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Research article

Changes of biochemical factors and the effect on recurrence of medullary thyroid carcinoma after surgery

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ABSTRACT

Objective: Medullary thyroid carcinoma (MTC) is a rare malignancy secreting calcitonin (Ctn). We aimed to analyze the relationship between Ctn levels at different time points in patients with MTC, and evaluate its predictive effect on recurrence.

Methods: A retrospective study of patients diagnosed with MTC in a large medical center were conducted in northern China. The interrelationships between preoperative Ctn, normalization of postoperative serum Ctn at the first month (NPS), and long-term biochemical cure as well as their predicting roles on structural recurrence were assessed.

Results: A total of 212 patients were included in this study. The median follow-up time was 59.5 months. The 5- and 10-year cumulative disease-free survival rates were 81.5 % and 66.8 %, respectively. NPS (OR: 216.33, 95 % CI: 28.69–1631.09, $P < 0.001$) and absence of structural recurrence (OR: 61.71, 95 % CI: 3.90–975.31; $P = 0.003$) were associated with biochemical cure. Non-biochemical cure (OR: 28.76; 95 % CI: 2.84–290.86; $P = 0.004$, HR: 14.63, 95 % CI: 2.27–94.07, $P = 0.005$), larger tumor size (OR: 8.79, 95 % CI: 2.12–36.40, $P = 0.003$, HR: 5.41, 95 % CI: 2.04–14.37, $P = 0.001$), and multifocality (OR: 4.02, 95 % CI: 1.06–15.17, $P = 0.040$, HR: 3.00, 95 % CI: 1.18–7.60, $P = 0.021$) were unfavorable independent predictors of structural recurrence and disease-free survival. For sporadic MTC confined to the thyroid lobe, there was no difference in biochemical or structural prognosis between the different surgeries in the subgroup analysis.

Conclusions: NPS, rather than preoperative Ctn, predicted long-term biochemical cure for MTC. Non-biochemical cure, larger tumor burden including larger tumor size and multifocality at initial surgery, served as worse prognostic predictors.

Abbreviations: CI, confidence interval; Ctn, calcitonin; DFS, disease-free survival; HR, hazard ratio; LNR, lymph node metastasis ratio; LLN, lateral lymph node; MTC, medullary thyroid carcinoma; OR, odds ratio; NPS, normalization of postoperative serum Ctn at first month.

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1. Introduction

Medullary thyroid carcinoma (MTC) is a malignancy originating from C cells of the thyroid gland and secreting hormones including calcitonin (Ctn) and carcinoembryonic antigen (CEA) [1]. It displays a more invasive course than differentiated thyroid carcinoma, predisposing to lymph node involvement and distant metastasis.

Ctn, a sensitive and accurate biomarker for MTC, serves as an indicator for preoperative diagnosis and postoperative surveillance of recurrence disease. It has been reported in the literature that stratification of preoperative basal Ctn levels correlated with tumor size, progression of lymph node involvement by region [2], numbers and rates [3], and depended on the disease stage [4]. Moreover, preoperative basal Ctn correlated with postoperative Ctn and the normalization of postoperative Ctn [4,5], and was predictive of biochemical cure [6].

Postoperative Ctn level has been identified as a significant indicator of locoregional recurrence/persistent disease and distant metastases [7], as well as recurrence-free survival [8–10]. The postoperative Ctn was reduced to normalization within 1 week in patients with fewer lymph node metastases and lower preoperative Ctn [11], to undetectable levels by 1 month after initial surgery in 97 % (41/42) of patients [12]. However, short-term Ctn normalization can't guarantee long-term biochemical cure and completely eradicate structural recurrence. Biochemical cure, defined as undetectable level of postoperative Ctn, is the most important factor affecting the prognosis of MTC. Previous study [13] reported that non-biochemical cure correlated with metastatic lymph nodes in the lateral neck. Patients who achieved biochemical remission after initial treatment were associated with a low risk of recurrence (3 %) [14] compared with those who failed to achieve biochemical cure [15]. In the literature, the standard of biochemical cure is not uniform due to the varying sensitivity, specificity, and reference values of different Ctn test kits. That is why the identification of biochemical cure is currently inconsistent [15,16].

Previous studies only focused on the effect of Ctn at a single time point on prognosis, but did not evaluate the relationship between Ctn levels at three different time points and the effect on prognosis. The aim of the present study was to evaluate the relationships between preoperative, the first month after surgery and long-term Ctn levels, as well as the prognostic value on structural recurrence and disease-free survival (DFS).

2. Materials and methods

2.1. Patient selection

Medical records of 212 consecutive series of adult patients diagnosed with MTC between February 2012 and February 2020 and who provided an informed consent were retrospectively analyzed. The inclusion criteria were: 1) initial surgery involving lymphadenectomy performed at our institution; 2) availability of preoperative Ctn data and complete pathological records; and 3) follow-up at our hospital. The Exclusion criteria were: 1) Pediatric patients; 2) those without data on preoperative Ctn; 3) those who did not undergo cervical lymph node dissection. Familial MTC was classified according to familial history, related endocrine tumors of multiple endocrine neoplasia syndromes, and a positive RET germ-line examination. MTC stage was reclassified according to the eighth revision of the American Joint Committee of Cancer TNM classification. Demographic, epidemiological, clinical, and pathological data, as well as preoperative and postoperative Ctn levels were retrieved from electronic medical records. The present study was approved by the Institutional Review Board. Written informed consent was obtained from the patients.

2.2. Surgical treatment and follow-up

All operations were performed by experienced and highly skilled surgeons. Hemithyroidectomy with central node dissection was performed for patients with sporadic MTC, with a solitary lesion measuring <2 cm and confined to the thyroid lobe. Total thyroidectomy with systematic compartment-oriented lymphadenectomy based on the surgical anatomy of the cervical mediastinal lymph node system, was performed for patients with familial MTC and sporadic MTC who presented with extrathyroid invasion and preoperative Ctn were greater than 200 ng/L.

The bilateral neck dissection was performed according to the ultrasound examination of the neck and preoperative Ctn were greater than 500 ng/L. For patients who underwent more than one surgical procedure with curative intent within 6 months, the initial and subsequent operations were viewed as a single sequence. Measurements of preoperative serum Ctn levels were carried out in all patients.

Generally, follow-up is performed early after surgery. Measurement of the postoperative serum Ctn levels was performed at the first month after surgery and repeated every 3–6 months according to the results. Neck ultrasound examination and chest computed tomography were performed every 6–12 months after surgery and repeated at 12–24 months. Emission computed tomography and positron emission tomography-computed tomography were performed when there was evidence of local-regional or distant metastases or when Ctn was persistently elevated. The development of cervical, mediastinum lymph node, and distant organ metastases >6 months after surgery (confirmed by radiological imaging and pathology) denoted recurrence. DFS was calculated from the date of MTC diagnosis to that of structural recurrence or last follow-up. The censoring date for the follow-up data was December 31, 2022.

2.3. Biochemical assays and definitions

Ctn was measured using Immulite 2000® Siemens with a sex dependent reference range (male <2–8.5 ng/L, female <2–5 ng/L) and a detection limits: <2.0 ng/L and >2,000 ng/L. A reduction in serum Ctn levels <5 ng/L for male and <8.5 ng/L for female at the first month after primary and curative surgery denoted normalization. Biochemical cure, was defined as undetectable levels of postoperative Ctn, as postoperative Ctn ≤2 ng/L before structural recurrence or at the last follow-up. Non-biochemical cure was defined as postoperative Ctn >2 ng/L at the last follow-up. Biochemical persistence, was defined as failed to achieve normalization of postoperative serum Ctn at the first month. Ctn normalized at the first month after surgery, then increased and failed to achieve normalization at structural recurrence or at the last follow-up, was biochemical recurrence. The lymph node metastasis ratio (LNR) was defined as the number of involved lymph nodes divided by the total number of dissected lymph nodes.

2.4. Statistical analysis

Data were analyzed using the SPSS software (for Windows, version 22.0; IBM Corp., Armonk, NY, USA). Continuous data were presented as means and standard deviations or median values with ranges. Discrete variables were described with rates (%), and differences between groups were analyzed using the x^2 test and Fisher's exact test. The cut-off values of preoperative Ctn in predicting lateral lymph node (LLN) metastasis and recurrence and LNR in predicting recurrence were determined using a receiver operating characteristic curve (ROC). Multivariate logistic regression models were constructed to analyze the independent factors contributing to preoperative Ctn, normalization of postoperative serum Ctn at the first month (NPS), and biochemical cure. Kaplan–Meier and log-rank tests were used to estimate the overall structural recurrence rate and DFS. Multivariate Cox proportional hazards regression models were utilized to analyze the independent factors contributing to DFS. Two-tailed P values < 0.05 denoted statistically significant differences.

3. Results

3.1. Characteristics of 212 patients with MTC

The study included 116 females and 96 males, with a median age of 52 years (range: 19–70 years). The median follow-up time was 59.5 months (range: 0–127 months). Ten patients were lost to follow-up. There were 198 (93.4 %) and 14 cases (6.6 %) of sporadic and familial MTC according to family history evidence of other manifestations of MEN syndromes, respectively. Bilateral thyroid involvement and multifocality were observed in 37 (17.5 %) and 70 (33.0 %) patients, respectively. Forty patients underwent hemithyroidectomy with central node dissection; 63 patients underwent total thyroidectomy with central node dissection; and 109 patients underwent total thyroidectomy with central and lateral node dissection. According to the eighth revision of the American Joint Committee of Cancer TNM classification, 61, 22, 27, and 102 patients were classified as having stage I, II, III, and IV disease, respectively.

Data on preoperative and postoperative serum Ctn at the first month was available for 212 and 194 patients, respectively. Data of 18 patients were not included because Ctn was measured with a different kit at different hospital. A total of 110 patients (51.9 %) achieved NPS, while six patients were in biochemical persistence. At the last follow-up, biochemical cure was achieved in 116 patients

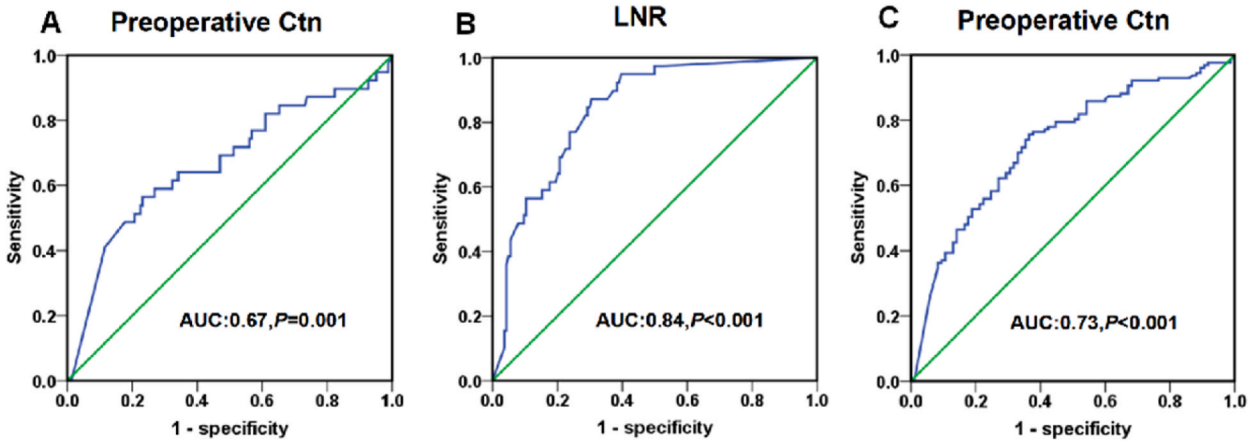

Fig. 1. ROC curve analyses of the optimal cut-off value of preoperative Ctn (**A and C**) for predicting structural recurrence and lateral lymph node (LLN) metastasis and the optimal cut-off value of LNR for predicting structural recurrence (**B**). The optimal cutoff values for preoperative serum Ctn and LNR were 2,000 pg/L and 0.3 according to structural recurrence, respectively. The optimal cutoff value of preoperative serum Ctn was for predicting lateral lymph node (LLN) metastasis was 300 ng/L.
AUC, area under the curve; Ctn, calcitonin; LNR, lymph node metastasis ratio; LLN, lateral lymph node; ROC, receiver operating characteristic.

Table 1
Univariate analyses of clinical, pathological, and biological factors related to preoperative Ctn, normalization of postoperative serum Ctn at the first month (NPS) and biochemical cure. The results demonstrated that multiple factors were related to preoperative Ctn, NPS and biochemical cure, and these three were also correlated.

Characteristic	Preoperative Ctn				NPS				Biochemical cure			
	≤1,600 ng/L (n, %)	>1,600 ng/L (n,%)	x^2	*P* value	Yes (n, %)	No (n, %)	x^2	*P* value	Yes (n, %)	No (n, %)	x^2	*P* value
Sex			3.62	0.057			10.55	0.001			12.29	<0.001
Female	88 (59.5)	29 (45.3)			71 (64.5)	35 (41.2)			76 (65.5)	35 (40.7)		
Male	60 (40.5)	35 (54.7)			39 (35.5)	50 (58.8)			40 (34.5)	51 (59.3)		
Age			0.15	0.698			0.45	0.503			0.00	0.981
≤50 years	93 (62.8)	42 (65.6)			70 (63.6)	58 (68.2)			74 (63.8)	55 (64.0)		
>50 years	55 (37.4)	22 (34.4)			40 (36.14)	27 (31.8)			42 (36.2)	31 (36.0)		
Subtype			–	1.000			–	0.215[a]			2.04	0.153
Sporadic	138 (93.2)	60 (93.8)			106 (96.4)	78 (91.8)			111 (95.7)	78 (90.7)		
Familial	10 (6.8)	4 (6.3)			4 (3.6)	7 (8.2)			5 (4.3)	8 (9.3)		
Multifocality			7.96	0.005			12.70	<0.001			17.69	<0.001
Solitary	108 (73.0)	34 (53.1)			86 (78.2)	46 (54.1)			93 (80.2)	45 (52.3)		
Multiple	40 (27.0)	30 (46.9)			24 (21.8)	39 (45.9)			23 (19.8)	41 (47.7)		
Bilateral tumors			3.63	0.057			9.86	0.002			16.02	<0.001
Unilateral	127 (85.8)	48 (75.0)			100 (90.9)	63 (74.1)			107 (92.2)	61 (70.9)		
Bilateral	21 (14.2)	16 (25.0)			10 (9.1)	22 (25.9)			9 (7.8)	25 (29.1)		
Extrathyroid invasion			10.78	0.001			24.90	<0.001			23.22	<0.001
No	116 (78.4)	36 (56.3)			95 (86.4)	46 (54.1)			99 (85.3)	47 (54.7)		
Yes	32 (21.6)	28 (43.7)			15 (13.6)	39 (45.9)			17 (14.7)	39 (45.3)		
Primary tumor size			62.35	<0.001			15.34	<0.001			19.55	<0.001
≤2 cm	119 (80.4)	15 (23.4)			83 (75.5)	41 (48.2)			89 (76.7)	40 (46.5)		
>2 cm	29 (19.6)	49 (76.6)			27 (24.5)	44 (51.8)			27 (23.3)	46 (53.5)		
T stage			22.87	<0.001			15.11	<0.001			17.52	<0.001
T1/T2	123 (83.1)	33 (51.6)			95 (86.4)	53 (62.4)			99 (85.3)	51 (59.3)		
T3/T4	25 (16.9)	31 (48.4)			15 (13.6)	32 (37.6)			17 (14.7)	35 (40.7)		
N stage			34.18	<0.001			52.56	<0.001			64.77	<0.001
N0	74 (50.0)	10 (15.6)			68 (61.8)	13 (15.3)			71 (61.2)	8 (93)		
N1a	25 (16.9)	5 (7.8)			17 (15.5)	10 (11.8)			18 (15.5)	12 (14.0)		
N1b	49 (33.1)	49 (76.6)			25 (22.7)	62 (72.9)			27 (23.3)	66 (76.7)		
Clinical stage			21.30	<0.001			41.24	<0.001			54.28	<0.001
I/II	73 (49.3)	10 (15.6)			67 (60.9)	13 (15.3)			70 (60.3)	8 (9.3)		
III/IV	75 (50.7)	54 (84.4)			43 (39.1)	72 (84.7)			46 (39.7)	78 (90.7)		
LNR			16.58	<0.001			58.74	<0.001			61.84	<0.001
≤0.3	102 (68.9)	25 (39.1)			92 (83.6)	25 (29.4)			95 (81.9)	23 (26.7)		
>0.3	46 (33.1)	39 (60.9)			18 (16.4)	60 (70.6)			21 (18.1)	63 (73.3)		
Preoperative serum Ctn			–	–			38.80	<0.001			34.91	<0.001
≤1,600 ng/L	–	–			97 (88.2)	40 (47.1)			101 (87.1)	42 (48.8)		
>1,600 ng/L	–	–			13 (11.8)	45 (52.9)			15 (12.9)	44 (51.2)		
NPS			37.77	<0.001							138.19	<0.001
Yes	97 (70.8)	13 (22.8)			–	–			104 (93.7)	6 (7.8)		
No	40 (29.2)	44 (77.2)			–	–			7 (6.3)	71 (92.2)		
Biochemical cure			34.91	<0.001			138.19	<0.001			–	–
Yes	101 (70.6)	15 (25.4)			104 (94.5)	7 (9.0)			–	–		
No	42 (29.4)	44 (74.6)			6 (5.5)	71 (91.0)			–	–		
Structural recurrence			16.72	<0.001			36.52	<0.001			54.07	<0.001
No	126 (88.1)	38 (63.3)			105 (95.5)	47 (60.3)			114 (98.3)	49 (57.0)		
Yes	17 (11.9)	22 (36.7)			5 (4.5)	31 (39.7)			2 (1.7)	37 (43.0)		

Ctn, calcitonin; LNR, lymph node metastasis ratio; NPS, normalization of postoperative serum Ctn at first month.
[a] Fisher's exact test, $^*P < 0.05$.

(54.7 %). Eighty-five patients (40.0 %) developed biochemical persistence, of which 46 patients (54.1 %) were alive in a disease-free state. Structural recurrence developed in 39 patients, the lungs were the most commonly affected distant organ (15/39 patients). Of the patients who did not achieve NPS, 71 failed to achieve biochemical cure and 31 developed structural recurrence. In contrast, in NPS patients, only 15 failed to achieve biochemical cure and 8 developed structural recurrence. For patients without biochemical cure, 37 patients developed structural recurrence, whereas only 2 patients with biochemical cure developed structural recurrence. The optimal cutoff values for preoperative serum Ctn and LNR were determined by ROC analysis according to structural recurrence (Fig. 1A and C, respectively). The optimal cutoff values of preoperative serum Ctn and the LNR were 1,600 (1,603) pg/L (sensitivity: 0.56; specificity: 0.77) and 0.3 (sensitivity: 0.87; specificity: 0.70), respectively. The optimal cutoff value of preoperative serum Ctn for predicting LLN metastasis was 300 ng/L, with a sensitivity of 0.89 and a specificity of 0.63 (Fig. 1B).

3.2. Clinical, pathological, and biological factors related to preoperative Ctn, NPS, and biochemical cure

Patients were grouped according to the preoperative Ctn levels (≤1,600 and > 1,600 ng/L), NPS or non-NPS, and the presence or absence of biochemical cure. In the univariate analysis, multifocality, extrathyroid invasion, primary tumor size >2 cm, T3/T4, N1b, clinical stage III/IV, LNR >0.3, and structural recurrence were significantly related to higher preoperative Ctn (>1,600 ng/L), NPS, and non-biochemical cure ($P < 0.05$). Male sex and bilateral tumors were related to NPS and biochemical cure, but not related to preoperative Ctn levels. In the univariate analysis, preoperative Ctn, NPS, and biochemical cure were correlated. There were no significant differences based on patient age and disease subtype. Table 1 lists the results of the univariate analyses of clinical, pathological, and biological factors related to preoperative Ctn, NPS and biochemical cure.

Multivariate logistic regression analyses were performed to evaluate associations between the selected factors and preoperative Ctn, NPS, and biochemical cure. Primary tumor size >2 cm (odds ratio [OR]: 27.00, 95 % confidence interval [CI]: 8.01–90.91, $P < 0.001$) and multifocality (OR: 3.12, 95 % CI: 1.14–8.58, $P = 0.027$) were independent positively associated with higher preoperative Ctn. The LNR (OR: 12.99, 95 % CI: 2.07–81.49, $P = 0.006$) was an independent factor negatively related to NPS. NPS (OR: 216.33, 95 % CI: 28.69–1631.09, $P < 0.001$) and absence of structural recurrence (OR: 61.71, 95 % CI: 3.90–975.31; $P = 0.003$) were independent factors related to biochemical cure. Table 2 lists the results of the multivariate logistic regression analyses of clinical, pathological, and biological factors related to preoperative Ctn, NPS and biochemical cure. NPS, rather than preoperative Ctn, was independently related to biochemical cure.

3.3. Univariate and multivariate analyses of clinical, pathological, and biological predictors of structural recurrence

Patients were classified according to structural recurrence. In the univariate analysis, male sex, multifocality, bilateral tumors, extrathyroid invasion, primary tumor size >2 cm, T3/T4, N1b, clinical stage III/IV, LNR >0.3, preoperative Ctn level >1,600 ng/L, NPS, and non-biochemical cure were predictors of structural recurrence ($P < 0.05$).

In the multivariate logistic regression analysis, non-biochemical cure was the strongest independent unfavorable predictor of structural recurrence (OR: 28.76; 95 % CI: 2.84–290.86; $P = 0.004$), followed by larger tumor size (OR: 8.79, 95 % CI: 2.12–36.40, $P = 0.003$) and multifocality (OR: 4.02, 95 % CI: 1.06–15.17, $P = 0.040$). Table 3 lists the results of analyses regarding clinical, pathological, and biological predictors of structural recurrence.

Table 2
Multivariate logistic regression analyses of clinical, pathological, and biological factors related to preoperative Ctn, normalization of postoperative serum Ctn at first month (NPS) and biochemical cure.

Characteristic	Preoperative Ctn			NPS			Biochemical cure		
	OR	95 % CI	*P* value	OR	95 % CI	*P* value	OR	95 % CI	*P* value
Male	–	–	–	0.59	0.15–2.36	0.459	5.21	0.97–28.00	0.055
Multifocality	3.12	1.14–8.58	0.027	1.01	0.16–6.46	0.995	0.83	0.11–6.51	0.857
Bilateral tumors	–	–	–	0.87	0.09–8.78	0.907	2.11	0.17–26.43	0.562
Extrathyroid invasion	0.77	0.22–2.65	0.676	2.99	0.47–19.17	0.248	2.14	0.25–18.03	0.484
Primary tumor size >2 cm	27.00	8.01–90.91	0.000	0.43	0.07–2.68	0.369	1.37	0.17–11.30	0.773
T3/T4	0.83	0.22–3.09	0.778	1.21	0.14–10.20	0.863	0.15	0.01–2.37	0.178
N stage			0.230			0.828			0.584
N1a	6.74	0.20–229.39	0.289	0.15	0.00–64.24	0.542	1.21	0.02–69.52	0.926
N1b	15.44	0.47–512.61	0.126	0.18	0.00–67.79	0.574	3.59	0.07–192.54	0.529
III/IV stage	0.23	0.01–5.91	0.378	2.01	0.01–614.98	0.810	1.24	0.03–44.42	0.908
LNR >0.3	0.65	0.17–2.53	0.538	12.99	2.07–81.49	0.006	0.84	0.11–6.16	0.860
Preoperative serum Ctn >1,600 ng/L	–	–	–	3.51	0.55–22.28	0.182	5.90	0.55–63.69	0.144
NPS	3.95	0.65–24.12	0.137	–	–	–	216.33	28.69–1631.09	<0.001
Non-biochemical cure	1.89	0.31–11.58	0.492	158.09	26.25–952.03	<0.001	–	–	–
Structural recurrence	0.34	0.09–1.23	0.099	0.40	0.06–2.74	0.351	61.71	3.90–975.31	0.003

*$P < 0.05$.
CI, confidence interval; Ctn, calcitonin; LNR, lymph node metastasis ratio; NPS, normalization of postoperative serum Ctn at first month; OR, odds ratio.

Table 3
Univariate and multivariate analyses of clinical, pathological, and biological predictors of structural recurrence.

Characteristic	Univariate analysis				Multivariate analysis		
	No (n, %)	Yes (n,%)	x^2	*P* value	OR	95 % CI	*P* value
Sex			3.91	0.048	1.22	0.41–3.64	0.725
Female	96 (58.5)	16 (41.0)					
Male	68 (41.5)	23 (59.0)					
Age			0.13	0.717			
≤50 years	106 (64.6)	24 (61.5)					
>50 years	58 (35.4)	15 (38.5)					
Subtype[a]			–	0.280			
Sporadic MTC	155 (94.5)	35 (89.7)					
Familial MTC	9 (5.5)	4 (10.3)					
Multifocality			13.19	<0.001	4.02	1.06–15.17	0.040
Solitary	121 (73.8)	17 (43.6)					
Multiple	43 (26.2)	22 (56.4)					
Bilateral tumors			8.76	0.003	0.79	0.20–3.11	0.735
Unilateral	142 (86.6)	26 (66.7)					
Bilateral	22 (13.4)	13 (33.3)					
Extrathyroidal invasion			13.57	<0.001	1.42	0.38–5.37	0.603
No	128 (78.0)	19 (48.7)					
Yes	36 (22.0)	20 (51.3)					
Primary tumor size			26.03	<0.001	8.79	2.12–36.40	0.003
≤2 cm	118 (72.0)	11 (28.2)					
>2 cm	46 (28.0)	28 (71.8)					
T stage			15.86	<0.001	0.94	0.21–4.11	0.930
T1/T2	131 (79.9)	19 (48.7)					
T3/T4	33 (20.1)	20 (51.3)					
N stage			30.48	<0.001			
N0	79 (48.2)	1 (2.6)					0.898
N1a	24 (14.6)	6 (15.4)			2.81	0.04–222.67	0.644
N1b	61 (37.2)	32 (82.1)			2.59	0.03–206.56	0.670
Clinical stage			26.84	<0.001	2.12	0.03–132.03	0.722
I/II	78 (47.6)	1 (2.6)					
III/IV	86 (52.4)	38 (97.4)					
LNR			41.75	<0.001	3.17	0.67–14.98	0.145
≤0.3	114 (69.5)	5 (12.8)					
>0.3	50 (30.5)	34 (87.2)					
Preoperative serum Ctn			16.72	<0.001	0.28	0.07–1.10	0.067
≤1,600 ng/L	126 (76.8)	17 (43.6)					
>1,600 ng/L	38 (23.2)	22 (56.4)					
NPS			36.52	<0.001	0.50	0.07–3.35	0.471
Yes	105 (69.1)	5 (13.9)					
No	47 (30.9)	31 (86.1)					
Biochemical cure			54.07	<0.001	28.76	2.84–290.86	0.004
Yes	114 (69.9)	2 (5.1)					
No	49 (30.1)	37 (94.9)					

CI, confidence interval; Ctn, calcitonin; LNR, lymph node metastasis ratio; NPS, normalization of postoperative serum Ctn at first month; OR, odds ratio.

[a] Fisher's exact test,*$P < 0.05$.

3.4. Univariate and multivariate analyses of clinical, pathological, and biological predictors of DFS

The 5- and 10- year DFS rates were 81.5 % and 66.8 %, respectively. The cumulative DFS rates for the 212 patients with MTC were illustrated in a Kaplan–Meier curve (Fig. 2). As shown in Table 4, all the factors that predicted structural recurrence were identified as predictors of DFS in the univariate analysis.

Consistent with the findings of structural recurrence, non-biochemical cure was the strongest independent unfavorable predictor of worse DFS (hazard ratio [HR]: 14.63, 95 % CI: 2.27–94.07, $P = 0.005$), followed by larger tumor size (HR: 5.41, 95 % CI: 2.04–14.37, $P = 0.001$) and multifocality (HR: 3.00, 95 % CI: 1.18–7.60, $P = 0.021$) in the multivariate analysis. The cumulative DFS rates, calculated according to biochemical cure, primary tumor size, and multifocality are presented in Fig. 3A, B and 3C.

3.5. Subgroup analysis of effects of different surgeries for sporadic MTC confined to the thyroid lobe

Although guidelines on MTC recommend the use of thyroidectomy with central neck dissection, adherence to this guidance in clinical practice is poor. In the present study, 40 patients who harbored sporadic MTC measuring <2 cm and confined to the thyroid lobe underwent hemithyroidectomy with central node dissection, while 62 patients underwent total thyroidectomy with central node dissection. The subgroup analysis did not demonstrate statistically significant differences in the preoperative Ctn levels, NPS, and

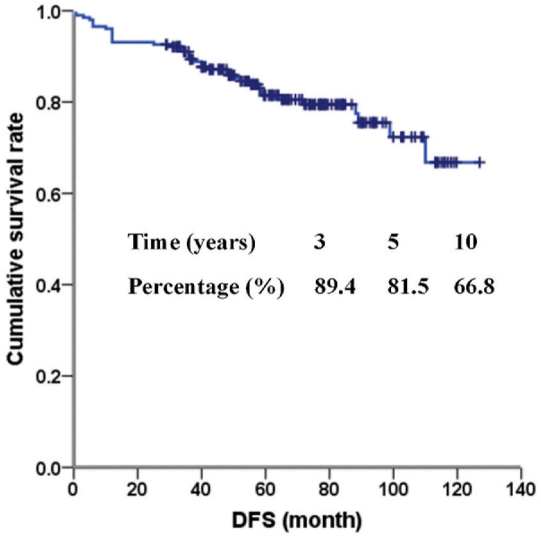

Fig. 2. The cumulative disease-free survival (DFS) rates of 212 patients with medullary thyroid carcinoma (MTC) at 3, 5 and 10 years were 89.4 %, 81.5 % and 66.8 %, respectively.

biochemical cure between the two groups. Furthermore, there was no difference in survival between the different surgery groups. The results are shown in Table 5.

4. Discussion

Preoperative Ctn correlated with tumor burden, LLN metastasis [2,17], failure to achieve biochemical cure [18]. Moreover, preoperative Ctn had prognostic impact on distant recurrence and/or carcinoma-related mortality [19]. It was reported that preoperative serum Ctn levels >309 pg/mL were the strongest independent predictor of recurrence [13]. Consistent with previous studies, preoperative Ctn was related to short-term normalization of serum Ctn, long-term biochemical cure, LLN metastasis and recurrence in present study in univariate analyses. However, in multivariate analyses, preoperative Ctn was not independently associated with NPS, biochemical cure or structural recurrence. These disparities might due to the selection of a more radical surgical strategy based on higher preoperative Ctn levels and the inclusion of surgery-related factors such as LNR in the final analysis, which reduced the impact of preoperative Ctn on biochemical and structural outcomes. Stratification of basal Ctn levels was associated with lymph node metastasis in different compartments [2]. Although no consensus has been attained, ATA guidelines suggest that prophylactic lateral neck dissection may be considered based on serum Ctn levels [1]. We performed ipsilateral neck dissection according to ultrasound and preoperative Ctn greater than 200 ng/L, while bilateral neck dissection was performed when preoperative Ctn was greater than 500 ng/L. The more potentially metastatic lymph nodes removed, the greater the possibility of postoperative Ctn normalization and biochemical cure. LNR reflects lymph node metastasis and the extent of surgery. The large total number of lymph nodes dissected leads to a smaller LNR and easier to achieve NPS. This explained why LNR, rather than preoperative Ctn, was an independent factor for NPS. Loss of the capacity for Ctn production in advanced MTC has been reported [13,20]. In the present study population, three patients had MTC with undetected preoperative Ctn.

Postoperative Ctn has been identified as a significant indicator of disease progression [21,22] and recurrence-free survival [8]. Kim et al. [10] reported that postoperative Ctn is a predictor of DFS. Postoperative normalization of Ctn is associated with an excellent survival rate (97.7 %) at 10 years [23]. The majority of available studies assessed the contribution of Ctn to biochemical cure and survival by examining its levels at 3–6 months after surgery [7,21,24,25]. The short-term normalization of Ctn after primary surgery have been investigated in previous studies. Andrade et al. [12] reported that following curative surgery, serum Ctn levels rapidly decline and became nearly undetectable within 1 month. Ctn levels typically normalized within 1 week and took longer in patients with high Ctn levels and lymph node metastases [11]. However, short-term normalization of Ctn was not strongly linked to biochemical cure and DFS [15]. Elevated postoperative Ctn was significantly associated with worse survival [7,16]. Studies conducted thus far have not examined whether Ctn levels at the first month after surgery can predict biochemical cure or structural recurrence. We demonstrated that of the patients who did not achieve NPS, 71 failed to achieve biochemical cure and 31 developed structural recurrence. In contrast, in NPS patients, only 15 failed to achieve biochemical cure and 8 developed structural recurrence. Univariate analyses exhibited apparent associations between NPS and biochemical cure and structural recurrence. Multivariate analyses showed that NPS was an independent predictor of biochemical cure, and biochemical cure was an independent predictor of recurrence. Therefore, the normalization of Ctn at the first month after surgery is critical for the biochemical and structural prognosis of MTC patients. According to ATA guidelines [1], serum levels of Ctn, should be measured 3 months, and if undetectable or within the normal range, they should be measured every 6 months for 1 year, and then yearly thereafter. When progressive increase in the basal serum

Table 4
Univariate and multivariate analyses of clinical, pathological and biological predictors of DFS.

Characteristic	Univariate Kaplan–Meier analysis			Multivariate Cox proportional hazards regression analysis		
	Mean DFS (months)	x^2	*P* value	HR	95 % CI	*P* value
Sex		4.27	0.039	1.45	0.65–3.21	0.361
Female	104.25 ± 3.48					
Male	98.39 ± 5.18					
Age		0.19	0.665			
≤50 years	100.74 ± 3.45					
>50 years	102.59 ± 5.68					
Subtype		2.66	0.103			
Sporadic MTC	105.73 ± 3.22					
Familial MTC	68.23 ± 9.42					
Multifocality		17.35	<0.001	3.00	1.18–7.60	0.021
Solitary	112.85 ± 3.17					
Multiple	81.33 ± 5.99					
Bilateral tumors		12.28	<0.001	1.01	0.42–2.46	0.971
Unilateral	109.00 ± 3.23					
Bilateral	77.47 ± 8.08					
Extrathyroidal invasion		10.61	<0.001	0.97	0.39–2.45	0.954
No	110.29 ± 3.56					
Yes	85.68 ± 6.09					
Primary tumor size		33.83	<0.001	5.41	2.04–14.37	0.001
≤2 cm	117.05 ± 2.88					
>2 cm	76.97 ± 5.48					
T stage		16.96	<0.001	1.07	0.38–3.00	0.897
T1/T2	111.60 ± 3.31					
T3/T4	78.71 ± 6.35					
N stage		37.16	<0.001			
N0	118.49 ± 1.23					0.815
N1a	99.17 ± 4.74			2.76	0.02–335.25	0.678
N1b	88.43 ± 5.45			3.51	0.03–432.79	0.609
Clinical stage		24.81	<0.001	1.04	0.10–107.64	0.986
I/II	118.46 ± 1.26					
III/IV	92.38 ± 4.55					
LNR		41.79	<0.001	2.09	0.55–8.02	0.282
≤0.3	122.26 ± 2.06					
>0.3	78.80 ± 5.07					
Preoperative serum Ctn		24.77	<0.001	0.66	0.28–1.55	0.337
≤1,600 ng/L	113.08 ± 3.12					
>1,600 ng/L	78.16 ± 6.25					
NPS		35.05	<0.001	0.44	0.12–1.62	0.215
Yes	114.96 ± 2.10					
No	80.30 ± 5.25					
Biochemical cure		52.47	<0.001			
Yes	117.75 ± 1.37					
No	80.40 ± 5.46			14.63	2.27–94.07	0.005

*$P < 0.05$.
CI, confidence interval; Ctn, calcitonin; DFS, disease-free survival; HR, hazard ratios; LNR, lymph node metastasis ratio; NPS, normalization of postoperative serum Ctn at first month.

Ctn level above 150 pg/mL, additional imaging should prompt during follow-up. According to the results of present study, we suggest that the Ctn levels must be measured as early as 1 month after surgery in order to predict the risk of biochemical and structural recurrence and to adjust the frequency of follow-up. Patients who failed to achieve NPS should shorten the time for retesting Ctn and prompt additional imaging regardless of whether Ctn levels are progressively over 150 ng/L, rather than waiting until 3 months later.

The currently available literature has highlighted the importance of biochemical cure. It is noteworthy that the identification of biochemical cure is inconsistent because of variability in Ctn measurements according to assay methods and commercial kits. Biochemical cure, once defined as normalization of postoperative Ctn, is defined as undetectable levels of postoperative Ctn nowadays. In the previous literature, up to 50 % of the patients failed to achieve biochemical cure, as evidenced by the persistent elevation of Ctn, and 10–25 % of the patients developed structural recurrence with MTC [10,17,26]. Lack of biochemical cure and extrathyroidal extension were related to lymph node metastasis in the lateral neck [3]. Failure to achieve postoperative biochemical remission was the strongest predictor of overall recurrence [24] and worse DFS [10]. For patients who achieved biochemical cure, the 5-year biochemical recurrence-free survival rate was 86.5 % [16] and the risk of recurrence was 3 % [14]. These data are consistent with the results of the present study, demonstrating that non-biochemical cure was the strongest independent prognostic indicator of structural recurrence and deteriorated DFS. Approximately 98.3 % of the patients (116/118) who achieved long-term biochemical cure were disease-free, with median follow-up of 59.5 months. Conversely, 44.0 % of the patients (37/84) who did not achieve biochemical cure developed structural recurrence. Therefore, active surveillance of the postoperative Ctn levels is necessary for patients who do not

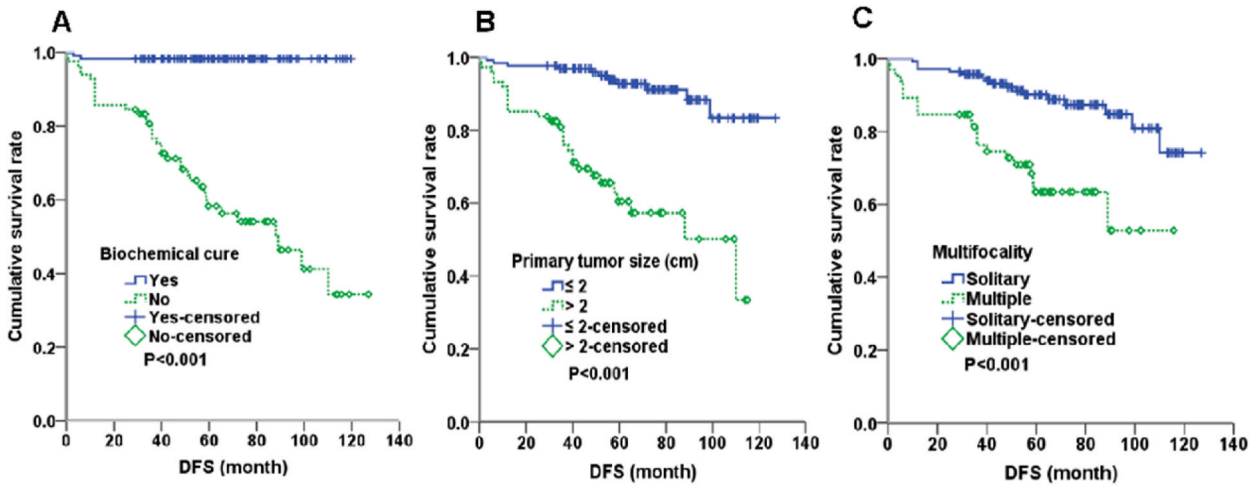

Fig. 3. Kaplan–Meier survival curves of 212 patients with medullary thyroid carcinoma (MTC) with regard to biochemical cure (**A**), primary tumor size (**B**), and multifocality (**C**). Patients with no biochemical cure, primary tumor size >2 cm and multifocality presented worse cumulative disease-free survival (DFS) ($P < 0.05$, log-rank test).

Table 5
Subgroup analysis of the effects of different surgeries on preoperative Ctn, NPS, biochemical cure, structural recurrence and DFS in 103 patients with sporadic MTC confined to the thyroid lobe.

Characteristic	Surgery		x^2	*P* value
	Hemithyroidectomy	Total thyroidectomy		
Preoperative Ctn[a]	(n, %)	(n, %)	–	0.479
≤1,600 ng/L	38 (95.0)	57 (90.5)		
>1,600 ng/L	2 (5.0)	6 (9.5)		
NPS			0.73	0.394
Yes	28 (73.7)	47 (81.0)		
No	10 (26.3)	11 (19.0)		
Biochemical cure			0.76	0.385
Yes	29 (74.4)	49 (81.7)		
No	10 (25.6)	11 (18.3)		
Structural recurrence[a]			–	0.256
No	34 (87.2)	58 (95.1)		
Yes	5 (12.8)	3 (4.9)		
DFS, mean ± SD (months)	109.37 ± 4.26	106.74 ± 2.77	0.28	0.598

Ctn, calcitonin; NPS, normalization of postoperative serum Ctn at first month; DFS, disease-free survival; SD, standard deviation.
[a] Fisher's exact test; *$P < 0.05$.

achieve a long-term biochemical cure.

In addition, we verified other independent predictors of structural prognosis. Larger tumor size has been documented to be associated with LLN involvement [26] and poor clinical outcomes [16,24,27]. Also, an increase in tumor size was linked to increased risk of structural disease recurrence and biochemical relapse after initial cure [16]. Furthermore, tumor size <2 cm was a favorable independent predictor of cancer-specific survival and overall survival [28]. Consistently, larger tumor size (>2 cm) was an independent predictor of structural recurrence and worse DFS in present study. Regarding multifocality, the majority of studies only focused on the largest lesion, thereby underestimating the tumor burden. All lesions can contribute to the progression of metastasis. Machens et al. [29] proved that, when the diameter of the largest primary tumor was the same, multifocality was an independent risk factor of lymph node metastasis. A recent study demonstrated that almost all patients with structural persistent disease harbored multifocal tumors, which was identified as an independent risk factor for the development of structural disease [30]. Multiple lesions increase the tumor burden, which is equivalent to increasing the tumor length and the risk of extrathyroidal extension, and further increasing the risk of lymph node metastasis and distant metastasis. Therefore, along with tumor diameter, multifocality acted as an independent influencing factor of recurrence.

Although total thyroidectomy with central lymph node dissection is considered a standard treatment strategy for MTC patients, according to data from several centers, only 35.5 % of the patients (216/609) underwent subtotal/total thyroidectomy with central neck dissection at the initial surgery in clinical practice [31]. Moreover, only 59 % of the patients with MTC underwent surgery in concordance with the American Thyroid Association guidelines [32]. Despite differences in the extent of the initial operation, the disease-specific survival rates were similar for patients treated with total thyroidectomy with central neck dissection and those who

underwent less extensive initial operations [33]. In patients with a tumor measuring <2 cm and limited in thyroid lobe, no difference in 5-year survival was observed among those who treated with total thyroidectomy and those who were underwent less extensive thyroidectomy [34]. Ito et al. [19] reported that the 15-year disease-specific survival rate was 100 % for patients with sporadic MTC who underwent hemithyroidectomy and none of the patients experienced recurrence in the preserved thyroid lobe. Our previous studies have revealed similar conclusions that patients with unilateral sporadic MTC who underwent total thyroidectomy had little benefit in terms of biochemical and structural prognosis [35–37]. We performed hemithyroidectomy with central node dissection for sporadic MTC patients with a solitary lesion measuring <2 cm and confined to the thyroid lobe. There was no statistically significant difference in biochemical factors between the groups and, importantly, the prognosis did not deteriorate. For highly selected patients, surgical complications and the risk of cardiovascular accidents caused by long-term replacement therapy of levothyroxine tablets after surgery can be avoided. Therefore, the extent of the initial operation should be tailored to individual patients.

In addition to Ctn, there are other biomarkers that play a positive role in follow-up and monitoring for recurrence of MTC. CEA, its value in MTC diagnosis and postoperative surveillance has a widespread acceptance [38]. Machens et al. [39] discovered that elevated preoperative CEA levels were associated with higher number lymph node metastases and high risk of LLN compartment involvement on the side of the primary tumor. It is not useful in the early diagnosis but for evaluating disease progression in patients with clinical evidence of MTC and for monitoring after surgery. Because of the late routine use of CEA testing in MTC and the personal choice of patients for economic reasons, CEA data was available only in 67 patients, that's why it is excluded.

Limitations can't be neglected in retrospective study. Firstly, this was a single-center study. Patients with MTC can survive for long periods of time even with residual, recurrent, or metastatic disease, so multi-center studies with larger sample size and long-term follow-up are warranted to provide substantial prognostic data. Secondly, other prognostic factors, such as postoperative Ctn doubling time and CEA, were not included in the study. However, the correlations between biochemical variables observed in this study remain valid.

5. Conclusions

We conducted a thorough analysis based on a large cohort to evaluate the relationships between Ctn levels at different time points, as well as their effects on prognosis. Normalization of Ctn 1 month after surgery rather than preoperative Ctn was an independent predictor for long-term biochemical cure. Biochemical cure, larger tumor size, and multifocality were identified as significant prognostic indicators of structural recurrence and DFS. We suggest that the Ctn levels must be measured as early as 1 month after surgery instead of 3 months as recommended by ATA guidelines in order to predict the risk of biochemical and structural recurrence and to adjust the frequency of follow-up. The present findings may provide comprehensive insight into the prognostic role of biochemical factors in patients with MTC.

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Ethics statement

This study was reviewed and approved by ethics committee of Tianjin Medical University Cancer Institute and Hospital, with the approval number: bc2022191.

All patients (or their proxies/legal guardians) provided informed consent to participate in the study.

All participants/patients (or their proxies/legal guardians) provided informed consent for the publication of their anonymised case details and images.

Data availability statement

The original data are available upon request.

CRediT authorship contribution statement

Fengli Guo: Writing – original draft, Formal analysis, Data curation. **Lijuan Li:** Writing – original draft, Investigation, Data curation. **Pengfei Gu:** Investigation, Formal analysis, Data curation. **Guoqiang Zhang:** Project administration, Formal analysis. **Xianhui Ruan:** Project administration, Investigation. **Jingzhu Zhao:** Software, Resources. **Xiangqian Zheng:** Validation, Supervision. **Songfeng Wei:** Writing – review & editing, Funding acquisition. **Ming Gao:** Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] S.J. Wells, S.L. Asa, H. Dralle, et al., Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma, Thyroid 25 (6) (2015) 567–610.
[2] A. Machens, H. Dralle, Biomarker-based risk stratification for previously untreated medullary thyroid cancer, J. Clin. Endocrinol. Metab. 95 (6) (2010) 2655–2663.
[3] E.M. Opsahl, L.A. Akslen, E. Schlichting, et al., The role of calcitonin in predicting the extent of surgery in medullary thyroid carcinoma: a nationwide Population-Based study in Norway, Eur. Thyroid J. 8 (3) (2019) 159–166.
[4] S.I. Ismailov, N.R. Piulatova, Postoperative calcitonin study in medullary thyroid carcinoma, Endocr. Relat. Cancer 11 (2) (2004) 357–363.
[5] D.T. Yip, M. Hassan, K. Pazaitou-Panayiotou, et al., Preoperative basal calcitonin and tumor stage correlate with postoperative calcitonin normalization in patients undergoing initial surgical management of medullary thyroid carcinoma, Surgery 150 (6) (2011) 1168–1177.
[6] R. Cohen, J.M. Campos, C. Salaun, et al., Preoperative calcitonin levels are predictive of tumor size and postoperative calcitonin normalization in medullary thyroid carcinoma. Groupe d'Etudes des Tumeurs a Calcitonine (GETC), J. Clin. Endocrinol. Metab. 85 (2) (2000) 919–922.
[7] A. Kotwal, D. Erickson, J.R. Geske, et al., Predicting outcomes in sporadic and hereditary medullary thyroid carcinoma over two decades, Thyroid 31 (4) (2021) 616–626.
[8] J.A. Meijer, S. le Cessie, W.B. van den Hout, et al., Calcitonin and carcinoembryonic antigen doubling times as prognostic factors in medullary thyroid carcinoma: a structured meta-analysis, Clin. Endocrinol. 72 (4) (2010) 534–542.
[9] P. Siironen, J. Hagstrom, H.O. Maenpaa, et al., Lymph node metastases and elevated postoperative calcitonin: predictors of poor survival in medullary thyroid carcinoma, Acta Oncol. 55 (3) (2016) 357–364.
[10] J. Kim, J. Park, H. Park, et al., Metastatic lymph node ratio for predicting recurrence in medullary thyroid cancer, Cancers 13 (22) (2021).
[11] A. Machens, K. Lorenz, H. Dralle, Time to calcitonin normalization after surgery for node-negative and node-positive medullary thyroid cancer, Br. J. Surg. 106 (4) (2019) 412–418.
[12] F. Andrade, G. Rondeau, L. Boucai, et al., Serum calcitonin nadirs to undetectable levels within 1 month of curative surgery in medullary thyroid cancer, Arch Endocrinol Metab 63 (2) (2019) 137–14112.
[13] H. Park, S.Y. Park, J. Park, et al., Prognostic value of preoperative serum calcitonin levels for predicting the recurrence of medullary thyroid carcinoma, Front. Endocrinol. 12 (2021) 749973.
[14] S. Franc, P. Niccoli-Sire, R. Cohen, et al., Complete surgical lymph node resection does not prevent authentic recurrences of medullary thyroid carcinoma, Clin. Endocrinol. 55 (3) (2001) 403–409.
[15] Y.Y. Cho, H.W. Jang, J.Y. Jang, et al., Clinical outcomes of patients with hypercalcitoninemia after initial treatment for medullary thyroid cancer and postoperative serum calcitonin cutoffs for predicting structural recurrence, Head Neck 38 (10) (2016) 1501–1508.
[16] S. Momin, D. Chute, B. Burkey, et al., Prognostic variables affecting primary treatment outcome for medullary thyroid cancer, Endocr. Pract. 23 (9) (2017) 1053–1058.
[17] M.M. Chandeze, S. Noullet, M. Faron, et al., Can we predict the lateral compartment lymph node involvement in RET-Negative patients with medullary thyroid carcinoma? Ann. Surg Oncol. 23 (11) (2016) 3653–3659.
[18] A. Machens, K. Lorenz, H. Dralle, Prediction of biochemical cure in patients with medullary thyroid cancer, Br. J. Surg. 107 (6) (2020) 695–704.
[19] Y. Ito, A. Miyauchi, M. Kihara, et al., Static prognostic factors and appropriate surgical designs for patients with medullary thyroid carcinoma: the second report from a Single-Institution study in Japan, World J. Surg. 42 (12) (2018) 3954–3966.
[20] S.J. Kim, H.J. Yun, S.J. Shin, et al., Serum Calcitonin-Negative medullary thyroid carcinoma: a case series of 19 patients in a single center, Front. Endocrinol. 12 (2021) 747704.
[21] K. Saltiki, G. Rentziou, K. Stamatelopoulos, et al., Small medullary thyroid carcinoma: post-operative calcitonin rather than tumour size predicts disease persistence and progression, Eur. J. Endocrinol. 171 (1) (2014) 117–126.
[22] P. Bumming, H. Ahlman, B. Nilsson, et al., Can the early reduction of tumour markers predict outcome in surgically treated sporadic medullary thyroid carcinoma? Langenbeck's Arch. Surg. 393 (5) (2008) 699–703.
[23] E. Modigliani, R. Cohen, J.M. Campos, et al., Prognostic factors for survival and for biochemical cure in medullary thyroid carcinoma: results in 899 patients, The GETC Study Group. Groupe d'etude des tumeurs a calcitonine, Clin Endocrinol (Oxf) 48 (3) (1998) 265–273.
[24] K.Y. Jung, S.M. Kim, W.S. Yoo, et al., Postoperative biochemical remission of serum calcitonin is the best predictive factor for recurrence-free survival of medullary thyroid cancer: a large-scale retrospective analysis over 30 years, Clin. Endocrinol. 84 (4) (2016) 587–597.
[25] C. Sparano, V. Adornato, M. Puccioni, et al., Early calcitonin levels in medullary thyroid carcinoma: prognostic role in patients without distant metastases at diagnosis, Front. Oncol. 13 (2023) 1120799.
[26] A. Machens, U. Schneyer, H.J. Holzhausen, et al., Prospects of remission in medullary thyroid carcinoma according to basal calcitonin level, J. Clin. Endocrinol. Metab. 90 (4) (2005) 2029–2034.
[27] H.S. Oh, H. Kwon, E. Song, et al., Preoperative clinical and sonographic predictors for lateral cervical lymph node metastases in sporadic medullary thyroid carcinoma, Thyroid 28 (3) (2018) 362–368.
[28] L. Chen, Y. Wang, K. Zhao, et al., Postoperative nomogram for predicting Cancer-Specific and overall survival among patients with medullary thyroid cancer, Int J Endocrinol 2020 (2020) 8888677.
[29] A. Machens, S. Hauptmann, H. Dralle, Increased risk of lymph node metastasis in multifocal hereditary and sporadic medullary thyroid cancer, World J. Surg. 31 (10) (2007) 1960–1965.
[30] L. Chen, W. Sun, K. Qian, et al., High ratio of early postoperative calcitonin to preoperative calcitonin could be a novel indicator of poor prognosis in patients with biochemical incomplete responses in sporadic medullary thyroid cancer, Endocr. Pract. 26 (7) (2020) 738–747.
[31] E.J. Kuo, S. Sho, N. Li, et al., Risk factors associated with reoperation and Disease-Specific mortality in patients with medullary thyroid carcinoma, JAMA Surg 153 (1) (2018) 52.
[32] B. Panigrahi, S.A. Roman, J.A. Sosa, Medullary thyroid cancer: are practice patterns in the United States discordant from American Thyroid Association guidelines? Ann. Surg Oncol. 17 (6) (2010) 1490–1498.
[33] R.W. Randle, C.J. Balentine, G.E. Leverson, et al., Trends in the presentation, treatment, and survival of patients with medullary thyroid cancer over the past 30 years, Surgery 161 (1) (2017) 137–146.
[34] R.W. Randle, M.F. Bates, D.F. Schneider, et al., Survival in patients with medullary thyroid cancer after less than the recommended initial operation, J. Surg. Oncol. 117 (6) (2018) 1211–1216.

[35] J. Zhang, P. Gu, D. Huang, et al., Surgical selection and prognostic analysis in patients with unilateral sporadic medullary thyroid carcinoma, Langenbeck's Arch. Surg. 407 (7) (2022) 3013–3023.
[36] W. Hao, J. Zhao, F. Guo, et al., The survival outcomes of prophylactic lateral neck dissection for medullary thyroid carcinoma, a retrospective cohort study, Clin. Otolaryngol. 48 (5) (2023) 734–739.
[37] G. Fu, X. Li, F. Guo, et al., Partial preservation of the normal thyroid gland based on tumor diameter may be possible in small medullary thyroid carcinoma: a two-center 15-year retrospective study, Front. Oncol. 13 (2023) 1216394.
[38] G. Scerrino, G. Cocorullo, G. Orlando, et al., Predictive factors for lymph node involvement in sporadic medullary thyroid microcarcinoma: a systematic review, Eur. Rev. Med. Pharmacol. Sci. 26 (3) (2022) 1004–1016.
[39] A. Machens, J. Ukkat, S. Hauptmann, et al., Abnormal carcinoembryonic antigen levels and medullary thyroid cancer progression: a multivariate analysis, Arch. Surg. 142 (3) (2007) 289–293, 294.