ORIGINAL ARTICLE

MEDULLARY THYROID CARCINOMA: PROGNOSTIC VARIABLES AND TUMOUR MARKERS AFFECTING SURVIVAL

Aamna Hassan, Maimoona Siddique*, Saima Riaz, Amina Iqbal Khan, Muhammad Khalid Nawaz*, Humayun Bashir

Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, *Pakistan Kidney and Liver Institute and Research Center, Lahore-Pakistan

Background Medullary thyroid carcinoma (MTC) is a relatively rare thyroid malignancy and its clinical course varies among patients due to its familial association. A number of prognostic factors have been studied, but the significance of these factors remains controversial. We evaluated the progression free survival (PFS) and overall survival (OS) of MTC and its association with tumour marker rising velocity and serum calcitonin (Ct) doubling time (DT). **Methods**: Analysis of 83 (8.7%) consecutive MTC patients registered at a single centre between 1995 and 2015. The impact of tumour respectability, TNM stage, multiple endocrine neoplasia (MEN) syndrome, local recurrence, Ct DT and Ct rising velocity on PFS and OS was analysed. Median follow-up was 4.3 years (range: 1–18 years). **Results**: Eighty-three (8.7%) of all thyroid cancers registered at our centre were MTC. Fifty-five males, 28 females. Mean age 39 years [range: 17–72 years]. Twenty-two were unresectable and 61 resectable. Five-year and 10-year OS was 84% and 77% respectively. Of 68 with follow up greater than a year; 20 (29.4%) were cured, 15 (22.1%) had biochemical evidence of disease, three (4.4%) had stable macroscopic disease and 30 (44.1%) had recurrent/progressive disease. Sixteen (23.5%) died. On multivariate analysis, T4 tumour, male gender, nodal and distant metastases, tumour resectibility, Ct DT less than two years and tumour marker rising velocity of greater than 0.05pg/ml/month were poor prognostic factors (*p*-value <0.05). Age and association with MEN syndrome had no statistically significant survival impact. Radiotherapy reduced local relapse in patients with nodal disease. Total thyroidectomy with nodal clearance lessened relapses. **Conclusion**: Clinical stage and pathological aspects are predictors of disease progression. Persistent biochemical evidence of MTC does not affect OS, however, Ct DT < 2 years and rapid rate of tumour marker rise predict disease progression.

Keywords: Medullary thyroid cancer; Calcitonin; CEA; Calcitonin doubling time; Multiple endocrine neoplasia; MEN

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INTRODUCTION

Medullary Carcinoma of Thyroid (MTC) accounts for 5–10% of all thyroid malignancies. It originates from parafollicular C cells which are part of the neuroendocrine system and secrete calcitonin (Ct), Carcinoembryonic Antigen (CEA) and chromogranins. These markers can be measured biochemically and immunohistochemically.[1]

The mainstay of treatment for MTC is adequate thyroid surgery and resection of cervical nodal disease. Radiotherapy may augment local control after surgery. The role of systemic treatment with curative intent after partial thyroidectomy is not well established.[2]

The essential diagnostic elements on follow up are neck ultrasonography and parallel measurement of Ct and CEA levels. A disproportionate increase of CEA levels as compared to Ct raises suspicion of poorly differentiated MTC.[3]

Medullary Carcinoma of Thyroid accounts for up to 13.4% of total thyroid cancer related deaths, with a 5-year survival of 78–91% and a 10-year survival of 40–75%. In patients presenting with advanced metastatic disease 10-year survival drops to 20%. The prognosis of MTC is worse than papillary and follicular thyroid cancers due to early spread and the lack of established effective systemic therapy.[4,5] Survival data on PTC and FTC in our population also shows a similar trend.[6,7]

Despite the relatively high survival rates, only 34–44% have untraceable Ct levels even after surgery and radiotherapy.[8,9] Elevated tumour markers can indicate disease much earlier than imaging-based localization of metastatic foci. The dynamics of Ct change can be assessed by calculating the time taken for Ct to double, the doubling time (DT). Studies by Giraudet *et al*[10], Gawlik *et al*[11] and a meta-analysis by Meijer *et al*[12] found that DT less than 2 years has a substantial prognostic influence on recurrence free survival.

Treatment for recurrent local or nodal MTC is resection or local irradiation. Early diagnosis of

loco-regional recurrence is the most important prognostic factor, allowing surgical resection before the appearance of distant metastases.[13]

Aims of our study were to determine a prognostic variable that predicts disease control and long-term survival and to study the influence of Ct rising velocity and Ct DT on PFS and OS.

MATERIAL AND METHODS

Retrospective review of electronic medical records of all patients with histological diagnosis of MTC between 1995 and 2015, registered at Shaukat Khanum Memorial Cancer Hospital and Research Center. Basic demographic data was evaluated for disease status and overall survival (OS). We analysed the association of several variables with PFS and OS; including gender, age at diagnosis, the histopathological findings, resectibility of the primary tumour, post-surgical Ct and CEA levels, the TNM stage, MTC as part of MEN Syndrome, treatment received at initial presentation and rate of rise of tumour markers. The minimum follow-up duration was one year. The study was approved by the institutional review board. As part of baseline staging work up, a non-contrast MRI scan of the neck was obtained in all patients to determine the resectibility of the primary tumour and for cervical nodal assessment. Unresectable tumour was defined as tumour directly invading into adjacent vascular, oesophageal or spinal structures. In case of suspicious cervical nodes, ultrasound guided fine needle aspiration (FNA) was performed to assess need for neck dissection. In patients who underwent partial surgical resections at outside hospitals, resectibility for completion thyroidectomy was also assessed by MRI scan. Contrast enhanced CT chest, abdomen and pelvis was performed to assess for MEN syndrome. During regular 6 monthly follow up, in case of serum tumour marker elevation; Ct and/or CEA, further imaging with CT scan, ultrasound or 18F-fluoro-2-deoxy-D-glucose positron emission tomography (18F-FDG PET/CT) was performed.

Each specimen received either after surgery at our hospital or as referred blocks from an outside hospital was reviewed by our expert histopathologists. Immunohistochemistry was done for Ct marker. Both plasma Ct and CEA levels were measured using Immulite 2000 instrument (Siemens kit), by chemiluminescent based technique. For Ct: detection limits were 5.0 pg/ml for females and 8.4 pg/ml for males; reference range was 2–2000 pg/ml. For CEA: sensitivity 0.15 ng/ml; reference range <5 ng/ml. Appropriate dilutions were prepared for concentrations more than 550 ng/ml of CEA.

Disease stage was depicted according to the American Joint Committee of cancer (AJCC) TNM staging system.[14] Briefly, T0 means no cancer; T1, tumour confined to the thyroid, ≤ 1 cm; T2, tumour confined to the thyroid, > 1 but ≤ 4 cm; T3, tumour confined to the thyroid, > 4 cm; T4, extra thyroidal invasion of the tumour. In addition, N0 means node negative; N1, node positive and M0 means no distant metastases; M1, distant metastases. Stage I disease corresponds to T1, stage II T2–4, stage III any TN1; stage IVA T4aN1bM0, stage IVB T4b, any NM0; stage IV C, any T, any NM1.

In some patients the histological specimen was received in fragments from outside hospital, and hence there was insufficient information regarding tumour size and TNM staging could not be documented.

All patients with radiologically resectable disease underwent total thyroidectomy. Referred patients with partial surgeries outside our hospital underwent completion thyroidectomy. Post-operative thyroxine was started to maintain a euthyroid state. External beam radiotherapy (XRT) was performed if significant remnant was documented in the thyroid bed and repeat surgery was not achievable. XRT was also delivered in cases of recurrent local or cervical nodal disease. In a few instances, chemotherapy was also delivered. Serum Ct dynamics were determined in all patients between 6 weeks to 6 months post thyroid surgery and thereafter on a 6 monthly to yearly basis. In patients with elevated Ct levels, the DT was calculated and used to stratify them into two groups; DT less than two years and DT greater than two years.

Ct rising velocity was calculated based on the following formula:

$$\text{Ct rising velocity} = \frac{\text{Ct at disease recurrence or progression} - \text{post surgical Ct}}{\text{Post-surgical Ct} \times \text{Time duration of rise (months)}}$$

At first postoperative visit and on subsequent six monthly follow up, the disease status was defined as:

1. Disease free - Ct below the upper limit of the laboratory reference range
2. Biochemical disease - persistently elevated Ct with no clinical or radiological evidence of disease
3. Recurrent disease - appearance of radiological or clinical disease with increase in Ct after normalization or stabilization of postsurgical Ct levels
4. Persistent disease - consistently elevated Ct levels and structural disease due to unresectable primary tumour or distant metastases at baseline.

Patients with persistent disease either had stable disease or progressive disease at new nodal or visceral sites and progressively rising tumour markers.[15,16]

At the end of the study period, disease outcome was categorized as alive without disease, alive with persistent disease or died due to disease. Percentiles and absolute

distributions were acquired for nominal variables. OS and PFS were visualized on Kaplan-Meier plots using SPSS-20. Difference between groups was evaluated through log-rank test of independence. Multivariate analysis was performed with Cox proportional hazards model using the enter mode. *P-value* <0.05 was considered to be statistically significant.

RESULTS

A total of 83 patients presented with MTC during the defined 20 years. This represented 8.7% of all thyroid cancer patients treated at our centre. There were 55 males (66%) and 28 (34%) were females. The mean age was 39 years [range: 17–72 years]. At baseline 61 (73.5%) were deemed resectable based on MRI neck findings and subsequently underwent thyroidectomy while 22 (26.5%) had unresectable disease due to gross vascular, oesophageal or spinal invasion on MRI scan. Of these, six had already undergone lobectomy at an outside hospital before being referred to our centre and the residual thyroid was unresectable. The remaining 16 with unresectable disease were not operated on. Twenty-six underwent unilateral or bilateral neck dissection and four had central neck compartment dissection.

TNM stage could not be determined in three (3.6%) due to incomplete histological information. Distant metastasis was present in 17 (20.5%) at baseline, out of which 15 progressed and six died. In our data 89% MTC were sporadic while 11% had associated familial MEN syndromes; seven had MEN IIA and two had MEN IIB. The details are in table-1.

Fifteen patients were lost to follow up within a year of diagnosis and were excluded from prognostic factor analysis. Of the remaining 68 with a median follow up of 4.3 years (range: 1–18 years), 20 remained disease free post-operatively (alive without disease) till the end of the study.

The 48 patients who had evidence of disease at initial follow up were classified as follows:

Fifteen had biochemical disease; all remained alive with disease. Fifteen had recurrent disease; eight died due to disease, five were alive with disease and two were lost to follow up. The median duration of development of radiologically detectable disease was one year (range: 2 months–8.5 years). Eighteen had persistent disease; three had stable macroscopic disease and 15 had progressive disease. At the end of follow up five were alive with disease, eight died due to disease and five were lost to follow up. Overall, 16 patients (23.5 %) died due to disease during follow up. Those who died of disease lived for an average of 5.7 years (range: 1–16 years) after diagnosis. At last follow up, the current status is unknown in 25 of 83. 5-year and 10-year OS of the remaining 58 patients was 84% and 77% respectively. Figure 1 shows disease status in relation to various stages of MTC. Serum Ct and CEA levels, done within six weeks to six months after total thyroidectomy, remained normal in 20. In the remaining 48 either Ct or CEA or both were elevated. Baseline Ct level was missing in three, CEA was available in 41. Tumour marker details are in table 2.

Of 30 with recurrent/progressive MTC, Ct level at the time of disease progression was not available in seven. In the remaining 23, serum Ct doubled in less than two years (median 1627; range: 80–128238 pg/ml) in 17; of which nine (53%) died over a mean duration of 6.3 years (1–16 years). Six with Ct DT >2 years are alive. In 53 of 68 the primary thyroid tumour was resectable. Forty-eight underwent total thyroidectomy and five had subtotal thyroidectomies prior to coming to our hospital. Seven patients with total thyroidectomy and one patient with sub-total thyroidectomy developed recurrence. Radiation therapy was given to 15 with irresectable thyroid and an additional eight received XRT to sites of recurrence. Of these, 12 died due to progressive disease. In total 12 with progressive disease were given chemotherapy; (Doxorubicin, decarbazine and capecitabine) of which three died and six were lost to follow up within one year of diagnosis. One patient was given radionuclide octreotide therapy and died due to progressive MTC disease with an overall survival period of 10.5 years.

Clinical and pathological variables were correlated with the patient disease status: disease free or with disease recurrence/progression. Male gender, TNM stage I-III, resectable disease, N0M0 disease at baseline, nodal dissection for cervical metastasis and normal postsurgical tumour marker levels were associated with a significantly better PFS and OS. (Figure-2 shows survival details.) Age had no statistically significant impact on PFS and OS of patients. Patients with post-surgical Ct greater than 50 pg/ml, CEA level greater than 100 ng/ml; Ct rising velocity greater than 0.05 pg/ml/month, Ct DT less than 2 years and extra thyroidal extension of tumour had poor PFS and OS (Details of *p*-values in table-3). Although three out of five MTC with MEN syndrome had progressive disease leading to death in one, no statistically significant difference in OS or PFS was seen.

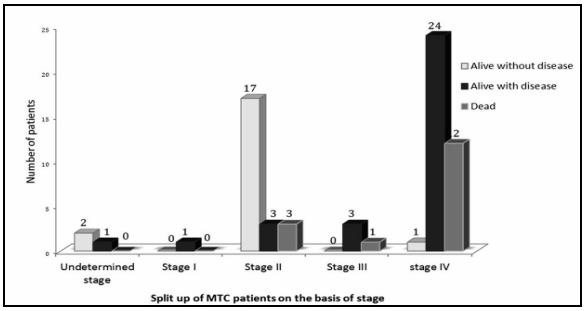

Figure-1: Various stages of MTC patients in relation to disease status

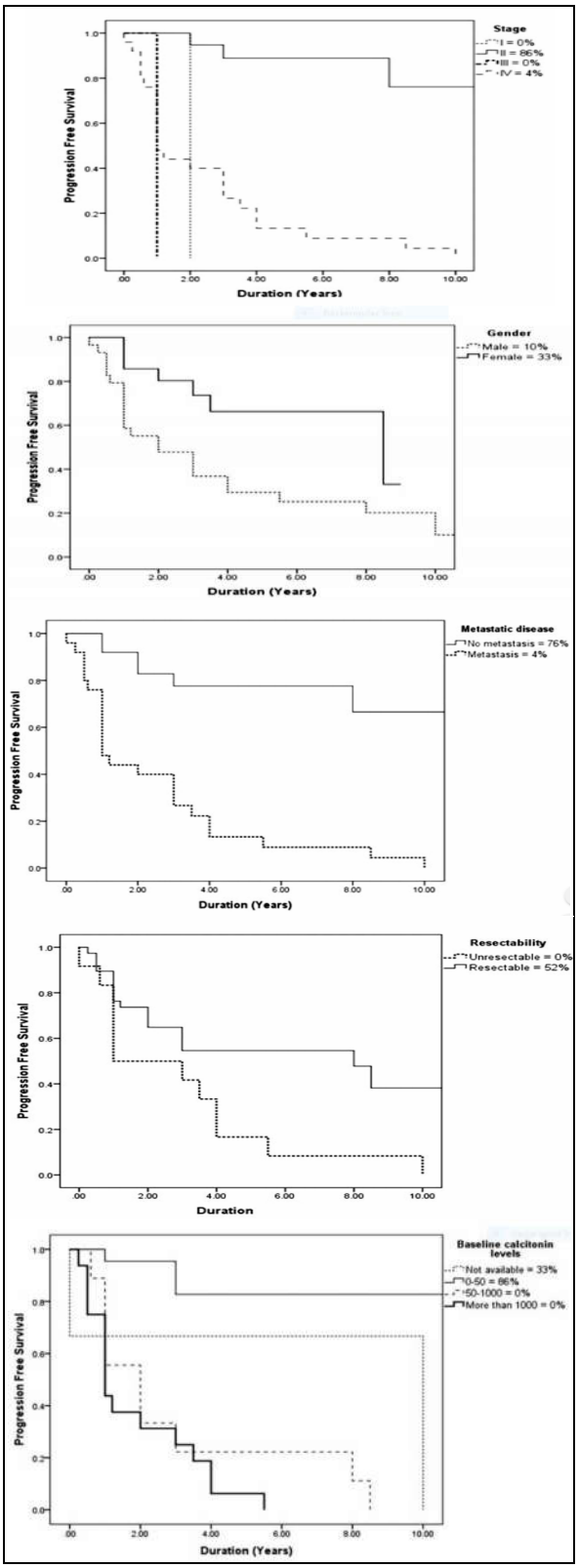

Figure-2: Kaplan-Meier curves displaying the 5-year and 10-year PFS of MTC cases in relation to TNM stage, gender, resectability, metastases and baseline calcitonin levels

Table-1: Clinical and pathological characteristics of 83 MTC patients

Characteristic	n	%
Male	55	66
Female	28	34
Age at diagnosis (years)		
≤40	49	59
>40	34	41
Sporadic MTC	74	89
MEN II associated MTC	9	11
Primary surgical resection		
Total thyroidectomy	61	73.5
Lobectomy/no thyroid surgery	22	26.5
Pathological TNM staging		
Undetermined	3	3.6
I	1	1.2
II	25	30.2
III	6	7.2
IV A	27	32.5
IV B	4	4.8
IV C	17	20.5

Table-2: Serum tumor markers – Ct and CEA in relation to MTC disease status

Tumor markers	Biochemical disease	Recurrent disease	Persistent progressive	Persistent stable diseases
Serum Ct median (range: pg/ml)	253 (12–1747)	513 (28–3913)	1308 (123–34122)	2000 (1208–18670)
CEA median (range: ng/ml)	28.8 (4.9–145)	112 (22–969)	196 (17.7–2228)	665 (523–807)

Table-3: Evaluation of Clinico-pathological variables as risk factors for PFS and OS

Variable	*p*-value for PFS	*p*-value for OS
Male vs. female	0.009	0.05
Age (years) >40 vs.<40	0.79	0.10
TNM stage: I-III vs. IVA/IVB/IVC	<0.001	0.01
Resectable vs. unresectable tumor	0.015	0.77
Metastases N_0M_0 vs. N_1/M_1	<0.001	0.001
Nodal dissection	0.006	0.04
Extra-thyroidal extension - T4 tumor	0.02	0.69
Post-surgical Ct level	<0.001	0.002
Post-surgical CEA level	0.009	0.13
Ct rising velocity >0.05 pg/ml/month	<0.001	0.002
Ct DT < 2 years	<0.001	0.001
Presence of MEN syndrome	0.85	0.84

DISCUSSION

The biological and clinical behaviour of MTC remains a predicament, making the prediction of OS difficult. Although some patients with advanced metastatic disease at the time of presentation have an extended event-free disease course, others die due to progressive disease within a short period of time.[17] Using the AJCC/UICC staging, Kloos *et al*[18] report a 5-year survival close to 100% in stage I, 93% in stage II, 71% in stage III and 21% in stage IV. In our study, the 5-year survival was 100% in stage I, 88% in stage II, 75% in stage III and 67.5% in stage IV. Our OS is 84%, compared to 51–79% cited in literature.[9,16,17,19,20]

Medullary Carcinoma of Thyroid is characterized by relatively slow tumour growth with

early nodal spread; modified central neck dissection is suggested for N1 disease. Due to high morbidity and lack of impact on long term survival, radical neck dissection is not routinely recommended unless there is vascular or skeletal muscular invasion.[17,21,22] In a study population of 32 cases, Rendal G. *et al*[23] found that out of 12 cases with nodal disease, concurrent hepatic and osseous metastasis was seen in 33-50% cases, with less frequent pulmonary and cerebral involvement (16%). In current study, out of 56% cases with nodal involvement at initial staging, concurrent osseous metastasis was seen in 16% with lesser frequency of visceral (hepatic, pulmonary and very rarely brain) involvement.

In our study, unresectable disease with extra-thyroidal extension and the presence of metastases at presentation were predictors of recurrence and progression. Stage III and IV disease had the greatest likelihood of detectable recurrence and persistence of disease. Total thyroidectomy improved OS even in advanced disease while nodal dissection carried a better PFS but not OS. M1 disease was associated with a higher mortality, which is comparable to other studies.[10,16,17,19,20]

Several studies[8,9,16,17] have concluded that age and sex has no statistically significant impact on survival, while some others[4,19,20] emphasized that age does have a significant impact on OS and disease specific survival. In our study, males had more aggressive disease with reduced PFS, however age at diagnosis had no statistically significant bearing on PFS or OS.

Regarding serum tumour marker dynamics, it has been suggested that serum Ct level of 1000 pg/ml (100 times the upper limit) is indicative of at least 1 ml of tumour tissue and persistent hypercalcitoninemia, 8–12 weeks post-operatively, is indicative of occult MTC. Ct may remain stable at an elevated level or it may rise rapidly [10]. It is unknown whether it adversely affects life expectancy since many MTC patients have a prolonged event free survival. Contrary to De Groot J. *et al*[9] and Bergholm *et al*[24] findings, elevated post-operative Ct in our study predicted poor survival. Postoperative Ct >50 pg/ml, Ct DT of less than or equal to two years and/or rising serum Ct velocity of greater than 0.05 pg/ml/month had significantly shorter PFS and OS. Pelligriti *et al*[25] and Clark *et al*[26] also found that postoperative Ct level and tumour stage were independent variables for finding detectable relapse.

In 2011 FDA approved Vandetanib for use in MTC patients. In our data only one patient with locally advanced, metastatic disease received Vandetanib for three months after which it was stopped due to intolerable side effects. The patients OS was 8 months. Interestingly our study had a low incidence of MEN associated familial MTC; the type of MTC whether sporadic or familial did not affect OS and PFS. However, no formal data on the incident number of MEN associated MTC exists for comparison in our population.

Limitations include retrospectively gathered data. Prospective studies however are not practical due to the long disease course of MTC and its relatively long-life expectancy. This study spanned two decades of data and treatment of MTC has evolved over this time period. Initially most patients received chemotherapy but over the last decade it was seldom used since there is not enough evidence to support the indiscriminate use of chemotherapy.

Ct and CEA measurements though available for most, were not available for some patient whose compliance with follow up visits was not constant.

In recent year due to high patient volume, the acceptance of patients with grossly invasive primary thyroid tumour into surrounding structures was restricted at our centre. Although this limited the overall number of patients with unresectable disease, there was still a significant number to allow for meaningful comparisons.

CONCLUSION

Clinical stage and pathological aspects of MTC are predictors of disease progression. Persistent biochemical evidence does not affect OS, however, Ct DT of less than 2 years and rapid tumour marker rise predict disease progression.

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AUTHORS' CONTRIBUTION

AH: Concept, data analysis, literature review, manuscript drafting, review and approval. MS: Concept, data collection, literature review, manuscript drafting and approval. SR: Concept, data analysis. AIK: Concept, manuscript approval. MKN: Concept, manuscript approval. HB: Concept, manuscript review and approval

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Address for Correspondence:

Aamna Hassan, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore-Pakistan
Email: aamnah@skm.org.pk