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Original Research Article

A Prospective Study on Medullary Carcinoma of Thyroid with Possible Clinical, Cytological and Histopathological Correlation

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Abstract

It is a prospective study done between 2010 to till date on 1123 thyroid lesions to estimate the incidence of medullary carcinoma of thyroid. Fine-needle aspiration (FNAC) was the initial diagnostic procedure to evaluate thyroid lesions. This study correlates FNAC cytology results with clinical, radiological and histopathological findings. Repeat FNAC and Ultrasound guided FNAC was done for inadequate samples and for difficult to palpate lesions. Medullary thyroid carcinoma is a hormone-producing malignant tumor that synthesizes calcitonin. MTC can be Sporadic or Familial. MTC is suspected after physical examination by measuring plasma calcitonin. For a positive diagnosis, histopathological confirmation is required. The extent of the tumor and the presence of metastatic spread are determined by using ultrasonography (USG), Computed tomography (CT) and Magnetic resonance imaging (MRI). ***Aims and objectives:*** To study the Incidence, cytological, histopathological and clinical correlation of medullary carcinoma of thyroid and to confirm the previous findings mentioned in the literature and to find any other additional findings from the histological and cytological view. To show the unique nature, rarity, and associations of medullary carcinoma. ***Marterials and methods:*** This study was conducted in the department of pathology in Mamata Academy of medical sciences Hyderabad and Mamata medical college. The material comprises of FNACs and thyroid specimens from Mamata General Hospital, Khammam and Mamata Academy of medical sciences from January 2010 to January 2020. Data was obtained from the surgical and pathology departments of Mamata General Hospital Khammam and Mamata Academy of Medical Sciences, Hyderabad Telangana. Routine Hematoxylin and Eosin, Pap stains were used to stain the smears and slides. For confirmation Congo red and calcitonin special stains were used and by checking baseline Calcitonin levels.

Keywords: Cytohistologic correlation, fine-needle aspiration, medullary carcinoma of thyroid, USG, CT, MRI.

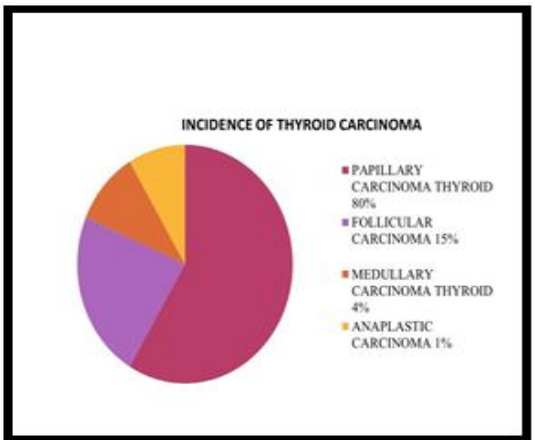
INTRODUCTION

Medullary thyroid cancer is the third most common of all thyroid cancers. Medullary thyroid carcinoma (MTC) is a malignant epithelial tumor of the thyroid gland that exhibits C-cell differentiation. C cells arise from the ultimo branchial body, which is derived from the fourth pharyngeal pouch, and they are found in the upper and middle areas of the thyroid lobes. Medullary thyroid carcinoma arises from perifollicular 'C' cells, it is a rare slow growing tumor located at the lateral upper 2/3rds of the thyroid. Molecular genetic testing is routinely performed to identify hereditary cases. In addition, understanding the molecular basis of both hereditary and sporadic MTC has led to the development of targeted therapy with tyrosine kinase.

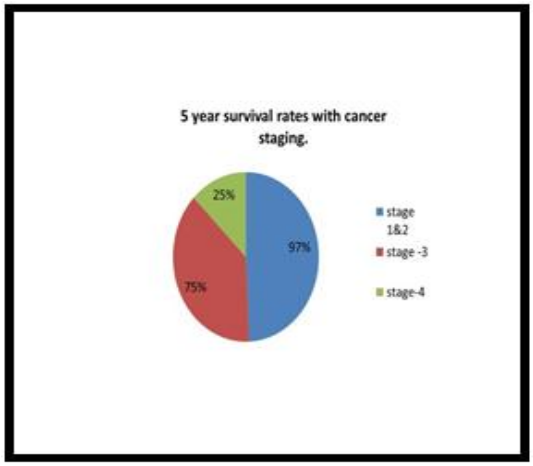
Inhibitors [1]. Medullary thyroid carcinoma is the first human malignancy known to be associated with a tumor marker, the hormone calcitonin, measurement of which enables diagnosis as well prognostication, following surgical resection of the primary thyroid tumor [2]. MTC may be sporadic (80%), or may occur as a manifestation of the hereditary syndrome MEN type 1 & 2 (20%). Medullary thyroid carcinoma is a tumor of the parafollicular C-cells. This tumor merits special attention because detection of the precursor lesion (C-cell hyperplasia**)** [3]. And the hallmark genetic mutation in the RET gene [4]. In specific cases can actually enable the prevention of this tumor.

Medullary thyroid carcinoma (MTC) arises from these cells and accounts for 1–2% of thyroid cancers. Although the majority of MTCs are sporadic, 25% of cases are hereditary and are found in multiple endocrine neoplasia (MEN) 2A or 2B syndromes, or as part of familial MTC based on a specific germline mutation in the *RET* proto-oncogene [4]. MTC is a

neuroendocrine tumor with unique clinicopathologic and radiologic features compared with other thyroid malignancies. Imaging plays an important role in the optimal management of this malignancy [5]. The incidence of medullary carcinoma thyroid is 4%, it comprises about 7% (5-10%) of all malignant tumors of thyroid and 15% of thyroid cancer deaths. It can occur in children and adults. Sporadic MTC does not run in families. Most MTCs are sporadic and mainly affects older adults. Hereditary MTC, which runs in families. MTCs can have a wide variety of divergent histologic patterns. Described histologic variants include spindle cell, papillary or pseudopapillary, follicular or glandular, clear cell, oncocytic, mucin producing, melanin producing, paraganglioma-like, and small cell, among others. Amyloid deposits are seen between tumor cells in about 70-75% of tumors, secondary to the extracellular deposition of insoluble, abnormal amyloid fibrils, comprising of calcitonin. The sensitivity of serum calcitonin was 100%, the specificity was 95.3%, and the positive predictive value is low and is 15%. Risk factors include, a family history of MTC, multiple endocrine neoplasia MEN), a prior history of pheochromocytoma, mucosal neuromas, hyperparathyroidism or pancreatic endocrine tumors.



Incidence and types of Thyroid cancer



5-year survival rates with cancer staging

RESULTS

Table-1: Incidence, Age wise and sex-wise distribution of medullary carcinoma thyroid

Age at presentation	Male Patients	Female Patients
0-1 years	- - -	- - -
2-10 years	- - -	- - -
11-20 years	- - -	- - -
21-29 years	- - -	- - -
30-39 years	2 patients	3 patients
40-49 years	5 patients	7 patients
50-59 years	3 patients	4 patients
60-69 years	- - -	- - -
70-79 years	- - -	- - -
80-89 years	- - -	- - -
90-100 years	- - -	- - -

Age and Sex- wise Distribution

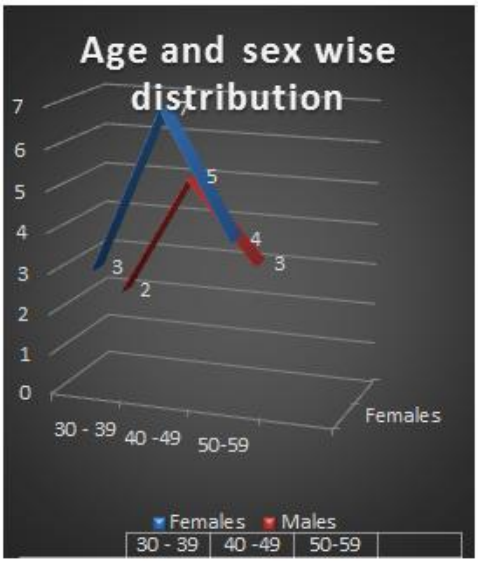


Chart-2

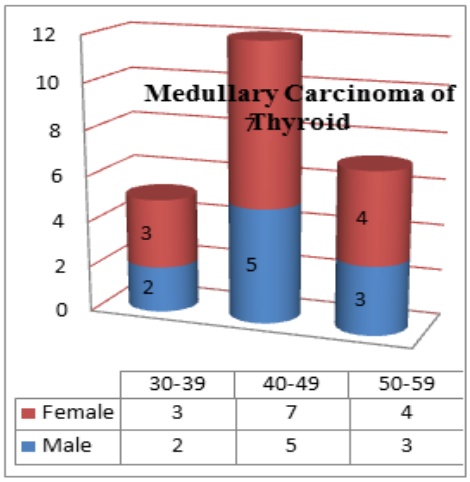


Chart-3

Table 2 &3: MCT- Etiology, Variants, Sex and Age with different parameters

Table-2

Type of MTC	Males	Females
Sporadic	7	11
Familial with MEN1		1
Familial with MEN 11		
Familial without MEN syndromes	2	3

Table-3

parameter	Males	Females
Mean age at presentation	7	11
Amyloid deposits		1
Increased calcitonin levels	In all cases	In all cases
Lymph node involvement	2	3

RESULTS

Of the 1123 individual thyroid FNAC performed during the 10-year study period, 2.53% cases were diagnosed as MCT, and subsequently underwent thyroidectomy. Among them 24 cases were concordant, whereas 4 cases had discrepancy even with repeat FNAC and were excluded from the study. Out of 24 cases 14 cases were noticed in females and 10 cases in males [Table-]. Mean age at presentation was 45 years. Age and sex wise distribution shown in Chart 1 and Chart 2. Sporadic type of MCT seen in 18 cases, 1 patient presented with Familial with MEN-1, Familial without MEN syndromes in 5 patients [Table-2].

Mean age at presentation was 45 years, Amyloid deposits seen in 5 patients and lymphnode involvement in 5 cases and increased Calcitonin levels noticed in all cases. [Table-3]. Mean age at presentation is 45 years. Amyloid deposits seen in 5 patients. Whereas increased Calcitonin was noticed in all the cases. Central group of lymphnode involvement was noticed in 5 patients. 18 cases were sporadic type of MCT and 1 case was Familial with MEN 1 type and 5 cases Familial without MEN syndromes. On FNAC dyscohesive clusters and sheets of spindle shaped, Plasmacytoid and occasional polygonal shaped thyrocytes were seen with ill-defined cytoplasm, eccentric nuclei in Plasmacytoid cells, salt and peppery chromatin, prominent nuclei and inconspicuous nucleoli. (Fig 1, 2 and 5). On Histopathology also spindle shaped cells seen with amyloid like acellular hyaline deposits in the background deposits (Fig 3 &4). Cyto and Histopathologically correlated pictures seen in Fig 5,6,7. Classic Variant of MCT with Scattered neoplastic cells with granular eosinophilic cytoplasm and salt and peppery chromatin in fig8 and Amyloid deposits on Congo red stain shown in Fig 9. (Fig 10& 11) Cytology pictures of MCT metastasis to lymph node show Plasmacytoid cells with eccentric nuclei, occasional spindle shaped cells and polygonal cells with speckled nuclear chromatin.

Comparison study

Tazeen Jeelani1, Danish Rafiq Comparison study: Histopathological and Cytological Correlation of Thyroid Nodules with Emphasis on Bethesda System for Reporting Thyroid Cytology 7 Year Study. In this study out of 21 histologically proven malignant cases, 18 were malignant on cytology also. There were three such cases which were benign on cytology but turned out to be malignant on histopathology; majority of the cases were reported in the age group 21–50 years with a mean age of presentation 37.6 years.

My study: In my study out of 1123 FNAC reports 28 cases were diagnosed as MCT on FNAC but only 24 cases were concordant with clinical, radiological and histopathological correlation. 4 cases had discrepancy even with repeat FNAC. Out of 24 cases 14 patients were Female and 8 were male patients. Majority of cases were reported in the age group of 40-49 years with a mean age of presentation was 45 years.

Comparatively my study is better than Tazeen Jelani and Danish Rafiq study. In My Medical College Technicians of cytopathology and Histopathology as well as Doctors are very experienced and well trained. So in my study there is good correlation between clinical, radiological, cytopathological and histopathological correlation.

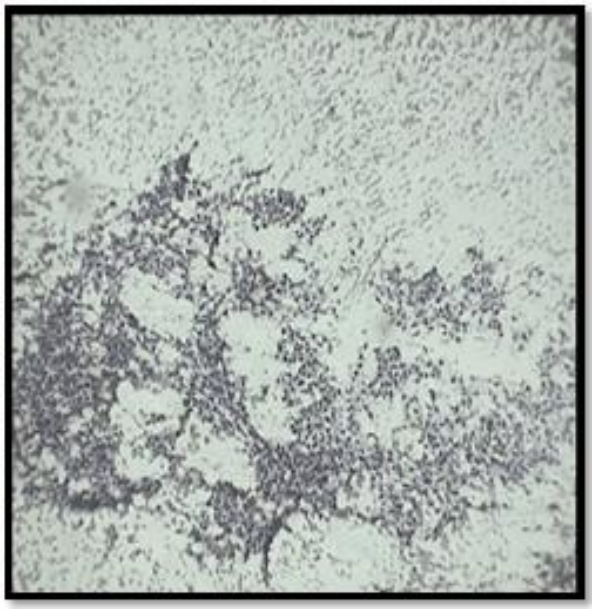


Fig-1: PAP 10x

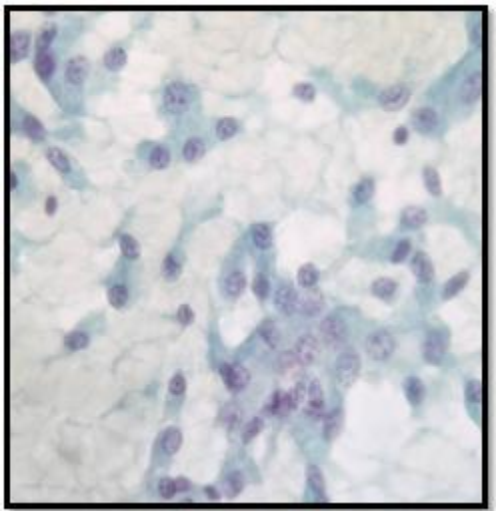


Fig-2: PAP 40x

Fig-1&2: Cytology Pictures: Loosely clustered dyscohesive spindle shaped, round, plasmatoid with eccentric nuclei and polygonal tumor cells with ill-defined cytoplasm

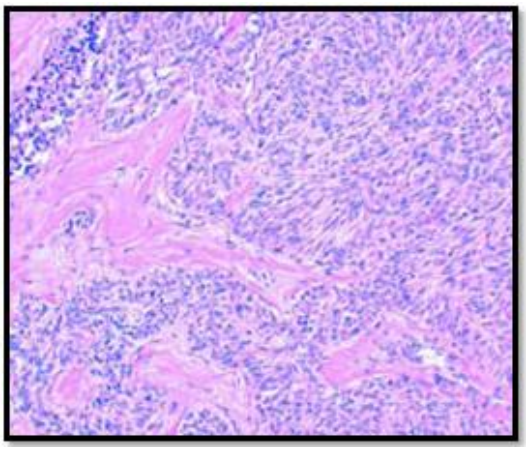


Fig-3: H&E 10x

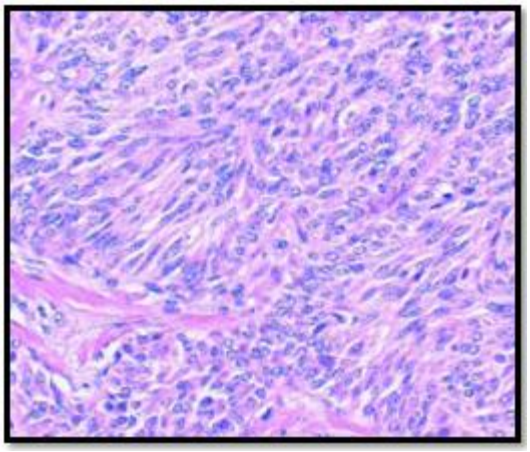


Fig-4: H&E 40x

Fig-3 &4: Histopathology Pictures: Spindle shaped cells with Amyloid deposits

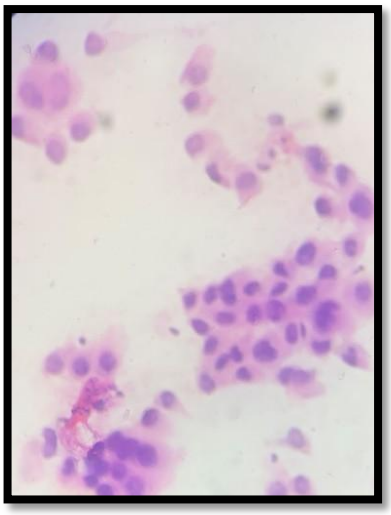


Fig-5: H&E 40x

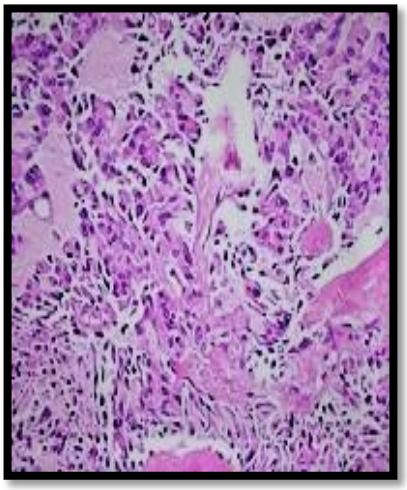


Fig-6: H&E 10x

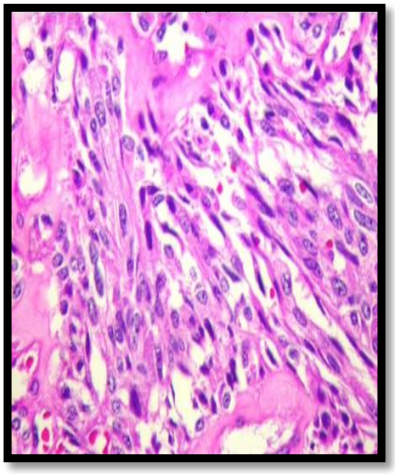


Fig-7: H&E 40x

Fig-5, 6&7: Cytological and Histopathological correlation of MCT with Amyloid Deposits and Spindle shaped cells, Plasmacytoid and polygonal cells seen

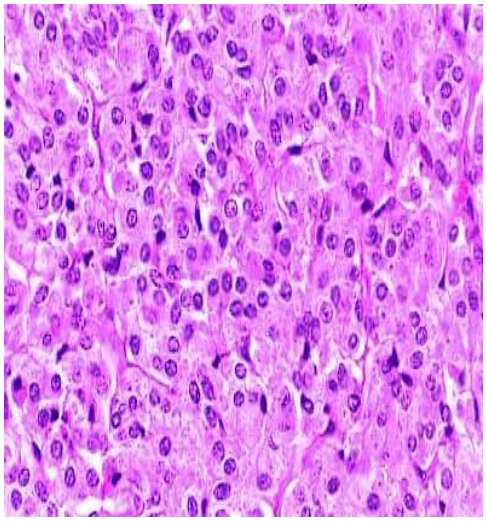


Fig-8: H&E 40x

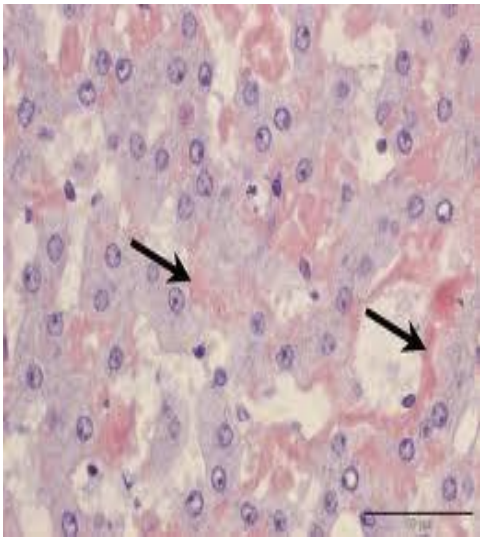


Fig-9: Congo red 100x

Fig-8&9 Classic Variant of MCT with Amyloid deposits on Congo red stain scattered neoplastic cells with granular eosinophilic cytoplasm and salt and peppery chromatin

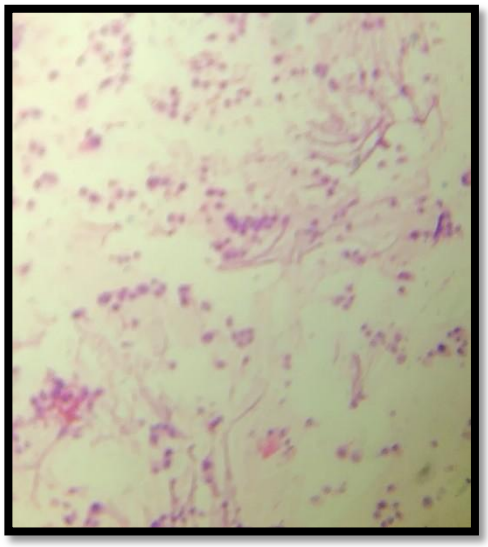


Fig-10: H&E 10x

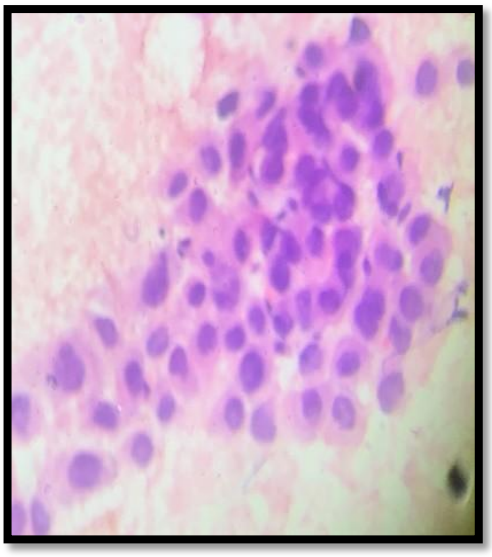


Fig-11: H&E 40x

Fig-10& 11: Cytology pictures of MCT metastatic to lymph node. Plasmacytoid cells with eccentric nuclei, occasional spindle shaped cells and polygonal cells with speckled nuclear chromatin

DISCUSSION

Thyroid neuroendocrine cells were first described in 1876 by Baber, and they were named C cells (CC) due to the secretion of calcitonin (CTN) by Pearse in 1966. MTC is frequently aggressive and metastasizes to cervical and mediastinal lymph nodes, Lungs, liver, and bones [5]. Measuring calcitonin levels in MCT has diagnostic and prognostic significance. Prognosis of MTC was found not to be related to histologic features dominant architectural pattern, cellular shape, presence of amyloid deposits or IHC pattern. Instead, survival was significantly correlated to age, sex, and stage of disease. The best prognosis was seen in women younger than 40 years and revealing an early stage of disease [6]. In familial cases, identification RET genetic mutation allows for early diagnosis and therapy. FNAC is considered a first line diagnostic test along with IHC. The diagnostic accuracy provided by FNAC for MTCs ranges from 50% to 82%, because cytological examination results have revealed diverse appearances include a variety of cellular morphologies, atypical cells shapes, and l ow cellularity in MTC [7,8]. DNA measurements added valuable information in assessing the prognosis of MTC [9]. Cytology evaluation alone is not enough for preoperative evaluation and to guide initial surgery [10]**.** Ultrasound-guide fine needle aspiration cytology (FNAC) of a thyroid nodule cannot always reliably distinguish between MTC and other thyroid neoplasms including adenomas. Sensitivity of FNAC was shown to be 63% vs. 98% for serum CTN measurement with only 74.5% cases diagnosed by FNAC in patients with elevated CTN level [11]. FNAC is a very important measure in the preoperative workup of patients with thyroid nodules; however, it is controversial due to questions of efficacy, accuracy, and cost-effectiveness

[12]. Serum CTN has also some limitations including high false positive results, low positive predictive value, and lack of agreement for CTN threshold to suspect MTC [12, 13]. Diagnosis of MTC in thyroid nodules with undetermined cytology using MTC gene classifier was shown to demonstrate a high sensitivity of 97.9%, specificity of 99.8%, and positive and negative predictive values of 97.9% and 99.8%, respectively [12]. If the preoperative diagnosis of MTC is missed and surgery starts with a diagnostic hemithyroidectomy, reoperation is needed to perform total thyroidectomy. A definitive diagnosis is often made only on surgical histopathology [14]. After a cancer diagnosis, staging provides important information about the extent of cancer in the body and anticipated response to treatment. People with a family history of medullary thyroid cancer (MTC), with or without multiple endocrine neoplasia type 2 (MEN 2), might have a very high risk for developing this cancer. Most doctors recommend genetic testing for these people when they are young to see if they carry the gene changes linked to MTC. For those who may be at risk but don't get genetic testing, blood tests and thyroid ultrasounds can help find MTC at an early stage, when it may still be curable. Poor prognostic factors include mean age older than 50 years, distant Metastasis and with other endocrine tumors due to MEN II-B syndrome. Residual disease or recurrence can be detected by measuring calcitonin every 4 months for the first few years and then every 6months for the rest of the life. MCT patients usually present with persistently increased calcitonin levels [2] Follow-up after surgical therapy for MTC typically starts 2–3 months postoperatively by obtaining new baseline CTN and CEA levels. Patients who have undetectable CTN levels postoperatively can be followed with measurements of serum CTN and CEA initially every 6 months for the first year and then annually [15].

CONCLUSIONS

FNAC, although not a substitute for conventional surgical histopathology, is considered a first line diagnostic**.** Test for evaluation of medullary carcinoma of thyroid along with immunocytochemistry. Early diagnosis and treatment would lead to a markedly improved cure rate of these neoplasms. Medullary thyroid carcinoma is the first human malignancy known to be associated with a tumor marker, the hormone calcitonin, measurement of which enables diagnosis as well as prognostication, following surgical resection of the primary thyroid tumor. The majority of the patients were diagnosed with stage IV and with increased serum calcitonin levels. It can be suggested that any patient's elevated postoperative CTN should be considered as metastatic disease of unknown location and should prompt comprehensive radiological evaluation. Follow-up after surgical therapy for MTC typically starts 2–3 months postoperatively by obtaining new baseline CTN and CEA levels. Patients who have undetectable CTN levels postoperatively can be followed with measurements of serum CTN and CEA initially every 6 months for the first year and then annually. I would like to express my gratitude to MMC and MAMS for their extended support.

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