporadic MTC patients

To address the study's objective, patients were divided based on age at diagnosis into two groups: group A (<65 years, n = 338, 78.2%) and group B (≥65 years, n = 94, 21.8%) **(Table 2)**.

Table 2. Comparison of analyzed features in group A (<65 yrs) and B (≥65 yrs).

Features		**Group A (<65) (338—78.2%)**	**Group B (≥65) (94—21.8%)**	p
Sex	M	145 (42.9)	43 (45.7)	0.62
	F	193 (57.1)	51 (54.3)	
Age (years)	Median (IQR)	49 (40–57)	70 (67–76)	<0.01
	Min–Max	(16–64)	(65–83)	
Pre-operative calcitonin [a]	≤100 pg/mL	112 (40.4)	35 (43.2)	0.66
	>100 pg/mL	165 (59.6)	46 (56.8)	
Tumor size [b] (cm)	Median (IQR)	1.5 (0.8–2.5)	1.6 (0.8–2.8)	0.7
	Min–Max	0.1–9	0.2–8	

Tumor size category	≤1 cm	121 (36.4)	35 (38.5)	0.81
	1.1–4 cm	190 (57.2)	49 (53.8)	
	>4 cm	21 (6.3)	7 (7.7)	
Multifocality	Yes	53 (15.7)	16 (17)	0.75
	No	285 (84.3	78 (83)	
mETE	Yes	67 (19.8)	19 (20.2)	0.93
	No	271 (80.2)	75 (79.8)	
Histologic pattern [c]	Conventional	117 (57.4)	40 (66.7)	0.2
	Spindle Cell	49 (24)	8 (13.3)	
	Others [d]	38 (18.6)	12 (20)	
T stage	T1a	115 (34)	32 (34)	0.92
	T1b	77 (22.8)	17 (18.1)	
	T2	67 (19.8)	22 (23.4)	
	T3	59 (17.5)	18 (19.1)	
	T4	17 (5)	4 (4.3)	
	Tx	3 (0.9)	1 (1.1)	
Central compartment lymph node dissection	Yes	296 (87.6)	82 (87.2)	0.93
	No	42 (12.4)	12 (12.8)	
Latero-cervical lymph node dissection	Yes	126 (37.3)	32 (34)	0.57
	No	212 (62.7)	62 (66)	
N stage	N0	157 (46.4)	47 (50)	0.91
	N1a	54 (16)	12 (12.8)	
	N1b	28 (8.3)	8 (8.5)	
	N1a + N1b	72 (21.3)	21 (22.3)	
	Nx	27 (8)	6 (6.4)	
M stage	M0	21 (6.2)	1 (1.1)	0.13
	M1	38 (11.2)	10 (10.6)	
	Mx	279 (82.5)	83 (88.3)	
Somatic mutation testing [e]	Positive	81 (60.9)	13 (48.1)	0.22
	Negative	52 (39.1)	14 (51.9)	
Somatic mutation type	RET M918T	56 (69.1)	7 (53.8)	0.28
	Others	25 (30.9)	6 (46.2)	
Follow-up time (months)	Median (IQR)	96 (56–144.3)	61 (38–106)	<0.01
	Min–Max	25–247	25–242	
Second neck surgery	Yes	40 (11.8)	8 (85)	0.36
	No	298 (88.2)	86 (91.5)	
Local treatments [f]	Yes	38 (11.2)	6 (6.4)	0.17
	No	300 (88.8)	88 (93.6)	
Systemic treatments	Yes	47 (13.9)	12 (12.8)	0.78
	No	291 (86.1)	82 (87.2)	
Type of systemic therapy	Chemotherapy	3 (6.4)	2 (16.7)	0.46
	TKI	39 (83)	8 (66.7)	
	Chemotherapy + TKI	4 (8.5)	1 (8.3)	
	Somatostatin analogs	1 (2.1)	1 (8.3)	
Clinical outcome	Excellent Response	175 (51.8)	54 (57.4)	0.51

	Biochemical Incomplete Response	57 (16.9)	10 (10.6)	
	Local Metastatic disease	23 (6.8)	6 (6.4)	
	Distant Metastatic disease	83 (24.6)	24 (25.5)	
Surgery site	Pisa	250 (74)	73 (77.7)	0.47
	No Pisa	88 (26)	21 (22.3)	

[a] available in 358/432—82.9%, [b] available in 423/432—97.9%, [c] available in 264/432—61.1%, [d] angiosarcoma, clear cell, follicular, oncocytic, papillary, small cell, [e] available in 160/432—37%, [f] external beam radiotherapy (ERBT), trans-arterial chemioembolization (TACE), trans-arterial radioembolization (TARE).

As expected, the median age differed markedly between the two groups (49 vs. 70 years, $p < 0.01$), while the proportion of females was similar (57.1% vs. 54.3%, $p = 0.62$). Other clinical characteristics at diagnosis were largely comparable: median tumor size was 1.5 cm in group A versus 1.6 cm in group B ($p = 0.70$), microcarcinomas occurred in 36.4% versus 38.5% of patients ($p = 0.81$), multifocal tumors were present in 15.7% versus 17% ($p = 0.75$), and minimal extrathyroidal extension (mETE) was seen in 19.8% versus 20.2% ($p = 0.93$). The distribution of histologic subtypes of MTC did not differ significantly between groups ($p = 0.2$).
Similarly, TNM staging was comparable across age groups, with no significant differences in T stage ($p = 0.92$), N stage ($p = 0.91$), or M stage ($p = 0.13$). The frequency of central and latero-cervical lymph node dissections was also consistent (87.6% vs. 87.2%, $p = 0.93$; 37.3% vs. 34%, $p = 0.56$), ruling out any bias from surgical intervention on nodal assessment. Furthermore, the occurrence and type of RET somatic mutations were similar in younger and older patients (prevalence $p = 0.22$; mutation type $p = 0.28$), and additional local or systemic therapies were administered at comparable rates.
Despite a significantly shorter median follow-up in older patients (group B: 61 months vs. 96 months in group A, $p < 0.01$), overall clinical outcomes did not differ significantly ($p = 0.16$).

Cancer-related mortality

Among the study population, 41 patients (9.5%) died due to MTC, all within the subset of patients with distant metastases (41/136, 30.1%), with deaths directly linked to disease progression. When stratified by age, 29 of 338 patients (8.6%) in group A and 12 of 94 patients (12.8%) in group B succumbed to the disease, a difference that was not statistically significant ($p = 0.22$). Nevertheless, Kaplan–Meier survival curves **(Figure 1)** indicated a clear survival advantage for younger patients [HR 2.5; 95% CI: 1.27–4.94, $p < 0.01$], with group A demonstrating higher overall survival than group B.

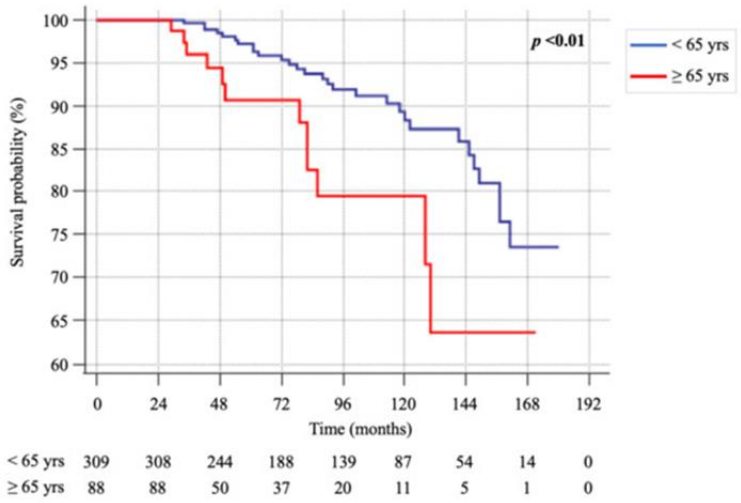

Figure 1. Kaplan–Meier survival curves comparing patients aged <65 years (group A) and ≥65 years (group B).

We further analyzed whether differences in disease severity at presentation contributed to outcomes in the subgroup of patients who died, as summarized in **Table 3**.

Table 3. Comparison of analyzed features in dead patients of group A and B.

Features		Group A Dead 29/338 (8.6%)	Group B Dead 12/94 (12.8%)	p
Sex	Male	21 (72.4)	10 (83.3)	0.46
	Female	8 (27.6)	2 (16.7)	
Age (years)	Median (IQR)	47 (41.5–58.5)	70.5 (67.3–74.3)	<0.01
	Min–Max	(26–64)	(65–79)	
Pre-operative calcitonin [a]	≤100 pg/mL	2 (10)	-	0.28
	>100 pg/mL	18 (90)	11 (100)	
Tumor size [b] (cm)	Median (IQR)	2 (1.2–3.8)	3 (2.2–4.5)	0.17
	Min–Max	0.2–9	0.3–8	
Tumor size category	≤1 cm	5 (17.9)	1 (9.1)	0.69
	1.1–4 cm	18 (64.3)	7 (63.6)	
	>4 cm	5 (17.9)	3 (27.3)	
Multifocality	Yes	8 (27.6)	5 (41.7)	0.38
	No	21 (72.4)	7 (58.3)	
mETE	Yes	15 (51.7)	6 (50)	0.92
	No	14 (48.3)	6 (50)	
Histologic pattern [c]	Conventional	3 (37.5)	3 (75)	0.07
	Spindle Cell	5 (62.5)	-	
	Others [d]	-	1 (25)	
T stage	T1a	4 (13.8)	2 (16.7)	0.36
	T1b	4 (13.8)	-	
	T2	4 (13.8)	3 (25)	
	T3	14 (48.3)	4 (33.3)	
	T4	3 (10.3)	2 (16.7)	
	Tx	-	1 (8.3)	
Central compartment lymph node dissection	Yes	23 (79.3)	10 (83.3)	0.68
	No	6 (20.7)	2 (16.7)	
Latero-cervical lymph node dissection	Yes	24 (82.8)	11(91.7)	0.46
	No	5 (17.2)	1 (8.3)	
N stage	N0	3 (10.3)	1 (8.3)	0.92
	N1a	1 (3.4)	1 (8.3)	
	N1b	11 (37.9)	5 (41.7)	
	N1a + N1b	13 (44.8)	5 (41.7)	
	Nx	1 (3.4)	-	
M stage	M0	3 (10.3)	1 (8.3)	0.97
	M1	15 (51.7)	6 (50)	
	Mx	11 (37.9)	5 (41.7)	
Somatic mutation testing [e]	Positive	21 (87.5)	5 (71.4)	0.31
	Negative	3 (12.5)	2 (28.6)	
Somatic mutation type	RET M918	16 (76.2)	4 (80)	0.86
	Others	5 (23.8)	1 (20)	
Follow-up time (months)	Median (IQR)	84 (53.5–131.5)	61.5 (36–81.8)	0.08
	Min–Max	31–167	28–160	
Second neck surgery	Yes	12 (41.4)	4 (33.3)	0.63
	No	17 (58.6)	8 (66.7)	
Local treatments [f]	Yes	14 (48.3)	6 (50)	0.92
	No	15 (51.7)	6 (50)	

Systemic treatments	Yes	21 (72.4)	9 (75)	0.87
	No	8 (27.6)	3 (25)	
Type of systemic treatment	Chemotherapy	2 (9.5)	1 (11.1)	0.91
	TKI	15 (71.4)	7 (77.8)	
	Chemotherapy + TKI	3 (14.3)	1 (11.1)	
	Somatostatin analogs	1 (4.8)	-	
Surgery site	Pisa	11 (37.9)	7 (58.3)	0.23
	No Pisa	18 (62.1)	5 (41.7)	

[a] available in 31/41—75.6%, [b] available in 39/41—95.1%, [c] available in 12/41—29.3%, [d] angiosarcoma, clear cell, follicular, mixed (papillary thyroid cancer/MTC), oncocytic, papillary, small cell, [e] available in 31/41—75.6%, [f] external beam radiotherapy (ERBT), trans-arterial chemioembolization (TACE), trans-arterial radioembolization (TARE).

No significant differences were observed, indicating that the clinical presentation of the disease had little influence on cancer-related mortality across the two age groups. Additionally, analysis of the interval between surgery and death (≤5 years, 5.1–10 years, 10.1–15 years, and >15 years) revealed no statistically significant variations **(Table 4)**.

Table 4. Death rate in patients of group A and B, divided by 5 years interval of follow-up.

Follow Up Time Interval (Years)		**Group A n° (%)**	**Group B n° (%)**	**p**
≤5	Alive	88 (89.8)	41 (87.2)	0.65
	Dead	10 (10.2)	6 (12.8)	
5.1–10	Alive	112 (90.3)	25 (86.2)	0.51
	Dead	12 (9.7)	4 (13.8)	
10.1–15	Alive	78 (91.8)	9 (81.8)	0.29
	Dead	7 (8.2)	2 (18.2)	
>15	Alive	31 (100)	7 (100)	-
	Dead	-	-	

Additionally, when patients were categorized into age quartiles at diagnosis (≤43, 44–54, 55–63, and ≥64 years), Kaplan–Meier survival analysis still revealed a modestly significant difference between the groups (p = 0.049) **(Figure 2)**, with those aged 64 years and older exhibiting poorer long-term survival.

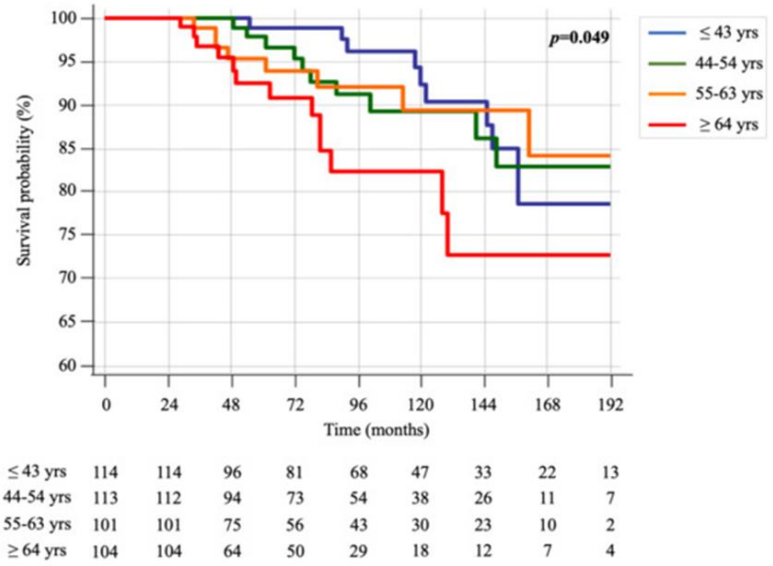

Figure 2. Kaplan–Meier survival curves for patients stratified by age quartiles (≤43, 44–54, 55–63, and ≥64 years).

Medullary thyroid carcinoma (MTC) is an uncommon malignancy, accounting for approximately 1–2% of thyroid cancers in the United States [1]. About 15–20% of MTC cases are hereditary, caused by germline RET mutations [12], while the majority are sporadic, with over half of these harboring somatic RET mutations [13]. MTC's ability to spread through both lymphatic and hematogenous routes places its prognosis between the favorable outcomes of differentiated thyroid cancer (DTC) and the poor prognosis of anaplastic thyroid carcinoma [3, 14]. Numerous epidemiologic and clinicopathologic factors contribute to the variable clinical course of MTC [15, 16].

Age is a well-established prognostic factor in DTC [17] and is incorporated into the AJCC staging system [18], with distinct age thresholds influencing stage and expected outcomes even for patients with similar tumor burden. This paradigm, however, does not apply to MTC [18]. While age is critical in hereditary MTC [19], its role in sporadic MTC—particularly regarding clinical presentation and prognosis—remains unclear.

In our study, no differences were observed in the clinical presentation between younger and older sporadic MTC patients. Similarly, the number and type of subsequent local or systemic treatments did not differ between age groups.

Previous studies have examined age as a factor in MTC outcomes [4, 5, 10]. For example, Sahli *et al*. [10], using the SEER database, analyzed 1,457 hereditary and sporadic MTC patients by age categories: 18–64 years, 65–79 years, and ≥80 years. While they noted less extensive surgery in older patients, consistent with our findings, the prevalence of lymph node or distant metastases did not differ by age.

In contrast, some reports have linked older age with more advanced disease. Kotwal *et al*. [4] found that patients older than 55 years had a higher likelihood of distant metastasis at diagnosis. Hamdy *et al*. [5], in a cohort of 31 MTC patients (hereditary and sporadic), reported that age >40 years increased the risk of distant metastasis twelvefold and was associated with shorter disease-free survival. Twito *et al*. [6] showed that age >45 years was linked to persistent biochemical or structural disease in a cohort of 193 MTC patients (18.1% hereditary) at a median follow-up of 7 years, although in sporadic cases, only distant metastasis at diagnosis correlated with disease persistence.

It is important to highlight that most prior studies included both hereditary and sporadic MTC. Given the distinct pathogenesis—hereditary MTC often develops rapidly, even in childhood [19]—combining these forms may confound the assessment of age as a prognostic factor. To reduce such bias, our study focused exclusively on sporadic cases.

Overall, cancer-related mortality in our cohort was 9.5%, consistent with previous reports [10], and the rate of death did not differ significantly between younger and older patients (8.6% vs. 12.8%, $p = 0.22$). Nevertheless, Kaplan–Meier analysis demonstrated longer survival in younger patients, who also had longer follow-up durations. This pattern was observed both when dividing patients into two age groups (<65 vs. ≥65 years) and when stratifying by age quartiles (≤43, 44–54, 55–63, ≥64 years). At the time of death, all patients, regardless of age, had developed distant metastases and succumbed to disease progression, independent of any local or systemic therapies administered.

Age has been investigated as a potential prognostic factor for mortality in multiple studies encompassing both hereditary and sporadic medullary thyroid carcinoma (MTC). In a multivariate analysis of 899 patients from the French Calcitonin Tumors Study Group (GETC), both age and disease stage emerged as significant predictors of survival [3], a finding that was similarly reported by Kebebew *et al*. [9] in 104 patients with MTC or C-cell hyperplasia. Subsequent studies have reinforced this association; for instance, Kotwal *et al*. [4] identified age >55 years as a strong predictor of poorer overall and disease-specific survival, while Sahli *et al*. [10] demonstrated that older adults and the super-elderly had disease-specific mortality rates 2.9 and 6.7 times higher than younger adults, respectively.

Unlike other studies, we examined RET somatic mutation prevalence and MTC histological variants in two patient subgroups. RET somatic mutations are established poor prognostic indicators for both initial tumor aggressiveness and survival in sporadic MTC [20], and aggressive behavior may also be influenced by histological variants [21]. However, the prevalence of RET mutations and histological variants did not differ between groups A and B.

We observed no differences in disease aggressiveness at presentation among patients who succumbed to MTC, and stratifying follow-up into 5-year intervals revealed no differences in mortality between the two groups. It is well recognized that older cancer patients generally have poorer outcomes due to multiple factors: cancer incidence rises with age [22], older patients often receive less aggressive treatment [23, 24], and comorbidities, which increase with age, are more common in cancer patients than in age-matched individuals without cancer [25, 26], frequently leading to less intensive therapy [27].

Although tumor burden at diagnosis was similar between groups, we hypothesize that older patients may experience a longer pre-clinical disease period, with unclear effects on ultimate outcomes. Furthermore, given the lack of differences in disease aggressiveness at presentation and in treatment modalities among deceased patients, it is plausible that the observed differences in survival may reflect age itself rather than disease characteristics.

Materials and Methods

We conducted a retrospective analysis of epidemiologic, clinical, and pathological data from 530 consecutive sporadic MTC patients surgically treated between 2000 and 2018 and followed at the Endocrine Unit of Pisa University Hospital. Patients with follow-up under 2 years (n = 98) were excluded, resulting in a final cohort of 432 cases. The study was approved by the local Ethics Committee (CEAVNO—Comitato Etico Area Vasta Nord-Ovest; protocol 57877), and all patients provided written informed consent for the use of their data for research purposes.

All patients underwent total thyroidectomy. Central compartment lymph node dissection was routinely performed except in cases incidentally discovered postoperatively, while latero-cervical lymph node dissection was reserved for patients with pre- or intra-operative evidence of metastasis. The majority (323/432; 74.8%) were treated at the Endocrine Surgery Unit of Pisa University Hospital, with histologic specimens from other centers reviewed by specialized endocrine pathologists.

Data collected included sex, age at diagnosis, preoperative basal serum calcitonin levels, TNM stage (AJCC 8th edition), tumor size, presence of minimal extrathyroidal extension (mETE), and multifocality. Additional treatments following primary surgery (e.g., second neck surgery, local or systemic therapy) and clinical outcomes at the last follow-up were recorded. Clinical outcomes were categorized as excellent response (basal and/or stimulated calcitonin below the upper limit of normal without structural disease), biochemical incomplete response (calcitonin above normal without structural disease), and structural incomplete response, further classified into local (cervical lymph node metastases or local recurrence) or distant metastatic disease, regardless of calcitonin values.

CT assays

All patients underwent periodic clinical evaluations following standard good clinical practice, which included serum calcitonin (CT) measurements, neck ultrasound (US), and thyroid hormone assessment to monitor the adequacy of L-T4 replacement therapy. During the study period (2000–2018), two different CT assays were used: from 2000 to 2013, serum CT was measured with an immunoradiometric assay (ELSA-hCT, CIS, Gif-Sur-Yvette, France) with a functional sensitivity of 10 pg/mL, whereas from 2014 onward, a chemiluminescent immunometric assay (Immulite, Siemens Healthcare Diagnostics, UK) was employed, featuring an analytical sensitivity of 2 pg/mL and upper normal limits of 11.5 pg/mL in females and 18.2 pg/mL in males.

To evaluate post-surgical clinical response, CT stimulation tests were performed in selected cases. Until 2013, pentagastrin (Pg; Peptavlon, Nova Laboratories, UK; 0.5 mg/kg i.v.) was used with blood samples collected pre-injection and at 2, 5, 15, and 30 minutes post-injection. From 2014, calcium infusion (2.3 mg/kg of calcium element) replaced pentagastrin, with blood sampling before and at 2, 5, and 10 minutes after infusion.

Histological analysis

MTC exhibits diverse histopathological patterns [21]. Tumors with the classical solid or trabecular architecture were classified as conventional, while less common variants included: (i) spindle cell variant, predominantly composed of spindle-shaped cells arranged in fascicles; (ii) papillary variant, featuring true papillae with fibrovascular cores; (iii) follicular variant, forming follicles resembling follicular tumors containing eosinophilic colloid-like material; (iv) oncocytic variant, with abundant granular eosinophilic cytoplasm; (v) clear cell variant, composed of cells with optically clear cytoplasm; and (vi) angiosarcoma-like pattern, where cells line vascular spaces mimicking angiosarcomas.

Molecular analysis

Sporadic MTC was defined by the absence of germline RET mutations, negative family history, and no laboratory or imaging evidence of other endocrine neoplasia. Germline RET analysis was performed postoperatively on EDTA-collected blood samples (2–5 mL), while somatic RET mutations were investigated in fresh tumor tissue

and archival paraffin-embedded sections. DNA extraction was conducted using QIAamp DNA Mini Kit (QIAGEN) or the Maxwell 16 Instrument (Promega). RET mutations in exons 5, 8, 10, 11, 13, 14, 15, and 16 were analyzed via direct sequencing following established protocols [28], and also by Ion S5 targeted NGS using a custom panel [29].

Neck ultrasound (US)

Neck US was performed using multifrequency 7.5–12 MHz linear transducers (AU 590 Asynchronous and MyLab 50; Esaote, Italy), evaluating all lymph node compartments. Suspicious lesions underwent US-guided fine needle aspiration cytology, with CT measurement in the needle washings. Additional imaging (CT, MRI) was conducted during follow-up as indicated.

Statistical analysis

Categorical variables were reported as counts and percentages, continuous variables as median (IQR). Associations between categorical variables were assessed with chi-square tests, and continuous variables with the Mann-Whitney U test. Age-related effects on survival were analyzed using Cox proportional hazards models; due to violation of the proportional hazards assumption over the full follow-up, survival analysis was restricted to <15 years, comparing patients grouped by age at diagnosis. A p-value <0.05 was considered statistically significant. Analyses were performed using SPSS version 20.0 (IBM, Armonk, NY, USA).

Conclusion

This study showed that older MTC patients (>65 years) presented similarly to younger patients (<65 years) in terms of disease characteristics. While the number of cancer-related deaths was comparable between the groups, older patients exhibited shorter survival times, as demonstrated by Kaplan-Meier analysis.

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