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Original Research

Oncological Outcome and Treatment Options of Medullary Thyroid Cancers: Experience at a Tertiary Cancer Centre

Raveena R Nair	Department of Surgical Oncology, Malabar Cancer Centre, Kerala, India.
Anoop Attakkil	Department of Surgical Oncology, Malabar Cancer Centre, Kerala, India.
Sandeep Vijay	Department of Surgical Oncology, Malabar Cancer Centre, Kerala, India.
Linu Thomas	Department of Surgical Oncology, Malabar Cancer Centre, Kerala, India.
Sajith Babu Thavarool	Department of Surgical Oncology, Malabar Cancer Centre, Kerala, India.

Introduction: Medullary thyroid carcinoma (MTC) is a rare type of thyroid cancer and the main treatment is surgery. The extent of surgery depends on the spread of tumour and often involves thyroidectomy and neck dissection. Recurrent or metastasis tumour can be detected with raising calcitoninand there are various options of treatment.

Methods: This was a retrospective study of MTC over seven years in a tertiary cancer centre which evaluated the treatment outcome and the non-surgical options available in recurrent and metastatic tumours.

Results: Among the 601 thyroid cancers, 34 patients (5.3%) were MTC, of which 29 were studied. Majority were women, below 60 years, were diagnosed with fine needle aspiration cytology of thyroid nodule or nodes and had raised calcitonin value (Ctn). The value of Ctn was correlated with tumour burden rather than extent (p=0.7). Recurrence was seen in 35% and all patients with locoregional recurrence had curative surgery whereas metastatic patients were offered palliative treatment. Acceptance of palliative treatment was less due to financial burden. The five year overall survival for nonmetastatic disease was 89.4 % and for patients with metastatic disease at presentation was 54.7 %.

Conclusion: The incidence of medullary thyroid carcinoma is low compared to the differentiated thyroid carcinoma. The main treatment is surgery and other treatment options are limited.

Introduction

Medullary thyroid carcinoma (MTC) is a rare type of thyroid cancer, which arises from the parafollicular cells and is regarded as a neuroendocrine neoplasm [1]. It occurs as a sporadic tumour in about 75%–80% patients and as a hereditary tumour in others [2]. The commonest presentation of MTC is a painless swelling in the thyroid gland. Less commonly, the patient may present with pain, dysphagia or hoarseness due to extension into the surrounding structures [3]. Cervical lymph node metastasis is common in MTC and seen in up to 75% of patients [4].

Serum calcitonin (Ctn) level is a highly sensitive and specific tumour marker for MTC and is raised

in almost all patients. The serum Ctn levels are positively correlated with the tumour spread and also predicts the lymph node extension [5, 6].

The treatment of non-metastatic MTC is total thyroidectomy with or without neck dissection [7] whereas for patients with metastatic disease it is palliative treatment with radiotherapy or systemic therapy [8]. There are various systemic treatment options like tyrosine kinase inhibitors (TKI) [9, 10].

Materials and Methods

This study was a retrospective analysis of patients who were diagnosed with medullary thyroid carcinoma from 2010 to 2017 in tertiary care cancer centre.Institutional ethics committee approval was obtained for this study.

Demographic details, clinical findings, radiologic assessment, staging, details of primary modality of treatment, follow up details are routinely recorded in the case files and were retrieved from them. Data were entered into EpiDataEntry software version v4.6.0.2 and statistical analysis was done using EpiData Analysis software v3.0.0.1 (EpiData Odense, Denmark). Means, median and standard deviations were used for descriptive statistics. Chi square test was used for comparing significance between categorical variables and Kruskal- Wallis H test was used for comparing continuous with categorical variables. For survival analysis, Kaplan–Meier method was used.

Results

There were 601 patients diagnosed with thyroid cancer during the study period from January 2010 to December 2017, out of which 34 patients had MTC accounting to 5.3% of the total thyroid cancers. Of this, 29 patients were selected for the study after excluding patients who had discordant diagnosis after the postoperative histopathology examination (twopatients) andlost to follow up before treatment (three patients).

The demographic details of patients are given in Table 1.

Variables	Number	Percentage (%)
Age group		
<30 years	03	10.3
30-60 years	21	72.4
>60 years	05	17.2
Gender		
Male	10	34.4
Female	19	65.1
Stage		
Stage 1	02	6.8
Stage 2	03	10.3
Stage 3	06	20.6
Stage 4A	11	37.9
Stage 4B	00	0
Stage 4C	07	24.1
Disease at presentation		
Localised	22	75.8
Metastaic	07	24.1
Type of Surgery		

No surgery	07	
Total thyroidectomy	06	28.5
Total thyroidectomy + CND	01	0.05
Total thyroidectomy + CND+ U/L ND	01	0.05
Total thyroidectomy + CND+ B/L ND	13	61.9
Initial surgery		
At our institution	17	77.2
At another institution	05	22.7

Table 1. Demographic Details of Patients with Medullary Thyroid Carcinoma Diagnosed During January 2010 to December 2017.

CND, Central Neck Dissection; U/L, Unilateral; ND, Neck Dissection; B/Bilateral

Among the 29 patients with MTC, the mean age was 48.3 years (SD+/-12.0), majority were below 60 years (82.7%) and 19 (65.1%) were women. Aspiration cytology was diagnostic of MTC in 24 patients whereasfive patients underwent thyroidectomy and post op histopathology revealed MTC. Calcitonin was elevated in 24 patientswho had preoperative testing and five patients who presented post thyroidectomy did not have baseline calcitonin value. At initial presentation there were 22 patients with loco regional disease and seven patients with distant metastasis. Majority of the patients (37.9%) presented in stage IVB (AJCC 8^{th} edition) and there were 24 (82.7%) patients with thyroid nodule withlymph nodemetastasis at presentation. Calcitonin level less than 500 pg/ml was seen in 16 non metastatic patients and five metastatic patients and more than 500 pg/ml, in six non metastatic patients and two patients with distant metastasis (p =0.49). The correlation between calcitonin value and the extent of disease was tested using Kruskal- Wallis H test and nosignificant correlation was found (p = 0.70).

All 22 patients with locoregional disease were treated with curative intent surgery (details are given in Table 2).

Patient ID	Age	Metastasis Site	Treatment offered	Treatment Taken	Follow Up	Survival
Patient 1	29	Bone	TKI/EBRT	EBRT	66 months	Expired
Patient 2	76	Lung	EBRT	Not taken	20 months	Expired
Patient 3	59	Bone (frontal)	WBRT	WBRT	05 months	Expired
Patient 4	65	Lung	EBRT	Not taken	14 months	Expired
Patient 5	50	Liver & Bone	BSC	BSC	09 months	Expired
Patient 6	50	Lung	EBRT/TKI	Not taken	36 months	Alive
Patient 7	49	Lung	BSC/TKI	TKI (sorafenib)	24 months	Expired

Table 2. Treatment Details of Patients with Metastatic Medullary Thyroid Carcinoma at Initial Presentation.

TKI, Tyrosine linase inhibitor; EBRT, External beam Radiotherapy; BSC, Best supportive care

Total thyroidectomy alone was done in one patient, total thyroidectomy with central neck dissection was done in four patients and total thyroidectomy with central and lateral neck was done in 17 patients.

Of the seven patients who had distant metastasis at initial presentation, four patientshad pulmonarymetastasis, two had bone metastasis and one patient had both liver and bone metastasis. Surgery was not done for any of the metastatic lesions. Palliative radiotherapy was given to two patients with bone metastasis for symptom relief and was achieved for three months until progression. Vandetanib was suggestedto three patients with metastatic disease but none could

afford the treatment and hence Sorafenib was given.

Recurrence was seen in seven (35%) patients among which all were detected with rising calcitonin, and further confirmed with imaging.Among the patients detected with recurrence, four had locoregional recurrence whereas the rest developed distant metastasis. Curative intent surgery was done in three of the four locoregional recurrent patients. One patient with large supraclavicular node was not operated and was given palliative radiotherapy and sorafenib. Palliative intent treatment was given in four patients (Table 3).

Patient ID	Age	Type of recurrence	Site of recurrence	Treatment for recurrence	Survival
Patient 1	50	Distant	Lung & Liver	BSC	Alive
Patient 2	39	Nodal	Level VI	Surgery	Alive
Patient 3	44	Distant	Lung & Bone	EBRT	Alive
Patient 4	55	Nodal	Supraclavicular	TKI (Sorafenib)	Expired
Patient 5	45	Nodal	Level III & IV	Surgery	Alive
Patient 6	44	Nodal	Level IV	Surgery	Alive
Patient 7	60	Distant	Lung	BSC	Alive

Table 3. Treatment Details of Patients with Recurrence Post Surgery For Metastatic Medullary Thyroid Carcinoma.

TKI, Tyrosine linase inhibitor; EBRT, External beam Radiotherapy; BSC, Best supportive care

In total, there were 14 patients with metastasis or recurrent disease, of which three had curative surgery. All the other eleven patients were offered vandetinib as palliative treatment option but none took this treatment. The median follow-up of the whole group was 51.7 months. The five-year overall survival of the whole group was 75 %, for the patients with nonmetastatic disease it was 89.4 % and for the patients with metastatic disease at presentation it was 54.7 %.

Discussion

In this retrospective review of medullary carcinoma of thyroid in a tertiary cancer centre, the incidence was found to be low (5.3%). The standard treatment gives good outcomes in patients with curative intent of treatment in non-metastatic operable patients (89.4% five-year survival).The outcome of metastatic or recurrent disease with palliative treatment is less (54.7 % five-yearoverall survival) though it is a better survival compared to the patients with palliative treatment in other sites of head and neck region. The unavailability of the newer treatment options in the country and the financial burden are hurdles to the treatment of recurrent or metastatic patients.

Though the incidence of thyroid cancers are high in Indian subcontinent [11, 12] the majority are differentiated thyroid cancers (82%) [13, 14]. The incidence of medullary carcinoma is 1-2 % among all the thyroid cancers in the literature [15, 16]. The reported data from India shows that the incidence is 3-5%, which is similar to our study (5.3%) [11].

The commonest presentation is with thyroid nodule followed by neck nodes and rarely metastatic symptoms [4]. The presence of neck nodal metastasis is reported usually in 75 % of patients as in our study (75.8%) which shows that local spread is an early presentation. But this has not caused a decrease in survival if treated adequately with surgery [7]. The addition of neck dissection along with thyroidectomy is the treatment of choice in these patients [17-19].

In our study, the correlation of calcitonin value was seen more with disease burden rather than the tumour spread (p=0.70). Bulky swelling in thyroid or multiple nodes in the neck had higher

calcitonin values even ranging to thousands whereas limited disease had calcitonin value less than hundred. Though the chance of calcitonin value rising increases with metastasis to neck nodes and or distant metastasis, it is not absolutely necessary. This finding was seen in our group of patients with localised bulky tumours having higher calcitonin values more than thousand and few metastatic tumours having value less than 500. This finding is contrary to the findings of Park H et al where they found that the level of calcitonin is predictive of spread into the lymph nodes.

The main treatment of MTC is surgery, which includes thyroidectomy and neck dissection [16]. A thorough surgical clearance of the nodal stations reduces the postoperative calcitonin to low levels which has prognostic significance. Neck dissection is done for the presence of suspicious nodes in neck or prophylacticallyfor patients with bulky thyroid nodules or with high calcitonin value. The size of thyroid nodule or the cut off value for calcitonin for prophylactic neck dissection is varying in literature [20-22].

The role of surgery in metastatic disease is mainly palliative thyroidectomy to prevent future airway compromise [19]. Other treatments offered for metastasis patients are palliative radiotherapy and chemo/ immunotherapy. Radiotherapy has been useful for symptomatic control in bone metastasis and inoperable neck diseases. Postoperative adjuvant radiotherapy to the neck and mediastinum is considered in patients at high risk for local recurrence (residual MTC, extrathyroidal extension, or extensive lymph node metastases) [8, 23]. Three patients in our cohort were given adjuvant radiotherapy forextra nodalextension and extensive lymph nodemetastasis even though there are no strong evidence or prospective trials comparing radiotherapy to observation alone.

Conventional chemotherapy has been found to have a lesser role in metastatic or recurrent inoperable medullary carcinoma with low response rate and no survival benefit. Promising results have been reported with treatmentusingmolecular agents inhibiting targets like the rearranged during transfection (RET) and several multikinase inhibitors (MKI) [9].The intracellular signalling pathways triggered by RET includes the RAS-RAF-MEK-ERK and the PI3K-AKT-mTOR pathways, which are potential targets. Different tyrosine kinase receptors are activated in MTC and hence tyrosine kinase inhibitors(TKIs) have been used in the management of MTC [24]. Vandetanib [10] and cabozantinib [9] have been approved for use in advanced and progressive MTC. They inhibit the RET and VEGFR pathways.

In a recent systemic review and meta-analysis by Zoe A Efstathiadou et al. Vandetanib is not available in India and cabozantinib is currently expensive treatment option. There is no level 2 evidence for sorafenib [25] but due to the easy availability and cost majority of the patients have been offered this treatment.

In conclusion, the incidence of medullary carcinoma is low and its survival is better compared to other head and neck malignancies after treatment. Preoperative calcitonin is not indicative of site of disease extension, but the tumour burden. Surgery is the only curative treatment option and no other treatments are available at the current time. Though there are chemo/immuno therapeutic options available with some evidence on its use in recurrent or metastatic tumours, these drugs have restricted use due to high cost and availability.

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Statement of Transparency and Principals:

· Author declares no conflict of interest

· Study was approved by Research Ethic Committee of author affiliated Institute.

· Study’s data is available upon a reasonable request.

· All authors have contributed to implementation of this research.

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