

CLINICAL SCIENCE

PROGNOSTIC INFLUENCE OF CLINICAL AND PATHOLOGICAL FACTORS IN MEDULLARY THYROID CARCINOMA: A STUDY OF 53 CASES

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OBJECTIVES AND INTRODUCTION: Medullary thyroid carcinoma, a neoplasia of intermediate prognosis and differentiation, does not always respond predictably to known treatments. This study aimed to correlate the clinical progression of surgically treated patients with clinical and pathological data.

METHODS: A total of 53 patients were followed for 75 months (mean average) in tertiary-care hospital. The clinical status of patients at the end of the study period was characterized to determine correlations with a range of disease aspects. A value of $p < 0.05$ was considered statistically significant.

RESULTS: Twenty-two patients (41.5%) were alive and disease-free at the end of the follow-up period; twenty-three patients (43.4%) had persistent disease; and eight patients (15.1%) had recurrent disease. Four patients (7.6%) died from medullary thyroid carcinoma with clinical and/or imaging evidence of neoplasia. The following aspects demonstrated statistically significant correlations with the final medical condition: positive initial cervical examination ($p = 0.002$); neoplastic extensions to the thyroid capsule ($p = 0.004$) and adjacent tissues ($p = 0.034$); cervical lymph node metastases ($p < 0.001$); diameter of neoplasia ($p = 0.018$); TNM (tumor, node and metastasis) Stage ($p = 0.001$) and evidence of distant and/or cervical diseases in the absence of a cure ($p = 0.011$). Through logistic regression, the presence of cervical lymph node metastases was considered an independent variable ($p < 0.001$).

CONCLUSIONS: Clinical and pathological aspects of patients with surgically treated medullary thyroid carcinomas are predictors of disease progression. Specifically, even treated cervical lymph node metastases are significantly correlated with disease progression.

KEYWORDS: Medullary thyroid carcinoma; Thyroid neoplasms; Multiple endocrine neoplasia; Prognosis; Cervical lymph node.

INTRODUCTION

Medullary thyroid carcinoma (MTC) is responsible for 3 to 15% of malignant thyroid tumors.¹⁻⁶ It is derived from C cells, which produce amines and peptides, such as calcitonin (CT). CT is used as a specific diagnostic and prognostic marker for MTC and has been identified in both the tumor specimens and serum of patients with MTC.⁴

Carcinoembryonic antigen (CEA) may also be a useful marker for MTC, but it is less specific and less sensitive than CT.⁷

MTC presents peculiar characteristics in various clinical presentations. Most MTC cases are sporadic. Others are inherited from germline mutations of the RET proto-oncogene and constitute familial presentations of the disease. In the inherited clinical presentation its transmission is autosomal dominant, with high penetrance, variable expressivity, and age dependence.⁸ Patients may be grouped into at least four distinct categories: MTC associated with MEN2A (multiple endocrine neoplasia type 2A); MTC associated with a subtype of MEN2A related to the presence of cutaneous injuries of lichen amyloidosis; MTC associated with MEN2B (MEN type 2B); and the isolated familial MTC, which lacks other related endocrinopathies.^{8,9}

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Advances in our understanding of the genetics of MTC have provided better accuracy in determining its clinical presentations, and investigational programs have been developed for the pre-symptomatic diagnosis of the familial form of the disease.⁸ Several RET proto-oncogene germline mutations have been reported to activate the RET protein receptor and are considered to be related to familial presentations of MTC. Nonetheless, little is understood regarding the biological aspects of MTC. Genotype-phenotype correlations have also been described since specific mutations of the RET proto-oncogene may lead to particular clinical manifestations of neoplasia.⁹⁻¹⁴

Surgery is currently the only effective treatment available,¹⁵⁻¹⁷ and the success of treatment depends strongly upon the clinical stage of the patient and the appropriateness of initial surgery. In addition to clinical presentation, tumor behavior and prognosis of patients with MTC are also varied. A tendency toward early metastatic lymph node dissemination has been observed.^{16,17} However, indolent cases can contrast with very aggressive ones.⁶ Long-term progression may be satisfactory for patients with high serum CT levels after surgery, and the lack of demonstrable metastatic or residual disease is not an uncommon situation.^{9,14,18-23} Some patients with evident metastatic disease may live for years, as well.⁹ Many studies have already attempted to determine predictive factors for prognostic impairment in patients with properly treated MTC. The results obtained have not been uniform, possibly because of the heterogeneity of patients. However, MTC is undoubtedly a disease that has the potential to be fatal.

In this study, we have identified clinical and pathological factors affecting clinical progression in surgically treated MTC patients.

METHODS AND MATERIALS

Patients

This study was approved by the ethics committee for human studies (CAPPESQ – number 16.416/02 – 12 June 2002). Fifty-three patients followed by the Head and Neck Surgery and Endocrinology Departments of the Faculdade de Medicina da Universidade de São Paulo in Brazil, were selected for retrospective analysis. All had been diagnosed with MTC and had undergone surgery as their initial therapy. Only patients whose clinical and pathological data were found in their medical records were included in the study. The median age of patients at the time of admission was 36 years (range, 9-69 years). Thirty-five patients (66.0%) were women. Thirty-four patients (64.1%) were considered sporadic; eighteen patients (34.0%) had MTC associated with MEN2A;

and one patient (1.9%) had MTC associated with MEN2B. None had the isolated familial presentation of the neoplasia.

After surgery, cure was defined as a drop in CT serum titer to or below the upper limit of the laboratory reference range; recurrence was defined as an increase in CT serum titer levels at least six months after the determination of cure. Either maintenance of CT serum titer levels above the reference limit or an increase above reference limits less than six months after an earlier reduction indicate neoplastic persistence.²⁴ Biochemical disease was defined in those patients whose serum CT levels remained high with no clinical and/or imaging evidence of cervical neoplasia or metastases. Relative values of serum basal CT and CEA were analyzed, and the number of increases in relation to the maximum reference value was examined. The maximum number observed during the progression of each patient was used for the analysis. Out-patient visits, accompanied by serum measurement of calcitonin and CEA, occurred every two months for the first year and biannually thereafter. At the time of the first postoperative ambulatory visit, conducted up to three weeks after surgery, patients were classified as cured or with persistent disease. CT and CEA measurements, however, were not always available in our laboratories, as patients compliance with ambulatory visits and laboratory controls were not constant.

Based on their medical condition during their last ambulatory visit, patients were classified as cured or not cured, which included those patients who were dead because of disease. Clinical progression was compared with clinical and pathological aspects. Four patient deaths in the whole group were attributed to MTC and they occurred at 14, 16, 19, and 88 months of clinical follow-up. Patients were followed for a median of 55 months (mean of 75 months; range, 4-225 months) from June of 1982 to February of 2006. The patient who was followed for only four months was alive and with biochemical disease at the last ambulatory visit.

Statistical Analysis

Percentile and absolute distributions were obtained for nominal variables. For numerical variables, inferential statistical measures were acquired through the Chi-Square test of independence and Fisher's exact test. Logistic regression was used for multivariate analysis. Odds ratios and confidence interval values were calculated through the association of independent and dependent variables in a bivariate analysis. Values of $p < 0.05$ were considered statistically significant. SPSS, version 13.0 (Statistical Package for the Social Sciences, Chicago, IL, USA) was used for the statistical analysis.

RESULTS

Twenty-nine patients (54.7%) were considered cured after the initial surgical treatment. Eight patients progressed with neoplastic recurrences. The 32 patients who were not cured were grouped as follows: 18 patients had only biochemical disease (56.25%); 7 patients had distant metastatic and cervical disease (21.9%); 6 patients had only cervical disease (18.75%); and 1 patient had only distant metastatic disease (3.1%).

For the 35 patients whose serum doses of calcitonin during the preoperative or immediate postoperative periods were measured, the values were calculated as a mean of 151.7 fold greater than the maximum laboratory reference value and a median of 17.66 fold greater than the maximum laboratory reference value (SD \pm 412.15 fold). Serum values of CEA were calculated at a mean of 10.27 fold greater than the maximum laboratory reference value and a median of 2.65 fold greater than the maximum laboratory reference value (SD \pm 15.12 fold).

Clinical and pathological variables were correlated with the patient being either cured or not cured as the final medical conditions. Variables that demonstrated statistically significant correlations are as follows: evidence of primary neoplasia and/or lymph node basins on initial cervical examination ($p = 0.002$); neoplastic extension through the thyroid capsule ($p = 0.004$) and to tissues adjacent to the gland ($p = 0.034$); diameter of neoplasia ($p = 0.018$); presence of cervical lymph node metastases ($p < 0.001$); TNM (tumor, node, metastasis) Cancer Stage^{25*} ($p < 0.001$) (Table 1); and presentation of disease among those who were not cured ($p = 0.011$) (Table 2). The presence of distant metastasis on admission did not demonstrate a statistically significant association with any of the defined final medical conditions. However, there was one patient for this variable (in costal arch), who died of the disease. Four patients died from MTC; all of these patients presented with clinical and/or imaging evidence of neoplasia.

Through logistic regression, only the presence of lymph node metastases was considered to be an independent variable ($p < 0.001$) (Table 3). Patients without cervical lymph node metastases were 24 times more likely to achieve a cure than those with regional disease.

Positive initial cervical examination ($p = 0.013$); neoplastic extension through the tissues adjacent to the thyroid ($p = 0.038$); presence of cervical lymph node metastases ($p < 0.001$); and TNM stage ($p < 0.001$) were

correlated with tumor persistence after the initial operation (as defined in "methods"). However, through logistic regression, only the presence of lymph nodes metastases was considered an independent variable ($p < 0.001$).

DISCUSSION

Cervical lymph node metastases and TNM stage were characterized as the most important prognostic factors for patients operated on for MTC, and they are correlated variables. Cervical lymph node metastases were identified in all of the patients who died, while only 2 of 26 patients with cervical metastatic impairment (7.7%) were cured. Among those patients who remained alive with the disease, more than 70% had cervical metastases at the initial surgical treatment. Of the subjects, 79% who progressed with clinical and/or imaging evidence of local and/or distant neoplasias had cervical metastases upon the initial staging. Cervical metastatic neoplasia has previously been associated with tumor stage,²⁶ increased risk of neoplastic progression, and prognostic impairment.^{6,14,15,18,23,27-29}

Almost half of patients studied were classified as stage IV using the TNM Stage System, and the predominance of patients admitted with advanced MTC is not exclusive to our case studies.^{14,15,27} In our analysis, only stage IV patients died. Seventeen of twenty-two stage I or II patients (77.3%) were alive and disease-free at the end of the follow-up periods. Furthermore, 25 of 32 patients whose tumors persisted or recurred (78.1%) had been classified as stages III or IV. Consulted authors^{1,14,18,26,30,31} also considered TNM stage a relevant prognostic factor.

Cervical lymph node metastases were identified in 20 of 33 patients with neoplasias of 15 mm in diameter or larger (60.6%) and in 6 of 18 patients whose primary tumors were smaller than 15 mm (33.3%). Therefore, only six of twenty-six patients with cervical lymph node metastases (23.1%) had primary tumors smaller than 15 mm. Among the patients who died, three had been treated for primary neoplasias larger than 30 mm, and one was treated for a neoplasia of 15 mm; all four already had cervical metastatic disease. Other investigators have also observed correlations between primary tumor dimensions and disease progression.^{14,15,28}

Patients with palpable MTCs frequently present with cervical lymph node metastases.^{1,20} Forty patients (75.5%) were identified through positive initial cervical physical examinations, a negative prognostic factor, as also observed by Kebebew *et al.*¹⁸ All patients whose neoplasias persisted

* **Tumor size** => **T1**: ≤ 2 cm; **T2**: > 2 cm and ≤ 4 cm; **T3**: > 4 cm or minimal extrathyroid extension; **T4a**: extrathyroid extension (resectable); **T4b**: unresectable extension. **Lymph node** => **N0**: no regional lymph node metastasis; **N1a**: metastasis to level VI; **N1b**: metastasis to unilateral, bilateral or contralateral cervical or superior mediastinal lymph nodes. **Distant metastasis** => **M0**: absent; **M1**: present. **Stages** => **I**: T1N0M0; **II**: T2N0M0; **III**: T3N0M0, T1-2-3N1aM0; **IVA**: T4a any N M0, T1-2-3N1bM0; **IVB**: T4b any N M0; **IVC**: any T any N M1.

Table 1 - Correlation of final medical condition with clinical and pathological variables

VARIABLE	FINAL MEDICAL CONDITION						p value
	Cured		Not Cured		TOTAL		
	n	%	n	%	n	%	
Age group (years)							
Up to 20	6	50.0	6	50.0	12	100.0	⁽¹⁾ 0.603
21 to 40	5	31.3	11	68.8	16	100.0	
41 or over	10	40.0	15	60.0	25	100.0	
Sex							
Male	9	50.0	9	50.0	18	100.0	⁽²⁾ 0.268
Female	12	34.3	23	65.7	35	100.0	
Diagnosis through screening							
Yes	7	46.7	8	53.3	15	100.0	⁽²⁾ 0.510
No	14	36.8	24	63.2	38	100.0	
Positive initial cervical examination							
Yes	11	27.5	29	72.5	40	100.0	⁽²⁾ 0.002*
No	10	76.9	3	23.1	13	100.0	
Systemic symptoms							
Yes	3	33.3	6	66.7	9	100.0	⁽¹⁾ 1.000
No	18	40.9	26	59.1	44	100.0	
Thyroid capsule invasion							
Yes	2	11.8	15	88.2	17	100.0	⁽²⁾ 0.004*
No	19	52.8	17	47.2	36	100.0	
Adjacent extension							
Yes	-	-	7	100.0	7	100.0	⁽¹⁾ 0.034*
No	21	45.7	25	54.3	46	100.0	
Tumor diameter (mm)[†]							
< 15	11	61.1	7	38.9	18	100.0	⁽¹⁾ 0.018*
≥ 15	9	27.3	24	72.7	33	100.0	
TNM stage [‡]							
I or II	17	77.3	5	22.7	22	100.0	⁽¹⁾ < 0.001*
III	1	14.3	6	85.7	7	100.0	
IV	2	9.1	20	90.9	22	100.0	
• Cervical lymph node metastases							
Yes	2	7.7	24	92.3	26	100.0	⁽²⁾ < 0.001*
No	19	70.4	8	29.6	27	100.0	
• Clinical presentation							
Sporadic	8	42.1	11	57.9	19	100.0	⁽²⁾ 0.782
Familial	13	38.2	21	61.8	34	100.0	
Initial calcitonin levels[‡]							
Up to 10x	6	54.5	5	45.5	11	100.0	⁽¹⁾ 0.280
>10x to 30x	1	12.5	7	87.5	8	100.0	
>30x to 100x	2	33.3	4	66.7	6	100.0	
> 100x	2	22.2	7	77.8	9	100.0	
High initial CEA levels ^f							
Yes	4	28.6	10	71.4	14	100.0	⁽²⁾ 1.000
No	3	37.5	5	62.5	8	100.0	

⁽¹⁾ By Fisher's exact test. ⁽²⁾ By Chi-Square test. ^(*) Significant association with p less than 0.05. ^(†) 51 patients. ^(‡) The number of increases in relation to the maximum laboratory reference value (relative values). For 34 patients. ^(f) 22 patients.

Table 2 - Correlation of final medical condition with progression presentation (patients not cured)

VARIABLE	MEDICAL CONDITION						⁽¹⁾ p-value
	AWD		DBD		TOTAL		
	n	%	n	%	n	%	
Only cervical disease	5	83.3	1	16.7	6	100.0	
Only distant metastasis	-	-	1	100.0	1	100.0	
Cervical disease and distant metastasis	5	71.4	2	28.6	7	100.0	0.011*
Biochemical disease ⁽²⁾	17	100.0	-	-	17	100.0	
TOTAL ⁽³⁾	27	87.1	4	12.9	31	100.0	

Condition of patient: AWD = alive with disease at the end of the follow-up; DBD = dead because of disease. ⁽¹⁾By Fisher's exact test. - Nil occurrences. ⁽²⁾Significant association with p less than 0.05. ⁽³⁾Without evidence of local or distant disease, despite the increase in calcitonin. ⁽³⁾Alive without disease were excluded

Table 3 - Logistic regression for cure (final medical condition)

VARIABLE	Odds ratio and Confidence Interval (95.0%)		p value
	Bivariate study	Adjusted	
• Lymph node metastases			
Yes	1.00	1.00	
No	28.50 (5.41 - 150.23)	24.42 (4.33 - 137.76)	p < 0.001*

^(*)Significant association with p less than 0.05

or recurred and who progressed with imaging and/or clinically evident active disease had also demonstrated clinical evidence of MTC on admission.

Neoplastic extensions to the thyroid capsule and to tissues adjacent to the thyroid correlated significantly with the final medical condition. No patient with neoplastic extension to tissues adjacent to the thyroid was cured. Among the 17 patients whose tumors affected the thyroid capsule, 13 also had cervical lymph node metastases, regardless of tumor size. Infiltration of tissues adjacent to the thyroid has previously been associated with a major risk of disease progression and death.^{23,26-28,32}

Advanced disease was not exclusive to older patients, and statistically significant correlations were not observed between age groups and progressions, as also reported by Weber *et al.*²⁷ This observation is contrary to other studies,^{1,6,14,15,18,22,28,30,31,33,34,35} which have stated that older patients generally had worse prognoses than younger ones. Statistical significance was also not obtained when sex was compared to clinical progression, as observed by other authors.^{22,27} The proportion of males with cervical metastases (44.4%, compared to 51.4% among women) and the proportion of stage IV men (50.0%, compared to 37.1% among women) were not significantly different from figures for females. Nevertheless, in the examined studies, female patients showed higher survival rates,^{1,6,14,15,18,30,34} even when compared to men affected by neoplasias of similar stages,¹

and a lower risk of disease progression.²⁸

Although the presence of systemic symptoms was not characterized as a prognostic factor, of the nine patients who reported these symptoms (diarrhea and/or weight loss), six had already had cervical lymph node metastases. Furthermore, there was only one patient with distant metastasis on admission. Three of the four patients who died reported systemic symptoms on admission. The global survival rate was already characterized as significantly lower among patients with diarrhea;¹²¹ in another study,¹⁸ all sporadic patients who reported systemic symptoms were classified as stage IV and died during the follow-up period.

Participation of the clinical presentation of MTC in the final medical conditions was not observed because the proportion of patients with cervical lymph node metastases and stage IV patients were also rather similar. Studies^{131,14,18,31} emphasized prognostic differences related to the clinical presentations of MTC, favoring those patients associated with MEN2A. Nonetheless, Hyer *et al.*¹⁵ and Ellenhorn *et al.*²² did not observe distinct progressions among sporadic and familial patients with cervical metastatic disease. Clinical disease presentation was also not characterized as a prognostic factor in a multivariate analysis led by Weber *et al.*²⁷ It is possible that the opportunity for early diagnosis of MTC afforded by MEN2A provides a prognostic advantage to patients over other MTC types. However, early diagnosis did not occur at a significant rate among our cases, including

those patients who were diagnosed through screenings.

The presence of distant metastasis at MTC diagnosis was reported in only one patient, and his death was attributed to neoplasia. The presence of distant metastasis at diagnosis also has prognostic relevance in the experience of other authors.^{14,15,28,29}

Therapeutic modalities were not analyzed because the variety of surgical approaches in the presence of very distinct clinical features did not allow for accurate analysis of their relationship to the prognosis. All patients were submitted to total thyroidectomy, except for two whose tumors were inoperable. Only nine patients were not submitted to any kind of cervical dissection, including those two with inoperable tumors. None of the 32 patients, whose tumors persisted or recurred, were subsequently cured, despite complementary operations (seven patients) or adjuvant therapies (eight patients).

The presence of active disease was considered a prognostic factor for death or survival. The four patients who died because of the disease had a progressed disease with clinical and/or imaging evidence of cervical and/or distant neoplasia. It has already been observed that 70% of deaths occur during the first five years of diagnosis³⁵ as a result of locally aggressive neoplasias.^{21,28}

Basal calcitonemia and serum CEA levels upon diagnosis of MTC were very diverse, and their values indicated considerable variability, mainly among patients with high levels of the markers. In the course of the studied clinical progression, 16 patients progressed with high levels of CT, up to 100 times the upper laboratory limits, and 14 maintained values over 100 times the upper laboratory limits. Of these 14 patients, 10 showed clinical and/or imaging evidence of cervical and/or distant disease, including those who died. A significant tendency towards high serum titers of basal CT in patients with advanced tumors was observed previously.¹ Some researchers^{22,23} have not observed a correlation between serum CT levels and prognosis, while other authors^{36,37} have identified pre- and postoperative

serum CT levels to be predictive elements of progression and have observed that all patients not cured had higher preoperative basal serum CT levels.

Of the 22 patients whose initial serum CEA levels were measured, eight were within normal limits despite the presence of MTC. Of the 26 patients not cured in whom the marker was measured, 11 patients who progressed to active disease had low serum CEA titers, thus, rendering the negative predictive value of this marker low. Modigliani et al.¹⁴ considered normal preoperative serum CEA values as predictors of cure and related them to pathological stages. Others³⁸ correlated serum CEA levels with success of the initial surgery, tumor dimensions, and presence of metastases.

In previous research,^{39,40} we observed a correlation between prognosis and the immunohistochemical expressions of metalloproteinases—enzymes related to the extracellular matrix and basement membrane degradation—in MTC surgical specimens. However, statistical parameters, such as sensitivity and specificity, showed that the presence of cervical lymph node metastases and TNM stage were the major variables.

At the end of the follow-up period, 22 patients (41.5%) were alive and without disease, 27 (50.9%) were alive with disease, and 4 (7.6%) had died because of MTC. These data are compatible with the findings of other authors.^{14,18,19,22,27,31}

CONCLUSION

The current study demonstrated that specific factors that determine the prognosis of individuals with MTC (positive initial cervical physical examination, neoplastic extension to thyroid capsule and adjacent tissues, diameter of the neoplasia, cervical lymph node metastases, TNM stage, and evidence of distant and/or cervical diseases in case of absence of cure) should be observed after diagnosis and surgery, so each case can be treated with the requisite attention and concern.

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