ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 05 | May - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

CLINICAL PRESENTATION AND ONCOLOGICAL OUTCOME OF MEDULLARY THYROID CARCINOMA: OUR 11 YEARS EXPERIENCE

Oncology

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ABSTRACT

Medullary thyroid cancer is neuroendocrine tumour arising from parafollicular C cells. Medullary thyroid carcinoma (MTC) is less common cancer of thyroid gland. It accounts for 3-5% of total thyroid cancer. Here we have done retrospective analysis of all cases of medullary thyroid carcinoma in terms of clinical presentation, pathology, surgical management, adjuvant therapy and subsequent survival. Our study shows the incidence of MTC out of all thyroid cancer is 4.06 % Median overall survival [OS] in absence of nodal and distant metastasis was found to 55 months (95% C.I. 43.260-66.740). Neck nodal metastasis was found statistically significant with overall survival. Median overall survival was found to be 39 months (95% C.I. 34.752-43.248, p value <.0001) in presence of nodal metastasis. Distant metastasis at presentation was found to be statistically significant when compared with overall survival. Median overall survival (OS) in presence of metastatic disease is found 28 months (95 % C.I 18.524-37.476, p value <.0001).This article will highlight the clinical presentation and oncological outcome of patients in Indian subcontinent.

KEYWORDS

Medullary Thyroid Carcinoma, Calcitonin, Ret Protooncogene.

INTRODUCTION

Medullary thyroid carcinoma (MTC) is less common cancer of thyroid gland. It accounts for 3-5% of total thyroid cancer. MTC arises from parafollicular C cells which are neural crest in origin. Hence it is considered as a neuroendocrine tumour and it secretes a variety of substances including calcitonin, vasointestinal peptides and serotonin. Parafollicular C cells are usually found at junction of upper one third and lower two third where most of MTC are found. Clinically MTC are presented as firm to hard, well encapsulated tumours. MTC can occur in form of sporadic and familial forms. MTC occurs as sporadic cases in about 75 % of patients and familial cases are found to be associated in about 25 % of patients Sporadic MTC are usually unilateral thyroid swelling whereas Familial MTC is multicentric. Familial MTC are associated with autosomal dominant germ line mutation of RET protooncogene which is located on chromosome no. 10. RET protooncogene codes for tyrosine kinase and its mutation in exon 10 to 16 leads to tyrosine kinase activation [1]. Multiple endocrine neoplasia (MEN) type II syndrome is most commonly associated with familial MTC accounting for almost 75 % of cases [2]. In small fractions of patients it may be associated with pheochromocytoma (50%) and parathyroid hyperplasia/ adenoma formation (20%–30%). MTC remain confined to thyroid gland for variable time then it spreads to regional lymph nodes followed by liver, lungs, bones and brain. Diagnosis is based on fine needle aspiration cytology (FNAC) [3]. Serum Calcitonin is a reliable tumour marker which has diagnostic as well as prognostic significance. Surgery is main stay of treatment as no other curative modality of treatment is available.

Here we would like to have retrospective analysis of all cases of medullary thyroid carcinoma in terms of clinical presentation, pathology, surgical management, adjuvant therapy and subsequent survival. This article will highlight the clinical presentation and oncological outcome of patients in Indian subcontinent.

MATERIAL AND METHODS

This study involves all patients of MTC who were presented during year January 2008 to December 2018 at our institute. Total 2389 patients of thyroid cancer were reported during this time period out of which 97 patients were diagnosed of MTC. Data was accessed through hospital information system and patients were followed up to December 2019. Facility of RET protooncogene is not available at our institute hence it was not done. Detailed family history is taken. Preoperative data is collected for age, gender, initial presentation and biochemical markers like serum Calcitonin, CEA, PTH, Urinary VMA and plasma free metanephrins. Diagnosis was based on either FNAC or review of slides and blocks if FNAC or surgery is done out of the institute. Details of surgeries performed outside were obtained from their operative notes and discharge cards. Final pathology details were collected for size and site of tumour, capsular infiltration, PNI, LVI, extrathyroidal invasion and lymph node status. Then on follow up serial serum calcitonin level were monitored. Disease free survival is calculated from surgery to recurrence or metastasis and overall survival is calculated from diagnosis to death or to last follow up date. Data is analyzed with SPSS system.

RESULTS

Our study shows the incidence of MTC out of all thyroid cancer is 4.06 % (97/2389). Out of total 97 patients 48 pts were male and 49 pts were females. Mean age of presentation is 42.86 years with range of 20 to 75 years. Total 50 patients (51.5%) were initially presented as thyroid swelling whereas 27 patients (27.8%) presented with both thyroid swelling and lateral neck nodes. 29 patients (29.9%) were operated outside of the institute, out of which 6 patients were planned for completion surgery. Total 21 patients (21.6 %) were initially presented with systemic metastasis [table no.1]. Most common site of metastasis in our study was Lung (8 patients) followed by Liver (5 patients) and Bones (4 patients). There were 4 patients which were presented with lung, liver and bony metastasis simultaneously. Two patients were presented with very advanced disease and stridor. Out of 97 patients 2 patients were found to have hyperparathyroidism and only presentation was renal calculi and renal osteodystrophy. FNAC was found to be diagnostic in 66 (68.04%) patients out of 97 patients. Surgery is offered in 53 patients at our institute. Serum calcitonin levels are compared with postoperative level by scatter plot [Figure no.1]. Survival is calculated using Kaplan-Meier curves. Median overall survival [OS] in absence of nodal and distant metastasis was found to 55 months (95% C.I. 43.260-66.740). Neck nodal metastasis was found statistically significant with overall survival. Median overall survival was found to be 39 months (95% C.I. 34.752-43.248, p value <.0001) in presence of nodal metastasis [Figure 2]. Distant metastasis at presentation was found to be statistically significant when compared with overall survival [Figure 3]. Median overall survival (OS) in presence of metastatic disease is found 28 months (95 % C.I 18.524-37.476, p value <.0001). On routine follow up serial Calcitonin monitoring was done in 62 patients. Out of these 22 patients developed metastasis on follow up. Most commonly developed lung metastasis in 13 patients, liver in 6 patients and multiple organ metastases is observed in 4 patients.

Presentation	No.of Patients	Percentage of patients
Thyroid swelling	50	51.5
Thyroid swelling + Nodes	27	27.8
Post Surgery	29	29.9
Systemic Metastasis	21	21.64
Stridor	2	2.06
Symptoms of Hyperparathyroidism	2	2.06

Table no. 1 showing clinical presentation of medullary thyroid carcinoma.

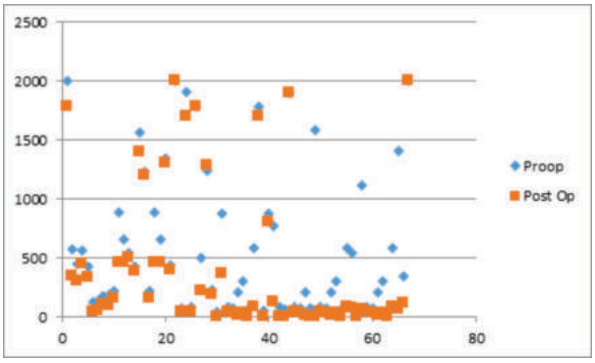

Figure 1 showing scatter plot with comparing pre and post op Calcitonin values

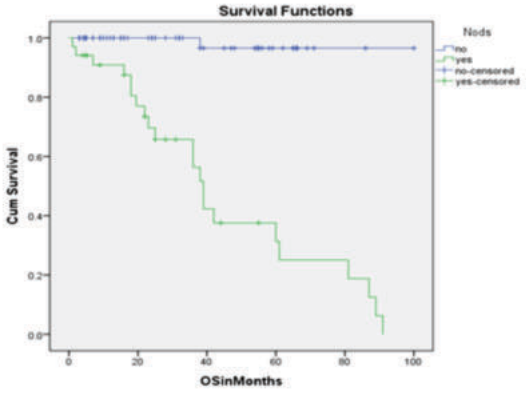

Figure 2 showing statistically significant impact of nodal metastases on OS.

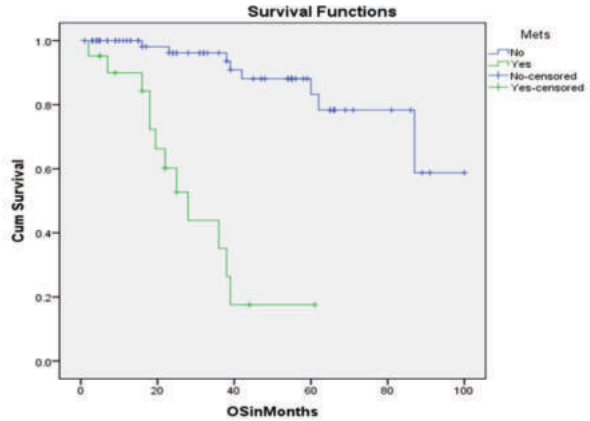

Figure 3. Showing statistically significant impact of distant metastases on OS.

DISCUSSION

Medullary thyroid cancer is neuroendocrine tumour arising from parafollicular C cells. These cells are neural crest in origin and concentrated at junction of upper one third and lower two third of thyroid gland. So it is the most common site where MTC develops. Parafollicular C cells can secrete variety of peptides and hormones including Calcitonin, Carcinoembryonic antigen, ACTH, synaptophysin, vasointestinal peptides, calcitonin gene related peptides etc. C cells are polygonal or spindle shaped cells which on IHC demonstrate staining for calcitonin, chromogranin, cytokeratin and CEA. MTC occurs most commonly in a sporadic form and it occurs less commonly as an autosomal dominant inherited disorder such as MEN2A, MEN2B, and familial medullary thyroid carcinoma (FMTC) [4].

Clinical presentation

Sporadic MTC are usually presented in 5th-6th decade of life with slight more in female patients**.** MEN2A and FMTC are usually presented in 3rd decade of life and MEN 2B are usually presented in less than 20 years of age. A patient with a sporadic MTC typically presents with palpable thyroid swelling with or without nodal mass. These tumours are usually solitary unilateral and can result in dysphagia, change in voice and upper airway obstruction like stridor. Increased level of Calcitonin can result in diarrhea, weight loss and flushing. About 10-15 % may presents with systemic metastasis most commonly to liver and lung. MTC associated with MEN 2 syndrome are usually presented with multicentric and bilateral disease. Clinically they may present with diarrhea, flushing and weight loss due to excess release of Calcitonin. They can be found associated with other diseases like pheochromocytoma, hyperparathyroidism or Cushing's syndrome. The diagnosis of MTC should be excluded for any patient who develops a thyroid nodule and/or elevated Calcitonin and/or CEA levels in the setting of FMTC or MEN disease [5].

Diagnosis

Diagnostic evaluation of MTC is dependent on radiological, pathological, biochemical and genetic evaluation. Ultrasound neck is the first initial investigation of choice to evaluate thyroid nodule. According to American Thyroid Association any thyroid nodule which on ultrasound shows solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule *with* one or more of the following features like irregular margins (infiltrative, microlobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of extrathyroidal extension has more than 70-90 % estimated risk of malignancy [6]. However, these features do not distinguish MTC from differentiated thyroid cancers Ultrasound is also useful to identify metastases in the central or lateral neck compartments. An abnormally round shape, loss of fatty hilum, blurred capsule, microcalcification and increased vascularity are features of metastatic lymph nodes [7]. Cross-sectional imaging with CT or magnetic resonance (MR) imaging is indicated only if there is clinical evidence of local invasion or to identify upper mediastinal and retropharyngeal nodes. Additional imaging with CT of the chest and abdomen (for liver metastases), radionuclide bone scanning (for skeletal metastases), Magnetic resonance imaging of the brain (for brain metastases), or fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT (for whole-body imaging) may be considered if distant metastases are suspected or the calcitonin level is >150 pg/ mL. The sensitivity of the FDG PET/CT examination for systemic staging is >70% if the calcitonin level is >1,000 pg/mL [8] Pathological confirmed diagnosis is based on Fine needle aspiration cytology (FNAC).Tumour typically composed of epitheloid and spindle cells. Tumour stroma usually has endocrine amyloid. IHC demonstrate staining for Calcitonin, chromogranin, cytokeratin and CEA.

Calcitonin and CEA are the most relevant tumor markers in patients with MTC, because their serum concentrations are known to be directly related to the C-cell mass. Serum calcitonin level may correlate with disease status but this not remains always true. Nodal and distant metastasis can cause serum calcitonin level in range of 10-40 pg/ml and 150 pg/ml to > 1000 pg/ml respectively [9]. CEA is found to be elevated in about 50 % patients of MTC.

A preoperative level more than 30 ng/ml is associated with poor prognosis [8]. ATA guidelines for MTC recommend that all patients with MTC should be offered germline RET-protooncogene testing and if it is identified all at-risk family members should be offered a prophylactic thyroidectomy prior to the development of MTC. They should undergo periodic screening for MTC with neck U/S and serum calcitonin levels, screening for pheochromocytoma should be done by measurement of plasma or 24-hour urine metanephrines and normetanephrines, and hyperparathyroidism should be screened with albumin-corrected calcium or ionized calcium and parathyroid hormone levels [10].

Treatment

MTC arises from parafollicular cells which do not concentrate iodine which make it not amenable to radioactive iodine therapy. These tumours do not respond to conventional cytotoxic therapy. Hence surgery remains standard of care. All patients should undergo fiberoptic laryngoscopy or mirror indirect laryngoscopy to asses vocal cord mobility. Surgery involves Total thyroidectomy with bilateral central compartment lymphnode dissection. If Lateral neck nodes are clinically palpable or present on ultrasound ipsilateral or bilateral modified radical neck dissection should be done [6]. Overall survival of patients statistically significant related to presence of nodal metastasis and distant metastasis. It was also seen in our study.

Hereditary MTC comprises of MEN 2A, FMTC and MEN2B syndromes.MEN2A and FMTC patients should be screened for pheochromocytoma and hyperthyroidism. Surgical treatment should involve Total thyroidectomy with therapeutic ipsilateral or bilateral central node dissection if calcitonin or CEA is elevated and if ultrasound suggests nodal involvement. Surgery should be performed by the age of 5 years. Lateral lymphnode dissection may be required in presence of high volume disease in central nodes. Patients presenting with hyperthyroidism should be evaluated intraoperatively. If there is single adenoma it should be excised. If its multiglandular disease then volume equivalent to one parathyroid can be left insitu. MEN 2B patients should be treated with total thyroidectomy with therapeutic ipsilateral or bilateral central node dissection before first year of life .

Patients are followed with serum calcitonin and CEA level. Locoregional recurrence or distant metastases can be seen in upto 50% of patients with MTC on follow up. Calcitonin levels are very sensitive for detecting either residual or recurrent disease. Patients with serum calcitonin level > 100 pg/ml usually indicate either residual disease in the neck or the presence of metastases. If there is locoregional recurrences surgical treatment is still preferred treatment modality. EBRT /IMRT may be considered in unresectable disease. Systemic therapy should be considered in presence of symptomatic and progressive metastatic disease. Oral tyrosine kinase inhibitors have shown to improved progression free survival. Drugs Vandetanib and Cabozantinib are category 1 recommendation according to NCCN guidelines [11-12].

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