Medullary thyroid carcinoma: multivariate analysis of prognostic factors influencing survival

Isabel Peixoto Callejo[a], José Américo Brito[b], Carlos Manuel Zagalo[a] and Jorge Rosa Santos[a]

[a]Department of Head and Neck Surgery. Portuguese Institute of Cancer. Lisbon, Portugal.
[b]Department of Mathematics. Physics and Computer Science. Faculty of Engineering and Applied Science. Ryerson University. Toronto, Canada.

Background. **Medullary thyroid carcinoma (MTC) is a rare development of thyroid cancer with a no negligible mortality rate. Our aim was to determine factors that predict outcome in patients with MTC.**
Methods. **We reviewed the records of all patients with MTC (n = 56) who underwent treatment at our institution between January 1990 and December 2000. Univariate and multivariate analysis of clinicopathologic predictors of MTC outcome were performed to identify subsets of patients with different probabilities in terms of overall survival, local recurrence, and distant metastases.**
Results. **Multivariate analysis demonstrated that a statistically significant decrease in overall survival is associated with T4b tumours (p = 0.06), the presence of distant metastases at the time of presentation (p = 0.033), lymphatic invasion (p = 0.099), and postoperative treatment (p = 0.045).**
Conclusions. **The analysis of survival curves of patients with MTC shows that the occurrence of locoregional and distant metastases occurs preferentially within the first 5 years, which identifies this as a crucial period for follow-up. In this series of patients with MTC, the tumours classified as T4b, metastases at presentation, the presence of lymphovascular invasion, and postoperative treatment were the most important prognostic features. At present, there is no available beneficial adjuvant therapy. However, as the development of molecular therapy progresses, it should be tested in clinical trials with the purpose of achievement of novel targeted therapies for selected MTC patients with risk factors.**

Key words: medullary thyroid carcinoma, RET, RTK, survival analysis, risk factors, lymphovascular invasion.

Correspondence: I. Peixoto Callejo.
Department of Head and Neck Surgery.
Rua Herminio Monteiro, 5-5.º A.
1750-401 Lisboa, Portugal.
E-mail: isabelcallejo@hotmail.com

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INTRODUCTION

Medullary thyroid carcinoma (MTC) is a rare tumour. It was recognized in the 1950s by Hazard et al[1] as a distinct entity; since than, several studies have focused on the identification of prognostic factors for MTC, although the value of this remains controversial. MTC arises from the parafollicular cells (C cells) of the thyroid gland[2]. It accounts for approximately 3% to 10% of all thyroid cancers and approximately 15% of all thyroid cancer-related deaths[3,4].

MTC can appear in sporadic and hereditary types. Patients with MTC should be screened for hereditary disease[5-7], which occurs in isolation, as familial MTC (FMTC), and as part of the multiple endocrine neoplasia (MEN) type II syndrome; both of these forms are inherited as an autosomal dominant trait[8,9]. MEN 2A, which was first described by Steiner at al[10], occurs with pheochromocytoma[11], whereas MEN 2B is associated with marfanoid habitus, mucosal neuromas, and ganglioneuromatosis[12].

The mutation responsible for the induction of atypical C cell proliferation is located in exon 10 or 11 of the RET proto-oncogene[5-7], and the sequential pathogenic pathway of MTC, arising from areas of C cell hyperplasia to multiple preinvasive microscopic foci, was recognized in the 1970s by Wolfe et al[13]. RET germ-line mutation belongs to receptor tyrosine kinases' (RTK) mutations. KIT RTK is the mainstay of gastrointestinal stromal tumours (GIST) pathogenesis[14,15], which led to the treatment of KIT-positive advanced GIST with molecular therapies[15]. It is reasonable to think of targeted molecular therapies for MTC, based upon an identical oncogenic pathway, the growth of cancer under the RTK oncogene activation. At present, the detection of mutations in the RET oncogene offers physicians the chance to perform prophylactic thyroidectomy in persons who carry this gene[5,16-18].

In about two-thirds of all cases of MTC, the initial disease is primarily locoregional, although in one-sixth of cases, primary development of distant metastasis is observed[19,20]. This study evaluates the impact of clinical and pathological factors on survival in 56 patients with MTC. The purpose was to determine the main risk factors that predict the clinical behaviour of MTC.

PATIENTS AND METHODS

Patients

The Portuguese Institute of Cancer serves as an oncological referral center for patients with neoplastic thyroid disease and maintains a database cancer registry of all patients with thyroid cancer on the basis of a confirmed report of thyroid malignancy. The study population consisted of patients evaluated and/or treated at our institution for MTC between January 1990 and December 2000. To meet the inclusion criteria, all patients had to have a histologically confirmed diagnosis of MTC, retrospectively determined. A total of 61 patients were identified, and five patients were lost to follow-up. Data on the remaining 56 patients was used for survival analysis.

We classified patients with MTC into three groups: sporadic, MEN 2A, and FMTC. The criteria used for the definition of these three groups were, respectively, patients without any first-degree relative with MTC or MEN 2 or the absence of a RET germ line mutation, patients with a first-degree relative with MEN 2A or MTC associated with pheochromocytoma and/or hyperparathyroidism, and patients with a first-degree relative with MTC but no evidence of the syndromes associated with MEN 2. We could not considerer MEN 2B, because no patients with MEN 2B were enrolled into the series.

Total thyroidectomy with central cervical lymph node dissection was the first surgical choice for all MTC patients. Patients with a MTC diagnosis after being submitted to a hemithyroidectomy, did not have modifications to thyroid surgery extension in the absence of contra-lateral thyroid lesions detected by ecography, negativity for RET oncogene, and a negative pentagastrin stimulation test. Incomplete resection was limited to patients with technically irressecable tumors, who were further submitted to postoperative irradiation. Lateral cervical lymphadenectomy was performed in the presence of pathologic lateral lymph nodes, tumour sized over 2 cm, and positive central nodes, being limited to one side in sporadic MTC (homolateral to the primary tumour, except in cases with obvious bilateral involvement), and bilateral in familial cases.

Follow-up data were obtained through the ROR cancer registry and from a review of the patients' clinical records. Information about macroscopic findings was obtained from surgical reports.

The study end points were death from thyroid carcinoma and tumour status (free of MTC or persistent MTC). Patients free of MTC were defined as having normal postoperative serum calcitonin levels with no evidence of local or distant MTC after tumour resection. Patients with elevated (basal or stimulated) postoperative serum calcitonin levels were classified as having persistent MTC.

Statistical methods

The follow-up interval was calculated in months and was defined as the time between the date of diagnosis and the date of event (death, recurrence, or metastasis) or last follow-up. The median follow-up period was 49 months (range, 2-128 months).

Continuous variables were evaluated using Student's t test or by analysis of variance for multiple group comparison, and the chi-square test was used for categorical data.

The Kaplan-Meier or product-limit nonparametric technique was used to estimate mean overall survival (OS), local recurrence-free survival (LRFS), and metastasis-free survival (MFS). The analysis was first computed considering cases of TNM stage altogether and then subsequently assessed for each TNM stage.

The prognostic factors, evaluated for the three groups of patients (OS, LRFS, and MFS), were: age and sex, presenting symptoms and signs, metastases at presentation, type of surgery and lymphadenectomy, tumour bilaterality and multifocality, tumour size, node status, stage grouping (AJCC, 6th edition), lymphatic and venous invasion, adjuvant treatment and postoperative serum calcitonin levels. Contingency tables were used to compare the survival time's distributions of the various subgroups and to identify univariate predictors of survival. Univariate predictors of survival were entered into a Cox proportional hazards model by using stepwise logistic-regression analysis to identify the independent predictors of survival. The best set of predictors of OS was selected that included only the dichotomous variables, and stepwise logistic regression using the maximum-likelihood method was implemented. The objective was to assess the type of relationship between those variables.

RESULTS

Patient and tumour characteristics

Patient characteristics are shown in table 1. Forty-eight patients (85.7%) had sporadic MTC, 6 patients (10.7%) had MEN 2A, and 2 patients (3.6%) had FMTC. There were 23 men and 33 women, with an

TABLE 1. **Clinical characteristics of patients according type of MTC**

Features	Sporadic	MEN 2A	FMTC	Total
N.° of patients	48	6	2	56
Age mean, range (years)	54.7; 26-86	24.3; 7-58	25; 13-37	50.4; 7-86
Male: female ratio	18:30	4:2	1:1	23:33
Clinical presentation				
Thyroid nodule	38	0	2	40
Enlarged neck nodes	10	2	0	12
Family history[a]	0	4	0	4
TNM stage				
I	6	4	1	11
II	4	0	1	5
III	8	0	0	8
IVA	22	1	0	23
IVB	4	0	0	4
IVC	4	1	0	5
Metastatic disease at presentation	4	1	0	5

[a]Patients at risk for hereditary MTC and screened with biochemical and/or genetic testing.

overall mean age at diagnosis for the study group of 50.4 years (range, 7 to 86 years). Patients with sporadic MTC (mean age, 54.7 years) were significantly older than patients with hereditary MTC (mean, 24.6 years) at the 5% level of confidence. The overall male: female ratio was 1.0:1.4, with no difference between the groups with sporadic and hereditary MTC.

In the sporadic group, 79.2% of patients presented with a thyroid mass and 20.8% had enlarged lymph nodes in the neck. The two patients with familial disease presented with thyroid nodules, whereas, in the subgroup of patients with MEN 2A, 33.3% had cervical disease and 66.7% were screened for MTC by calcitonin measurement and/or genetic testing.

In the overall group of patients, the rate of metastatic disease at presentation was 9% (n = 5). Patients with sporadic MTC with distant metastases at presentation (n = 4) did not present with systemic symptoms (bone pain, flushing, and/or diarrhoea) attributable to their tumour. Another patient presenting with bone and hepatic metastases had a positive germline RET mutation associated with local advanced disease.

Total thyroidectomy was performed in 49 patients (87.5%); the remainder underwent hemithyroidectomy (8.9%) or incomplete resection for two patients (3.6%) with advanced local disease. All the patients with hereditary MTC (n = 8) had total thyroidectomy

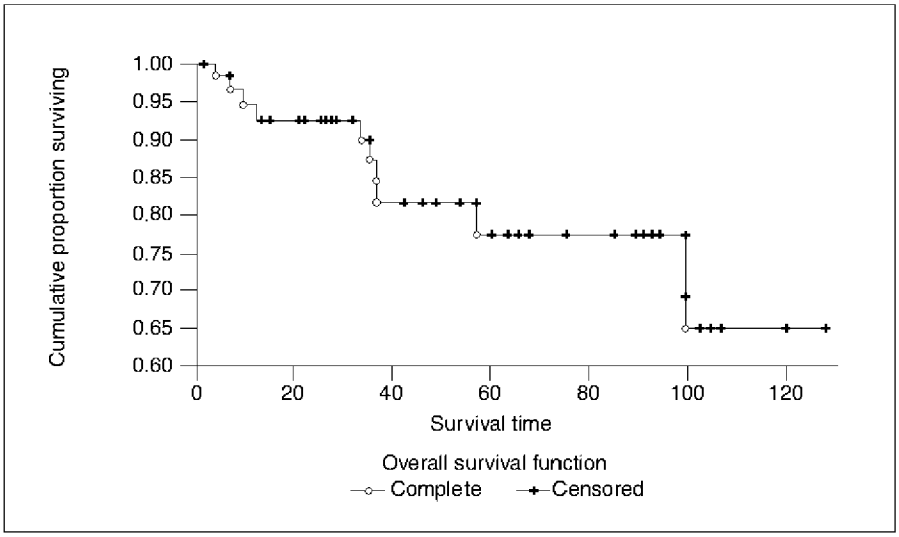

Fig. 1. Overall survival curve (in months) in 56 patients with medullary thyroid carcinoma.

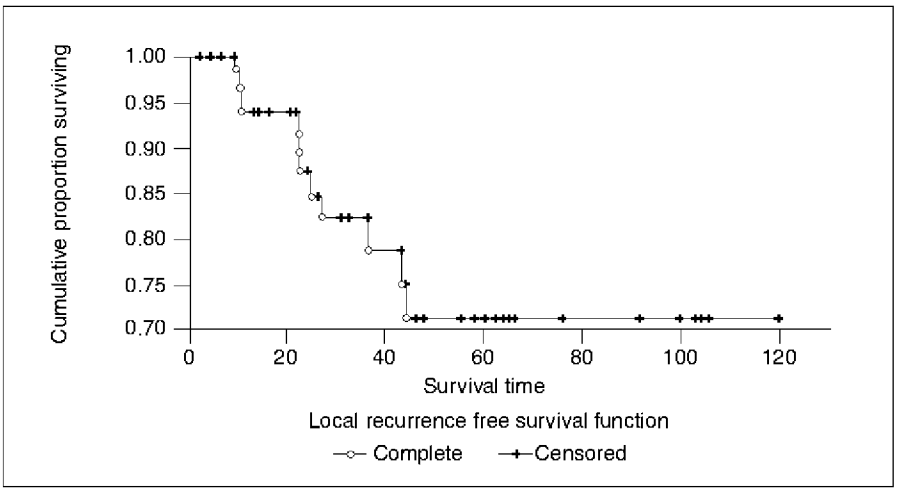

Fig. 2. Local recurrence-free survival curve (in months) in 56 patients with medullary thyroid carcinoma.

without cervical lymph-node dissection, except for two patients with MEN 2A who had a cervical central and lateral lymph-node dissection (LND). LND was performed at various extensions: one-compartment LND in 5.4% (3/56), three-compartment LND in 51.8% (29/56), and four-compartment LND in 7.1% (4/56). Nodal disease was present in 62.5% of patients according to the results of the examination of lymph nodes retrieved by surgery. Only 3 patients had node metastasis classified as N1a. The remaining 57.1% of patient's nodal disease corresponded to N1b.

Bilateral tumors and multifocal disease had both identical expressions on the overall group of patients with MTC (14.3%), with both assuming more prevalence in hereditary MTC ($p < 0.05$). The presence of lymphatic vessel invasion and venous invasion was analysed, with a higher percentage of venous invasion (46.4%) comparing with lymphatic involvement (37.5%). External beam radiotherapy (RT) was given to 6 patients with irressecable tumors, and only one patient was given chemotherapy.

Survival analysis

For the whole group, 46 patients (82.1%) remain alive, and 10 (17.8%) have died. The cause of death was medullary cancer for all patients. At the last follow-up, 37.5% of the patients with MTC were free of

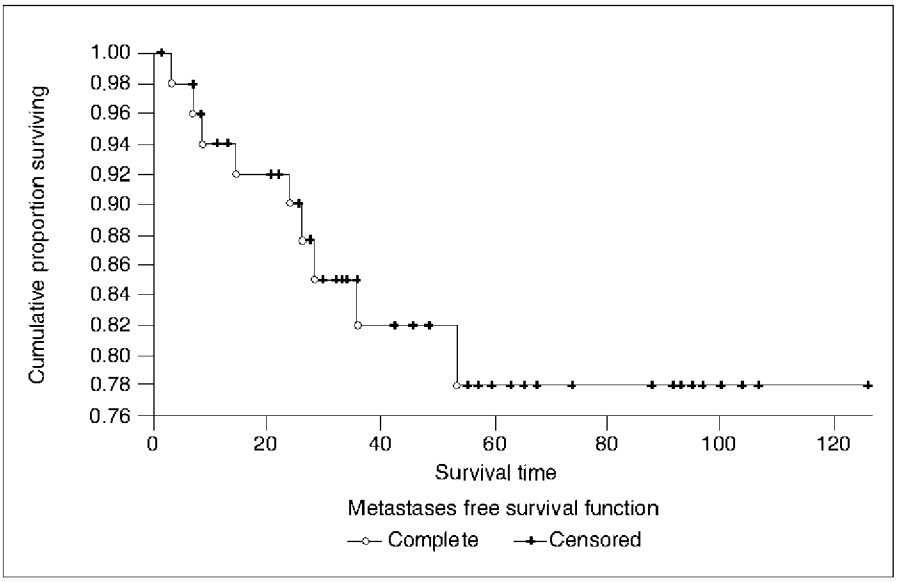

Fig. 3. Metastasis-free survival curve (in months) in 56 patients with medullary thyroid carcinoma.

TABLE 2. **Evaluation of clinicopathologic variables for all patients with MTC in univariate and multivariate analysis**

Clinicopathologic variables	Univariate	p value	Multivariate	p value
Age	NS	–		
Sex	NS	–		
Clinical presentation	S	0.004	NS	–
Metastatic disease at presentation	S	0.0001	S	0.033
Primary tumour (T)				
T1	NS	–		
T2	NS	–		
T3	NS	–		
T4A	NS	–		
T4B	S	0.014	S	0.06
Regional lymph nodes (N)	S	0.014	NS	–
Stage grouping (TNM)	S	0.0007	NS	–
Bilateral tumours	NS	–		
Tumour multifocality	NS	–		
Lymphatic vessel invasion	S	0.002	S	0.099
Venous invasion	NS	–		
Treatment				
Extent of thyroidectomy	S	0.032	NS	–
Lymph-node dissection	S	0.025	NS	–
Adjuvant treatment	S	< 0.00001	S	0.045
Postoperative serum calcitonin level		S	0.007	–

S: significant; NS: not significant.

disease, 18% had asymptomatic persistent MTC, 16% had local disease, and 9% had distant disease.

The mean OS for all patients with MTC was 82.47 months. The 5- and 10-year OS was 77.5% and 65%, respectively (fig. 1). The 5- and the 10-year LRFS were estimated at 72% (fig. 2), and the 5 and the 10-year MFS were estimated at 78% (fig. 3).

Survival analysis was also assessed for each stage of TNM. However, only for stages IVA and IVC was it possible to apply the product-limit method, because of the excessive amount of censored data. The mean OS for patients with MTC stage IVA was 86.42 months. For the same group, the 5 and 10-year OS was estimated at 81% and 61%, respectively. In addition, 5 and the 10-year LRFS were estimated at 60%, and the 5 and the 10-year MFS were estimated at 66%. It was also possible calculate the mean OS for patients with category IVC disease, which was 18.8 months, although it was not feasible by any other statistical calculus.

Univariate analysis demonstrated that a statistically significant decrease in OS is associated with clinical presentation ($p = 0.004$), the extent of thyroidectomy ($p = 0.032$), cervical lymph-node dissection ($p = 0.025$), metastatic disease at presentation ($p = 0.0001$), primary tumour ($p = 0.014$), regional lymph nodes ($p = 0.014$), stage of disease ($p = 0.0007$), lymphatic vessel invasion ($p = 0.002$), adjuvant treatments ($p < 0.00001$), and the postoperative level of serum calcitonin ($p = 0.007$).

The following factors were significantly associated with a decrease in survival according to Cox regression analysis (table 2): extra thyroidal invasion with a clear decrease in the probability of survival in patients with T4b tumours ($p = 0.06$, fig. 4), the presence of distant metastases at presentation ($p = 0.033$, fig. 5), the presence of lymphatic invasion ($p = 0.099$, fig. 6), and postoperative treatment ($p = 0.045$, fig. 7). For both LRFS and MFS, we did not find significant predictors of survival in either univariate or multivariate analysis.

The significant dichotomous predictors were incorporated into a stepwise logistic regression using the maximum-likelihood method to look for any kind of association between them. The beta coefficient was calculated for each significant factor. The following multivariate model was selected by this approach of the logit of OS: $g(x) = ß_0 + e^{ß1}$ (MDP) $+ e^{ß2}$ (LVI) $+ e^{ß5}$ (AT), where $ß_0 = 4.1$ is $p = 0.001$, $ß_1 = -2.56$ is $p = 0.52$, $ß_2 = -2.48$ is $p = 0.49$, and $ß_5 = -3.31$ is $p = 0.01$. The results show no significant associations between the predictors, which means that they are independent from each other.

DISCUSSION

MTC has been the subject of numerous studies[17,18,21-35] whose main purpose was the determination of predictors of prognostic importance. Yet this type of tu-

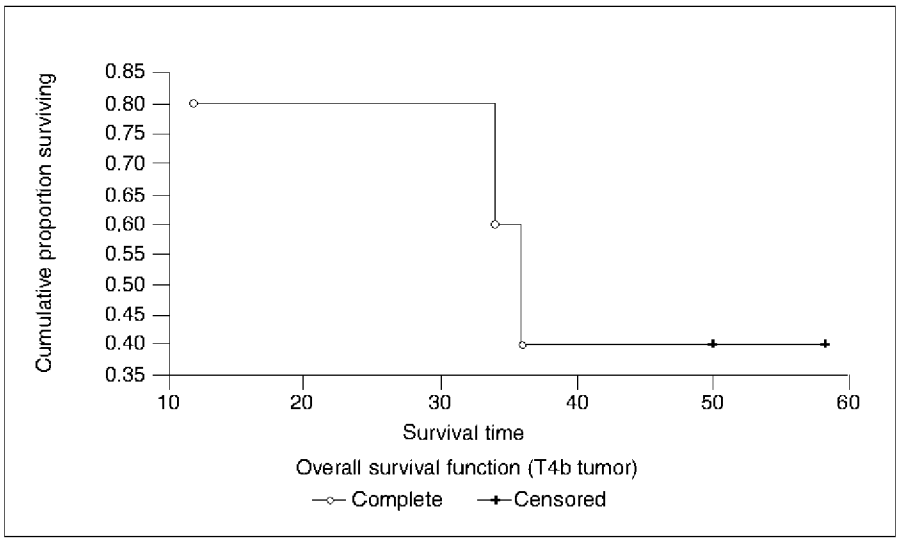

Fig. 4. Impact of T4b tumours on overall survival (in months) in 56 patients with medullary thyroid carcinoma.

mour continues to pose a challenge with regard to predicting its behaviour and strategies of treatment.

One of the reasons for the difficulty in predicting the clinical outcome for patients with MTC has been the lack of consistency in large multicenter studies, which have been characterized by incomplete data and the inclusion of variable diagnostic criteria. Single-institutional studies, although they have smaller cohorts, demonstrate the inclusion of more reliable criteria, which provides a chance for the comprehensive evaluation of the important factors that determine the outcome of this particular disease. This series fulfils this item.

Like other series, whereas sporadic MTC accounts for 75%-95% of all cases[22-25], we have found that 85.7% of patients have sporadic disease, compared with 14.3% of patients having hereditary disease. The recent trend toward a higher frequency of hereditary MTC observed in contemporary series[17,18,26,27], due to the screening programs for patients with genetic analysis, is not evident in our study. We have used a similar method for the diagnostic evaluation of nodular thyroid disease since 1997[6]. Therefore, we could assume that the high value found for sporadic disease in the Portuguese population, is either related to the as-yet insignificant time of evaluating patients sub-

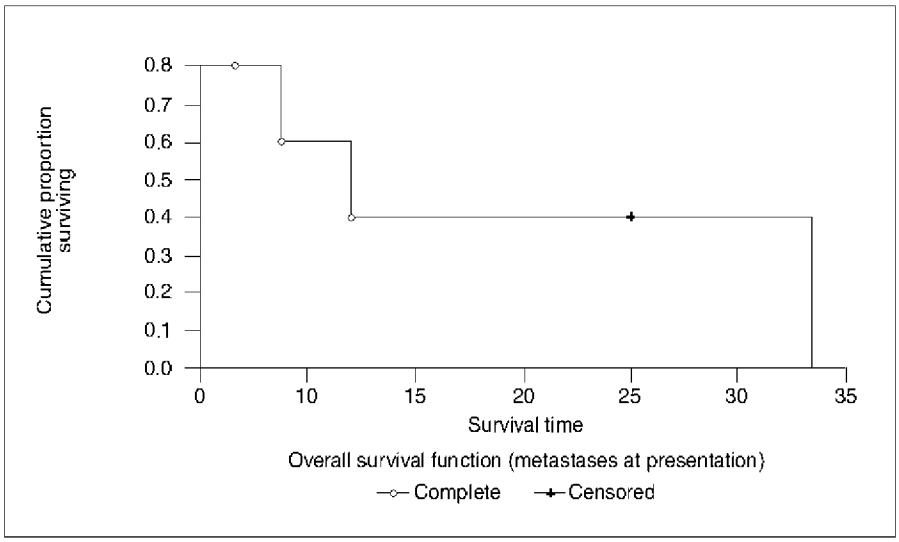

Fig. 5. Impact of metatases at presentation on overall survival (in months) in 56 patients with medullary thyroid carcinoma.

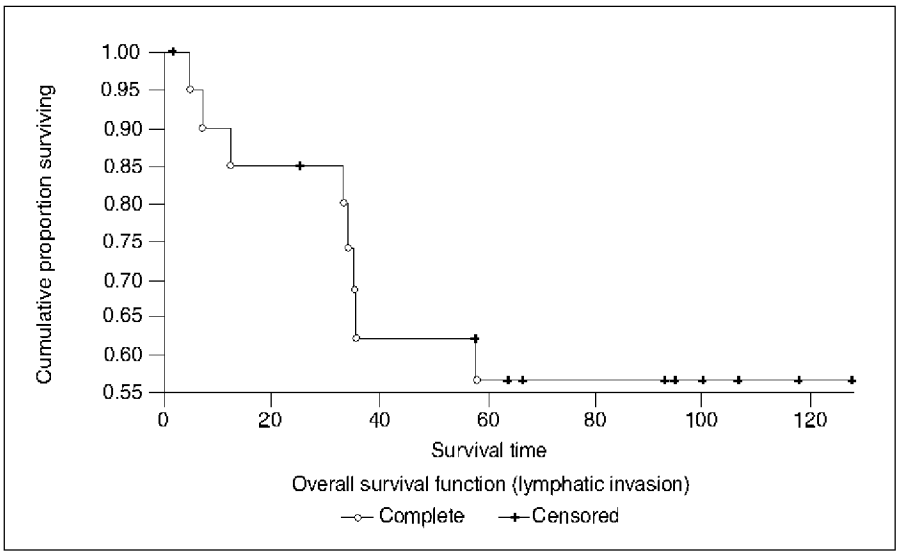

Fig. 6. Impact of lymphatic invasion on overall survival (in months) in 56 patients with medullary thyroid carcinoma.

mitted to genetic testing or reflects the type of disease more prevalent in Portuguese population.

The mean age in our series is similar to that of the three largest published series[22,23,28]: 50.4 years (range, 7-86 years), with the highest incidence in the fifth decade for sporadic disease and in the second decade for hereditary disease. Both sexes were nearly equally affected (male: female ratio, 1.0:1.4), which is consistent with the observations of others[22,29]. Our data did not confirm both epidemiological factors as positive predictors, and this conclusion has been corroborated by other authors[22,29].

The 5-year and 10-year OS was 77.5% and 65%, respectively, which is similar to the results in other published series of MTC (fig. 1)[22-24,29-35]. The 5-year and 10-year LRFS was 72%, which highlights the fact that, after a certain period of time the probability of local recurrence is exactly the same. This cut-off was calculated to be 46 months (fig. 2). The same rationale is applicable to MFS, where the 5-year and 10-year rate was 78% and the period since the possibility of occurrence of metastases was identical at 54 months (fig. 3). Therefore, we conclude that the analysis of the LRFS and MFS curves for MTC shows that a local recurrence occurs preferentially within the first four years, whereas the chance of manifestation of distant disease occurs primarily within the first 5 years. These results highlight the necessity of the implementation of a closed period of follow-up for MTC, with clinical, laboratory, and radiological examinations being done every 3 to 6 months for the first 5 years.

The incidence of patients with regional node metastases are quite similar to that found in a French series (62.5% vs 63%)[35], which is higher than the median value found for all the literature combined (range, 43%-50%)[22-32]. Also notably, we found that the majority of patients with nodal metastases in our series had advanced local disease (pN1b, 57.1%), which probably reflects a referral centre bias.

The analysis of the mean OS found for the overall group of patients and those classified as having types IVA and IVC, respectively, 82.47, 86.42, and 18.8 months highlights a sharp decrease in the OS in patients with IVC, compared with patients who had stage IVA and the whole group of patients. These observations emphasize the existence of a sharp decrease in the OS of patients with distant metastases that has statistical significance importance. We conclude that MTC is a disease in which the event of haematogenous spread leading to distant metastases, rather than local progression, is the main factor influencing the survival rate of patients with MTC.

In this study, we did find out that T4b tumors were an independent predictor of disease specific-survival on multivariate analysis (fig. 4). In fact, the probability of survival for a patient with a stage T4b tumour is approximately 6% of the probability of survival for a patient with a stage T1 tumour. Tumours extending through the thyroid capsule (pT4) were reported as the only important prognostic factor by Tennvall et al[34]. This parallels the findings of Schroder et al[35] and Treseler[28], who confirmed that this factor is an independent risk factor for mortality according to multivariate analysis. Nevertheless, there is a difference between our findings and previous ones. This concerns the more accurate definition of the levels of extrathyroidal invasion, outlined in the last revision of TNM classifications (AJCC, 6th edition, 2003). There are three levels of invasion beyond the thyroid

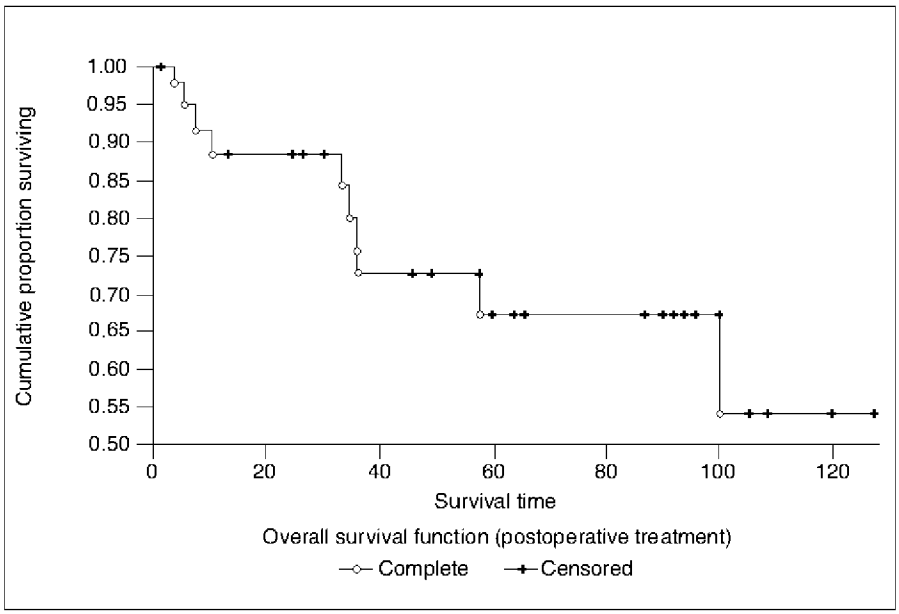

Fig. 7. Impact of adjuvant therapy on overall survival (in months) in 56 patients with medullary thyroid carcinoma.

capsule: T3 tumours, corresponding to minimally extrathyroidal invasion; T4a tumours, which harbours tumours with invasion of vital neighbours structures; and, finally, T4b tumours, indicated by invasion of carotid/mediastinal vessels or prevertebral fascia. We conclude that only the presence of the third level of invasion (T4b) serves as an independent prognostic factor for OS of patients with MTC.

In this series, the presence of distant metastases at the time of diagnosis appeared to be significantly associated with increased mortality in MTC, with the risk proved to be independent of other factors (fig. 5). These findings are in keeping with some[28,31] but not all[22,23,29,30,35] previous studies. The differing results probably depend on patient selection that may assume additional importance on the prediction of disease risk, retrieving the value given by previous studies to distant metastases. Although hereditary MTC is generally diagnosed, in younger patients, with initially localized disease, we had a patient with MEN 2A who presented with hepatic and bone metastases at the time of diagnosis. This woman was 58 years old, with stage T3N1b disease, and did fine after total thyroidectomy and three-compartment LND. She was alive after 19 months of follow-up, without local recurrence. Notably, it is important to recognize that prolonged survival is still possible with metastatic disease[22].

This study has assessed the prognostic importance of lymphatic and venous invasion in patients with MTC. The presence of lymphatic channel invasion is generally accepted as a marker of biologic aggressiveness on the metastatic process and is seen as a signal of eventual systemic dissemination[36]. Although we found out that venous invasion does not show statistically significance on univariate analysis, the presence of lymphatic vessel invasion turned out to be meaningful in predicting the outcome of the disease. The analysis of the survival curve showing the influence of lymphatic invasion in survival of MTC patients (fig. 6) reveals a sharp decrease in the OS after 32 months. It is reasonable to say that, in the near future, with the development of biotherapy, the identification of lymphatic invasion in patients with MTC could constitute an inclusion criterion to submit these patients to trials with new molecular targeted agents.

Another parameter assessed was adjuvant treatment, which, in our series, was a positive predictive factor. In agreement with one of the largest series[22], we found lower survival among patients receiving RT (fig. 7). In the absence of prospective randomized trials, the effective benefits of adjuvant treatments are not definitive, and several are under further investigation; moreover, associated mortality, morbidity, and late functional results are frequently underestimated[37,38]. We advocate the rationale of performing RT in patients with local disease that not manageable by surgical means.

In summary, we have shown that the presence of T4b tumours, distant metastases at the time of diagnosis, lymphatic vessel invasion, and postoperative treatment are probably the characteristics that allow us to best define the level of risk from the disease. Future studies of genetic profiling for prognosis and treatment will be essential in the development of new therapeutic strategies.

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