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Survival in medullary thyroid carcinoma patients who fail to achieve a biochemical cure: implications of postoperative 1-month calcitonin levels and targeted therapy

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Abstract

Purpose The survival rate of patients with medullary thyroid carcinoma (MTC) who fail to achieve a biochemical cure after surgery is reduced. This study aimed to investigate the prognostic factors affecting the survival of MTC patients who do not achieve a biochemical cure after surgery.

Methods Cox univariate and multivariate proportional hazard models were used to determine the influence of different variables on overall survival (OS). Pearson's chi-square test was used for categorical variables, and paired t-test was used for continuous variables.

Results In our study of 277 MTC patients treated between 2012 and 2022, there were 96 with raised postoperative 1-month calcitonin (Ct) levels (0–9.52 pg/ml). The overall survival (OS) rates of patients with high postoperative 1-month Ct values at 1, 3, and 5 years were 97.9%, 94.6%, and 86.8%, respectively. The univariate analysis revealed that patients with a postoperative 1-month Ct > 441.9 pg/ml had a greater risk of mortality than patients with postoperative 1-month Ct values ranging from 9.52 to 73.4 pg/ml ($p = 0.043$). Subsequent analyses revealed that receiving targeted therapy did not improve the OS of patients with distant metastasis among those with high postoperative 1-month Ct values ($p = 0.527$).

Conclusion This study confirmed that MTC patients who did not achieve biochemical remission after surgery had an increased risk of death when the Ct level was > 441.9 pg/ml 1 month after surgery. Additionally, for MTC patients who have not achieved biochemical remission and have experienced disease progression or distant metastasis after surgery, the use of targeted therapy does not prolong survival.

Keywords Medullary thyroid carcinoma, Calcitonin, Overall survival, Targeted therapy

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Introduction

Medullary thyroid carcinoma (MTC) is a malignant tumour arising from thyroid parafollicular C cells and accounts for approximately 3-5% of all thyroid malignancies [1, 2]. C cells actively secrete a variety of compounds, including calcitonin (Ct) and carcinoembryonic antigen (CEA) [3, 4]. The serum Ct level serves as the most specific and sensitive marker for the initial diagnosis and postoperative monitoring of MTC [5]. Previous research has established that postsurgery Ct levels within the normal range (less than 10 pg/ml) signify a biochemical cure [6]. Following radical surgery, approximately 40-80% of patients achieve a biochemical cure, with a corresponding 10-year survival rate of 97.7% [7–9]. For those who fail to achieve a biochemical cure after surgery, the 5-year and 10-year survival rates are approximately 80.2% and 70.3%, respectively [9].

Total thyroidectomy is the most effective treatment for achieving a cure in MTC [10]. For patients whose disease progresses after surgery and cannot undergo reoperation or those who experience symptomatic manifestations such as severe diarrhoea, targeted therapy has shown promise in extending progression-free survival and ameliorating symptoms. Nevertheless, patients ultimately face disease progression due to resistance to kinase inhibitors [11, 12]. Consequently, the optimal multimodal treatment approach for MTC patients without a biochemical cure remains debatable. Given the rarity of MTC, current research into the prognosis and treatment of patients who have not achieved a biochemical cure is limited. Therefore, this study aimed to explore the prognosis of patients who did not achieve a biochemical cure after surgery and to assess the impact of targeted therapy on the survival of patients experiencing disease progression.

Patients and methods

Patients

A consecutive cohort study of 277 patients with patients with primary medullary thyroid carcinoma (MTC) patients at the China National Cancer Center (CNCC)/ Cancer Hospital Chinese Academy of Medical Sciences between January 2012 and December 2022 was retrospectively recruited. The following was the inclusion criteria: 1. All patients had pathologically confirmed MTC and received primary surgery;2. The following were the exclusion criteria: (1) Not received R0 surgical resection; (2) No postoperative 1-month Ct levels;3. Lost follow-up. A total of 96 MTC patients with postoperative 1-month Ct exceeding normal levels and 158 MTC patients with normal postoperative 1-month Ct values were ultimately included (Fig. 1). The ethics committee of the CNCC, has approved the study, and written consent was obtained from all patients.

Clinicopathologic characteristics of all patients were recorded and analyzed, including age, sex, preoperative diarrhea condition, thyroid surgery method, central/ lateral neck dissection, T stage, N Stage, M stage and received targeted therapy. TNM stage were assessed for diagnosis using the AJCC 8th edition criteria for MTC

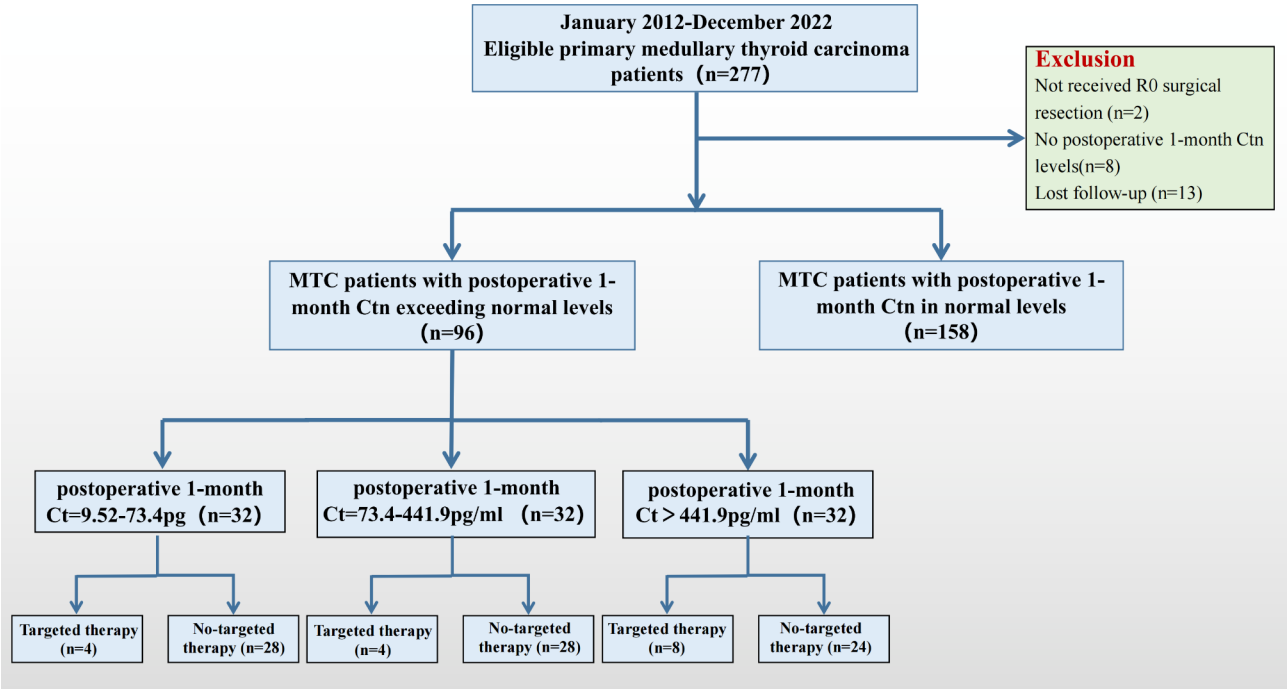

Fig. 1 Flow diagram of the present study

classification. Histopathological slides for each case were reviewed by two pathologists from our institution. All thyroid function tests were performed in the same laboratory at our hospital: serum calcitonin (Ct) (reference: 0-9.52 pg/ml).

Outcomes and follow-up

The primary outcome was progression-free-survival (PFS) and overall survival (OS). PFS defined as the period from primary surgery to the date of locoregional recurrence or distant metastasis disease during the follow-up time. Locoregional recurrence includes local recurrence and regional recurrence, which confirmed by imaging examination and puncture pathology or after surgery. Local recurrence implies recurrence in the thyroid bed, and nodal recurrence should be considered regional recurrence. Distant metastasis was verified by nuclear bone scan, MRI, or CT. OS defined as the period from the date of surgery to the date of death or the end of follow-up. Follow-up was performed according to National Comprehensive Cancer Network recommended schemes and included postoperative outpatient or telephone interviews. The last follow-up date was the date of death or March 29, 2024, whichever came first.

Statistical analysis

To investigate the impact of various variables on OS, we utilized Kaplan–Meier analyses, Cox univariate and multivariate proportional hazard models. The Cox regression analysis was employed to generate hazard ratios and their associated 95% confidence intervals (95% CIs). Using the Pearson's chi-square test for categorical variables and the paired t-test for continuous variables. The significance level was set at $P<0.05$. All statistical tests were two-sided in all results, and P values <0.05 were considered statistically significant.

Results

Patient characteristics

A total of 96 MTC patients with postoperative 1-month Ct values exceeding normal levels and 158 MTC patients with normal postoperative 1-month Ct values were enrolled. The clinicopathologic features of the patients are summarized in Table 1. The median ages of the two groups were 49±13.3 years and 48.5±13.0 years, respectively. In the group of patients with high postoperative 1-month Ct levels, the proportion of male patients was 61.5%, which was greater than that in the group with normal Ct levels ($P=0.006$). The median preoperative Ct level was 2893±10056.74 pg/ml in the high postoperative 1-month Ct group, which was greater than that in the postoperative 1-month normal Ct group ($P=0.000$). There were differences in surgical methods between the two groups. In the high postoperative 1-month Ct group, 92 (95.8%) patients underwent total thyroidectomy; central neck dissection was performed unilaterally in 31 (32.3%) patients and bilaterally in 63 (65.6%) patients; and lateral neck dissection was performed unilaterally in 38 (39.5%) patients and bilaterally in 44 (45.8%) patients. In terms of TNM stage, the proportions of patients in the T3-T4 and N1b stages and stage IV were greater in the high postoperative 1-month Ct group ($P=0.000$). In the high postoperative 1-month Ct group, the percentages of positive lymph nodes in patients with 11 to 20 lymph nodes and >20 lymph nodes were 32.3% and 38.5%, respectively, which were greater than those in the normal Ct group ($P=0.000$). Furthermore, 55 (57.3%) patients in the high postoperative 1-month Ct group had multifocal disease ($P=0.000$). In the high postoperative 1-month Ct group, a total of 16 (16.7%) patients received TKI-targeted therapy, 13 of whom received anlotinib. One patient who progressed after sorafenib treatment and was switched to anlotinib, 2 patients received vandetanib, and one patient received tafitinib malate. No patients in the normal Ct group received targeted therapy 1 month after surgery. All patients underwent R0 resection, and none of them received postoperative radiotherapy.

In the high postoperative 1-month Ct group, the median follow-up time was 60.0 months. By the end of the follow-up period, 43 (44.8%) patients had disease progression. A total of 21 (21.9%) patients experienced locoregional recurrence, and 22 (22.9%) patients experienced distant metastasis, with distant metastasis primarily in the lung (54.5%), bone (50.0%) and liver (18.2%). The PFS rates at 1, 3, and 5 years were 82.3%, 69.6%, and 60.9%, respectively. A total of 12 (12.5%) patients died, and the OS rates at 1, 3, and 5 years were 97.9%, 94.6%, and 86.8%, respectively.

Comparison among MTC patients with different postoperative 1-month Ct levels

The calcitonin cut-off was chosen so that the number of patients in each calcitonin level group was approximately one-third of the high 1-month Ct level patients studied. The calcitonin levels in Group 1, Group 2, and Group 3 ranged from 9.52 to 73.4 pg/ml, 73.4 to 441.9 pg/ml and >441.9 pg/ml, respectively. The clinicopathological characteristics of the three groups of patients were compared with those of the normal controls via chi-square tests, as indicated in Table 2. There were no significant differences in age or sex among the four groups. The median preoperative Ct levels of Group 2 (Ct=73.4 to 441.9 pg/ml) and Group 3 (Ct>441.9 pg/ml) were greater than those of the normal group. In Group 3 (Ct>441.9 pg/ml), a greater proportion of patients (12.5%) had distant metastasis before surgery ($p<0.001$). The mortality rate of patients in Group 3 (Ct>441.9 pg/ml) was 25.0%,

Table 1 Clinical and Pathologic Characteristics of all MTC patients

Variable	High 1-month postoperative Ct levels *N* = 96	Normal 1-month postoperative Ct levels *N* = 158	P value
Age (years)			
Median ± SD	49 ± 13.3	48.5 ± 13.0	0.943
Sex			
Female	37 (38.5%)	90 (57.0%)	**0.006**
Male	59 (61.5%)	68 (43.0%)	
Preoperative diarrhea			0.159
No	91 (94.8%)	155 (98.1%)	
Yes	5(5.2%)	3(1.9%)	
Preoperative Ct (pg/ml)			**0.000**
Median ± SD	2893 ± 10056.74	284 ± 1428.32	
Thyroid surgery method			**0.010**
Lobectomy	4 (4.2%)	19(12.0%)	
Total thyroidectomy	92 (95.8%)	139 (88.0%)	
Central neck dissection			**0.030**
No	2 (2.1%)	4 (2.5%)	
Unilateral	31(32.3%)	76(48.1%)	
Bilateral	63 (65.6%)	78 (49.4%)	
Lateral neck dissection			**0.000**
No	14 (14.6%)	85 (53.8%)	
Unilateral	38(39.5%)	49(31.0%)	
Bilateral	44 (45.8%)	24 (15.2%)	
T stage			**0.000**
T1	23(24.0%)	112 (70.9%)	
T2	14(14.6%)	21(13.3%)	
T3	40(41.7%)	19(12.0%)	
T4	19(19.8%)	6(3.8%)	
N stage			**0.000**
N0	6 (6.3%)	78 (49.4%)	
N1a	9 (9.4%)	35 (22.2%)	
N1b	81 (84.4%)	45 (28.5%)	
Number of positive nodes			**0.000**
0–10 nodes	28(29.2%)	132(83.5%)	
11–20 nodes	31(32.3%)	12(7.6%)	
> 20 nodes	37(38.5%)	14(8.9%)	
M stage			0.108
M0	91 (94.8%)	156 (98.7%)	
M1	5 (5.2%)	2 (1.3%)	
TNM stage			**0.000**
I	3 (3.1%)	66 (41.8%)	
II	2 (2.1%)	14(8.9%)	
III	11 (11.5%)	29 (18.4%)	
IV	80 (83.3%)	49 (31.0%)	
Multifocality			**0.000**
No	41 (42.7%)	118 (74.7%)	
Yes	55 (57.3%)	40 (25.3%)	
Postoperative 1-month Ct (pg/ml)			
Median ± SD	154 ± 12518.64	1.31 ± 1.95	0.123
Targeted therapy			
No	80 (83.3%)	158 (100.0%)	**0.000**
Yes	16 (16.7%)	0 (0.0%)	

Abbreviations: SD, Standard Deviation; Ct, calcitonin;

Table 2 Clinical and pathologic characteristics of MTC patients with different postoperative 1-month Ct levels

Characteristics	Normal (*N* = 158), n%	Group1 (*N* = 32), n%	Group2 (*N* = 32), n%	Group3 (*N* = 32), n%	*P* value[a]	*P* value[b]	*P* value[c]
Age (years)					0.477	0.824	0.730
median ± SD	48.5 ± 13.0	49.1 ± 12.7	46.7 ± 10.2	46.4 ± 16.6			
Gender					0.053	0.053	0.179
Female	90 (57.0%)	12(37.5%)	12(37.5%)	14(43.8%)			
Male	68 (43.0%)	20(62.5%)	20(62.5%)	18(56.3%)			
Preoperative Ct (pg/ml)					0.315	**0.001**	**0.000**
mean ± SD	284 ± 1428.32	2075.3 ± 1726.6	4928.2 ± 6046.8	11359.3 ± 14871.2			
Thyroid surgery method					0.207	0.207	0.207
lobectomy	19(12.0%)	1(3.1%)	1(3.1%)	1(3.1%)			
Total thyroidectomy	139 (88.0%)	31(96.9%)	31(96.9%)	31(96.9%)			
Central neck dissection					**0.011**	0.343	0.343
No	4 (2.5%)	2(2.96.3%)	0(0.0%)	0(0.0%)			
Unilateral	76(48.1%)	7(21.9%)	12(37.5%)	12(37.5%)			
Bilateral	78 (49.4%)	23(71.9%)	20(62.5%)	20(62.5%)			
Lateral neck dissection					**0.032**	**< 0.001**	**< 0.001**
No	85 (53.8%)	10(31.3%)	4(12.5%)	0(0.0%)			
Unilateral	49(31.0%)	12(37.5%)	13(40.6%)	13(40.6%)			
Bilateral	24 (15.2%)	10(31.3%)	15(46.9%)	19(59.4%)			
T stage					**0.001**	**< 0.001**	**< 0.001**
T1	112 (70.9%)	12 (37.5%)	6 (18.8%)	5(15.6%)			
T2	21(13.3%)	4 (12.5%)	6 (18.8%)	4 (12.5%)			
T3	19(12.0%)	12 (37.5%)	16(50.0%)	12 (37.5%)			
T4	6(3.8%)	4 (12.5%)	4 (12.5%)	11(34.4%)			
N stage					**< 0.001**	**< 0.001**	**< 0.001**
N0	78 (49.4%)	4(12.5%)	2(6.3%)	0(0.0%)			
N1a	35 (22.2%)	6(18.8%)	3(9.4%)	0(0.0%)			
N1b	45 (28.5%)	22(68.8%)	27(84.4%)	32(100.0%)			
Number of positive nodes					**< 0.001**	**< 0.001**	**< 0.001**
0–10 nodes	132(83.5%)	14(43.8%)	9(28.1%)	5(15.6%)			
11–20 nodes	12(7.6%)	13(40.6%)	11(34.4%)	7(21.9%)			
> 20 nodes	14(8.9%)	5(15.6%)	12(37.5%)	20(62.5%)			
M stage					0.427	1.000	**0.008**
M0	156 (98.7%)	31(96.9%)	32(100.0%)	28(87.5%)			
M1	2 (1.3%)	1(3.1%)	0(0.0%)	4(12.5%)			
Multifocal					0.427	**0.007**	**< 0.001**
No	118 (74.7%)	14(43.8%)	16(50.0%)	11(34.4%)			
Yes	40 (25.3%)	18(56.3%)	16(50.0%)	21(65.5%)			
Targeted therapy					**0.001**	**0.001**	**< 0.001**
No	158 (100.0%)	28(87.5%)	28(87.5%)	24(75.0%)			
Yes	0 (0.0%)	4(12.5%)	4(12.5%)	8(25.0%)			
Survival status					1.000	0.376	**< 0.001**
Alive	151(95.6%)	31(96.9%)	29(90.6%)	24(75.0%)			
Death	7(4.4%)	1(3.1%)	3(9.4%)	8(25.0%)			

Abbreviations: SD, Standard Deviation; Ct, calcitonin;

[a] *P* value Normal vs. Group 1(Ct = 9.52-73.4pg/ml)

[b] *P* value Normal vs. Group 2(Ct = 73.4-441.9pg/ml)

[c] *P* value Normal vs. Group 3(Ct > 441.9pg/ml)

which was higher than the 4.4% reported in the normal group ($p<0.001$).

Predictive factors for OS in MTC patients with high postoperative 1-month ct values

The univariate analysis presented in Table 3 revealed that postoperative OS was significantly correlated with M stage ($p=0.016$), postoperative 1-month Ct level ($p=0.036$), and targeted therapy ($p<0.0001$). Specifically, patients with a postoperative 1-month Ct>441.9 pg/ml demonstrated a greater risk of mortality than patients with postoperative 1-month Ct values ranging from 9.52 to 73.4 pg/ml (hazard ratio=8.44, 95% CI: 1.07–66.65, $p=0.043$) (Fig. 2A). Further multivariate analysis revealed that targeted therapy was an independent risk factor for postoperative OS. Patients who underwent targeted therapy faced an increased risk of mortality (hazard ratio=10.98, 95% CI: 2.74–44.00, $p=0.001$) (Fig. 2B).

Effect of targeted therapy on OS

MTC patients with different high postoperative 1-month Ct levels

On the basis of the univariate analysis presented in the supplementary table, there was no significant correlation between targeted therapy and OS in Group 1 or Group 2. However, the results of Group 3 (Ct>441.9 pg/ml)

Table 3 COX univariate and multivariate analysis of OS in MTC patients with high postoperative 1-month Ct levels

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age (years)				
Median ± SD	1.05(1.00-1.10)	0.074	/	/
Gender				
Male	1.38(0.41–4.58)	0.602	/	/
Preoperative Ct levels				
Median ± SD	1.000	0.483	/	/
Thyroid surgery method				
Total thyroidectomy	0.05(0.00-4989.80)	0.603	/	/
Central neck dissection		0.134	/	/
No	Ref	Ref		
Unilateral	0.09 (0.08–1.02)	0.052		
Bilateral	0.28(0.04–2.25)	0.232		
Lateral neck dissection		0.545	/	/
No	Ref	Ref		
Unilateral	1.66(0.19–14.85)	0.651		
Bilateral	2.71(0.33–22.15)	0.353		
T stage		0.858	/	/
T1	Ref	Ref		
T2	56240.82(0.00-1.101E + 147)	0.948		
T3	88953.24(0.00-1.7333E147)	0.946		
T4	133785.74(0.00-2.6084E147)	0.944		
Lymph node status			/	/
Positive(N1a + N1b)	22.16(0.001-890002.33)	0.567		
Number of positive nodes		0.456	/	/
0–10 nodes	Ref	Ref		
11–20 nodes	77215.9(0.00-6.786E + 132)	0.940		
> 20 nodes	178179.2(0.00-1.564E + 133)	0.936		
M stage				
M1	6.91(1.44–33.13)	**0.016**	1.63(0.32–8.21)	0.554
Multifocal				
Yes	1.12(0.37–3.41)	0.846	/	/
Postoperative 1-month Ct levels		**0.036**		0.346
9.52-73.4pg/ml	Ref	Ref	Ref	Ref
73.4-441.9pg/ml	1.98(0.18–21.89)	0.576	2.43(0.22–26.98)	0.469
>441.9pg/ml	8.44(1.07–66.65)	**0.043**	4.40(0.54–36.07)	0.168
Targeted therapy				
Yes	15.58(4.29–56.67)	**< 0.0001**	10.98(2.74-44.00)	**0.001**

Abbreviations: SD, Standard Deviation; Ct, calcitonin; HR, Hazard Ratio; CI, Confidence Interval; Ref, reference;

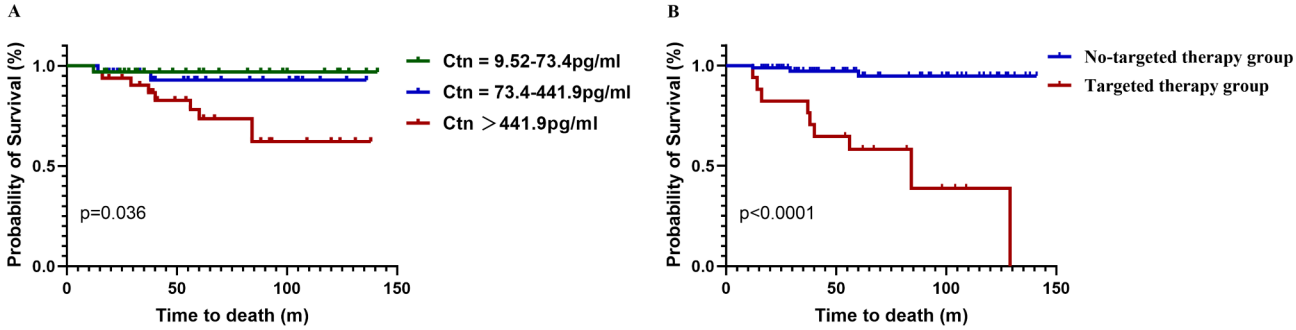

Fig. 2 Comparison of overall survival in MTC patients with high postoperative 1-month Ct levels according to **(A)** postoperative 1-month Ct levels **(B)** targeted therapy

Table 4 MTC patients with postoperative disease progression

Variable	No targeted therapy group (*N*=27)	Targeted therapy group (*N*=16)	*P* value
Age (years)			0.657
Mean ± SD	46.6 ± 17.0	48.8 ± 12.2	
Gender			0.965
Female	12 (44.4%)	7 (43.8%)	
Male	15 (55.6%)	9 (56.2%)	
Preoperative Ct (pg/ml)			0.259
Mean ± SD	5353.4 ± 6558.2	8606.5 ± 11461.1	
T stage			0.828
T1	3 (11.1%)	1 (6.3%)	
T2	4 (14.8%)	1 (6.3%)	
T3	13 (48.1%)	10(62.5%)	
T4	7 (25.9%)	4 (25.0%)	
N stage			
N0	3 (11.1%)	1 (6.3%)	1.000
N1a	1 (3.7%)	0 (0%)	
N1b	23 (85.2%)	15 (93.8%)	
M stage			
M0	26 (96.3%)	13 (81.3%)	0.137
M1	1 (3.7%)	3 (18.8%)	
Multifocal			
No	13 (48.1%)	5 (31.3%)	0.278
Yes	14 (51.9%)	11 (68.8%)	
Postoperative1-month Ct levels			
9.52-73.4pg/ml	8(29.6%)	4 (25.0%)	0.842
73.4-441.9pg/ml	5(18.5%)	4 (25.0%)	
>441.9pg/ml	14 (51.9%)	8 (50.0%)	

Abbreviations: SD, Standard Deviation; Ct, calcitonin;

revealed that patients who underwent targeted therapy faced an increased risk of mortality (hazard ratio=5.02, 95% CI: 1.20–21.17; p=0.028).

MTC patients with postoperative disease progression

In our cohort, 43 (44.8%) patients experienced disease progression after surgery, with 16 patients receiving targeted therapy and 27 patients not receiving targeted therapy. A chi-square analysis was performed to compare the baseline data of the targeted and nontargeted therapy groups, and no variables differed between the groups (P>0.05) (Table 4). Kaplan–Meier analysis revealed that the overall survival of patients in the nontargeted therapy group was notably greater than that of patients in the targeted therapy group (P=0.010) (Fig. 3A).

Effect of targeted therapy on the OS of MTC patients with distant metastasis

In our cohort, 22 patients developed distant metastasis after surgery, with 16 patients receiving targeted therapy and 6 patients not receiving targeted therapy. Kaplan–Meier analyses revealed that there was no significant difference in overall survival (OS) between patients who received targeted therapy and those who did not receive targeted therapy (P=0.527) (Fig. 3B).

Disscusion

A previous study involving 235 MTC patients who underwent surgical treatment revealed that failure to achieve a biochemical cure after initial treatment was an independent predictor of local recurrence, which occurred in approximately 23% of patients during long-term follow-up [13]. Another study by Jung et al. involving 331 MTC patients reported that the structural recurrence rate and disease-related mortality rate in patients who did not achieve biochemical remission (serum Ct levels≥10 pg/ml) after surgery were 15.5% and 21.4%, respectively [14]. In our study, 96 patients with MTC who did not achieve a biochemical cure after R0 surgical resection were included, and the locoregional recurrence and distant metastasis rates were 21.9% and 22.9%, respectively, while the mortality rate was 12.5%.

Previous studies on the effect of postoperative calcitonin on the prognosis of MTC patients are limited. Saltiki et al. focused on MTC patients whose tumour diameter was ≤1.5 cm and reported that postoperative Ct levels were the only significant predictor associated with 10-year disease progression. Specifically, postoperative Ct levels≥14.5 pg/ml associated with disease progression [15]. Clark et al. demonstrated that basal Ct levels

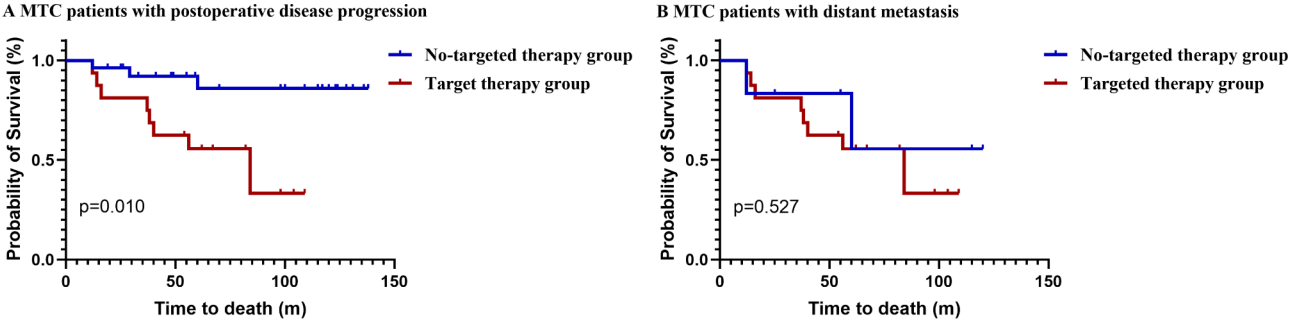

Fig. 3 Kaplan–Meier estimates of the impact of targeted therapy on survival of MTC patients with **(A)** postoperative disease progression **(B)**distant metastasis

exceeding 100 pmol/L after thyroidectomy were associated with reduced disease-free survival in patients [16]. Furthermore, Ho et al. revealed an association between postoperative calcitonin and disease-specific survival in MTC patients. The risk of death in patients with postoperative Ct levels of 1000 pg/ml was notably greater than that in patients with postoperative Ct levels of 10 pg/ml [17]. Grozinsky-Glasberg et al. further confirmed that postoperative serum calcitonin levels were among the main determinants of the survival rate of MTC patients and could serve as a surrogate indicator of tumour burden [18]. However, current research has not yet established a specific unified cut-off value for postoperative Ct levels that can predict the long-term survival of MTC patients. To further explore the role of postoperative Ct levels in predicting the long-term survival of MTC patients with high postoperative 1-month Ct levels, patients were divided into three groups: the Ct=9.52–73.4 pg/ml, Ct=73.4 to 441.9 pg/ml and Ct>441.9 pg/ml groups. Compared with patients in the normal calcitonin group, patients in the Ct>441.9 pg/ml group had the highest average preoperative calcitonin level, the highest proportion of patients with preoperative distant metastasis, the highest proportion of patients who received targeted therapy after surgery, and the highest number of deaths. Univariate analysis of the correlation between different postoperative 1-month Ct levels and OS in MTC patients revealed that patients with Ct levels>441.9 pg/ml had an 8.44-fold greater risk of death than patients with Ct=9.52–73.4 pg/ml. However, further multivariate analysis revealed that the calcitonin level 1 month after surgery had no significant effect on postoperative OS in MTC patients with high postoperative 1-month Ct values. However, when the postoperative 1-month Ct level was greater than 441.9 pg/ml, the risk of death tended to increase.

According to the ATA guidelines, initiating TKI therapy is recommended for patients with imaging evidence of disease progression or patients with symptomatic disease [10]. A number of previous clinical trials have validated that targeted drugs can decelerate disease progression and ameliorate symptoms. A recent meta-analysis encompassing 33 studies, involving 99 patients with metastatic MTC and 16 patients with disease progression, revealed that among patients treated with TKIs, 46.2% exhibited overall stable disease and 22.9% experienced disease progression [19]. A study that enrolled 58 patients with progressive MTC treated with anlotinib reported an objective response rate (ORR) of 56.9%, and a PFS rate at 48 weeks of 85.5% [20]. Another study by Li et al. included 91 patients with unresectable locally advanced or metastatic MTC and indicated that the median PFS in the anlotinib group was significantly longer (20.7 months vs. 11.1 months) [21]. Despite the promising impact of targeted therapies on PFS and symptom management for patients with metastatic MTC, the persistent challenge lies in inevitable disease progression due to drug resistance, rendering metastatic MTC an incurable cancer. Current research on the long-term clinical outcomes of targeted therapies remains limited, with a retrospective study of 78 stage IV MTC patients showing that the use of tyrosine kinase inhibitors (TKIs) did not significantly improve overall survival (OS) [22]. In our study, 43 (44.8%) patients experienced disease progression after surgery, with 16 patients receiving targeted therapy and 27 patients not receiving targeted therapy. Interestingly, a comparison of OS between MTC patients with high postoperative 1-month Ct who received targeted therapy and those who did not revealed that targeted therapy did not yield improved OS in MTC patients with postoperative disease progression. Moreover, an evaluation of the impact of targeted therapy on the survival of MTC patients who did not achieve biochemical remission with distant metastasis further confirmed that targeted therapy failed to extend the overall survival of patients with distant metastasis.

Our study has several limitations that should be acknowledged. First, the retrospective design of the study necessitates the consideration of potential confounding factors that could impact patient prognosis.

This article concludes that targeted therapy does not improve the overall survival of patients; however, it cannot be clearly stated that targeted therapy directly causes patient death. Because many confounding factors, including medication timing, treatment duration, and dosage, can affect the efficacy of targeted therapy. Additionally, the relatively small sample size of the study, attributed to the low incidence of medullary cancer, underscores the need for prospective, multicentre, large-sample clinical trials in the future. These trials are essential for obtaining more reliable and comprehensive data to improve our understanding of the efficacy of targeted therapies in managing metastatic MTC.

Conclusions

In this study, we found that for MTC patients who did not achieve biochemical remission after surgery, the risk of death increased when the postoperative 1-month Ct level was greater than 441.9 pg/ml. Furthermore, our findings indicate that for MTC patients who have not achieved biochemical remission and subsequently experience disease progression or distant metastasis after surgery, the utilization of targeted therapy does not prolong patient survival.

Supplementary Information

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Supplementary Material 1

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Author contributions
YXS study design, data acquisition, data analysis and interpretation, statistical analysis, manuscript preparation, manuscript editing, manuscript review, approval of final manuscript, agrees to be accountable; YQH data acquisition, data analysis, manuscript editing manuscript review, approval of final manuscript, agrees to be accountable; ZRK and BAZP study concept, manuscript editing, manuscript review, approval of final manuscript, agrees to be accountable; HL and YDN data acquisition, data analysis, approval of final manuscript, agrees to be accountable; SYL and SN study concept, study design, manuscript editing, manuscript review, approval of final manuscript, agrees to be accountable.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval
Approval of the research protocol by an Institutional Review Board: The study was approved by the Ethics Committee of the National Cancer Hospital.

Conflict of interests
The authors have stated that they have no conflict of interest.

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