

## ORIGINAL ARTICLE

## MEDULLARY THYROID CARCINOMA: A 20-YEAR EXPERIENCE FROM A CENTRE IN SOUTH INDIA

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**Background:** Management of medullary thyroid carcinoma (MTC) remains controversial despite many advances over the past five decades. We attempt to review the presentation, management and prognosis of MTC at our institution over the last two decades.

**Methods:** We conducted a retrospective review of the records of 40 patients with MTC over a period of 20 years.

**Results:** Ten patients had hereditary MTC and 30 had sporadic MTC. The mean age of presentation was 41 years. Sixty-five per cent of the patients had a definite thyroid swelling and 43% had lymphadenopathy at the time of presentation. Total thyroidectomy with a central neck dissection was carried out in 82.5% of patients. Adjuvant therapy was given in 75% of patients because of extensive/residual disease. Postoperative hypercalcaemia was seen 73% of patients. <sup>131</sup>I metaiodobenzylguanidine scanning was carried out in 16 patients with persistent hypercalcaemia; the uptake was positive in 10 and negative in 6, indicating a positivity of 62%.

**Conclusion:** Medullary thyroid carcinoma accounts for 2.5% of thyroid carcinomas. There is a small male preponderance. In our series <sup>131</sup>I metaiodobenzylguanidine scan had a better positivity than what has been reported in the published work. Persistent postoperative hypercalcaemia was associated with a poorer prognosis that did not reach statistical significance.

**Key words:** calcitonin, <sup>131</sup>I metaiodobenzylguanidine scanning, medullary thyroid carcinoma.

Abbreviations: EBRT, external beam radiotherapy; FNAC, fine-needle aspiration cytology; MIBG, metaiodobenzylguanidine; MTC, medullary thyroid carcinoma; RAI, radioactive <sup>131</sup>I therapy.

### INTRODUCTION

Medullary thyroid carcinoma (MTC) is an uncommon malignancy. Management of MTC remains controversial despite many advances over the last five decades. The identification of a genetic basis for hereditary forms of MTC has added to the knowledge of this disorder and has resulted in early detection of tumour in susceptible individuals. However, the majority of MTC is sporadic in occurrence (70–80%).<sup>1</sup> Some hereditary tumours are associated with other endocrine neoplasms (multiple endocrine neoplasia – type 2). The hallmark of these tumours is the presence of increased serum calcitonin levels as a marker. The prognosis is generally believed to be intermediate to that of differentiated carcinomas at one end of the range and anaplastic carcinomas at the other. Some basic controversies remain regarding the optimal surgical management of MTC, which includes the extent of cervical lymph node dissection. Adjuvant therapies like radiation therapy, chemotherapy and radioiodine therapy have doubtful benefits. In this study we review the clinical presentation, surgical

and adjuvant therapies, outcomes and follow-up data of patients with MTC over a period of 20 years.

### MATERIALS AND METHODS

This was a retrospective case review of the records of patients with proven MTC, who presented to our institution over the 20 years from 1982 to 2002. An analysis of their clinical profile, histopathology, surgical, radioisotope and other therapeutic data was carried out. Statistical analysis was carried out with the SPSS (SPSS Inc., IL, USA) software package 11.0.1.

### RESULTS

In all, 40 patients were studied (Table 1). There was a male predominance with 23 men and 17 women. The age of the patients ranged from 9 to 73 years. The mean age at presentation was 41 years.

Most of the patients presented with a thyroid swelling (65%) of whom half had lymphadenopathy at the time of presentation. Details of the initial clinical presentation are given in Table 2.

There were 10 patients with a hereditary MTC, four of whom had familial MTC (all from the same family), two had MEN 2A and four had MEN 2B. Pheochromocytoma was the initial presentation in three of the patients within the MEN 2 subgroup. Siblings from three families were screened for hereditary MTC with a combination of clinical examination and calcium-stimulated calcitonin estimations. Screening was positive in only

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**Table 1.** Master table for patients with medullary thyroid carcinoma

ID (n)	Age (years)	Sex	Duration of symptoms†	Family history	Preoperative calcitonin‡ (pg/mL)	FNAC§	Surgery	Postoperative hypocalcaemia	Postoperative calcitonin‡ (pg/mL)	Postoperative MIBG scan	Metastasis	Postoperative follow up (months)	Survival
1	35	M	6	None	5560	Diagnostic	Yes	Persistent	245	ND	None	90	Alive
2	57	M	3	None	1308	Diagnostic	Yes	Persistent	1328	ND	Multiple sites	2	Alive
3	34	F	5	None	NC	Diagnostic	Yes	None	<16	No uptake	None	31	Alive
4	23	M	24	None	NC	ND	Yes	None	1268	Lung & liver uptake	Multiple sites	123	Alive
5	32	M	24	None	NC	ND	Yes	Persistent	1054	Lung uptake	Lung	79	Alive
6	67	M	6	None	NC	Inadequate	Yes	None	65	No uptake	None	119	Alive
7	46	F	60	None	194	Diagnostic	Yes	None	194	ND	None	31	Alive
8	49	F	12	None	NC	Diagnostic	Yes	None	1000	No uptake	None	26	Not known
9	12	F	0	None	NC	ND	Yes	Persistent	1000	No uptake	Bone	85	Died
10	56	M	60	None	NC	Diagnostic	Yes	None	5338	Local (neck & mediastinal) uptake	Lymph nodes	22	Alive
11	38	M	5	None	1268	Diagnostic	Yes	None	1268	Lung uptake	Lung	170	Alive
12	33	F	12	None	NC	Diagnostic	Yes	None	1268	ND	Lung	97	Alive
13	50	F	3	None	30 100	ND	Yes	None	30 100	No uptake	Lymph nodes	37	Alive
14	26	M	0	None	NC	ND	Yes	Persistent	1243	Lung & liver uptake	Multiple sites	36	Alive
15	40	F	12	None	NC	Suspicious	Yes	None	1268	ND	None	33	Alive
16	27	M	24	None	NC	Suspicious	Yes	None	>1000	Local uptake	None	5	Alive
17	37	M	0	None	NC	ND	Yes	None	411 200	Local uptake	Multiple sites	106	Alive
18	35	M	48	None	1300	Diagnostic	Yes	Persistent	4984	Local uptake	Lymph nodes	9	Alive
19	32	M	84	None	NC	Suspicious	Yes	None	1308	ND	Multiple sites	6	Alive
20	65	M	48	None	NC	ND	Yes	None	ND	ND	Lymph nodes	216	Alive
21	56	F	2	None	NC	Suspicious	Yes	None	ND	No uptake	Multiple sites	1	Died
22	56	M	152	None	NC	Suspicious	Yes	None	1000	Local uptake	Lymph nodes	12	Alive
23	34	F	3	None	NC	Suspicious	Yes	Persistent	<16	ND	None	84	Alive
24	54	F	7	None	NC	Suspicious	Yes	None	22	ND	None	8	Alive
25	38	M	10	None	NC	ND	Yes	None	92	No uptake	None	42	Alive
26	53	M	1	None	NC	ND	Yes	None	ND	ND	None	3	Alive
27	73	M	6	None	NC	Diagnostic	No	None	<16	ND	None	39	Alive
28	47	M	0	None	NC	ND	Yes	None	1000	ND	None	7	Alive
29	48	M	6	None	NC	Diagnostic	Yes	None	<16	ND	Multiple sites	77	Alive
30	26	M	18	Yes	NC	ND	Yes	None	1000	Report missing	Lymph nodes	204	Alive
31	30	M	1	None	1000	Diagnostic	Yes	None	<16	ND	None	147	Alive
32	44	M	21	None	196	ND	Yes	Transient	<16	No uptake	None	7	Alive
33	27	F	48	Yes	NC	Inadequate	Yes	Persistent	184	ND	None	66	Alive
34	31	F	12	Yes	1382	ND	Yes	None	645	No uptake	None	208	Alive
35	57	F	84	Yes	3740	Suspicious	Yes	None	1308	No uptake	None	66	Alive
36	09	F	0	Yes	132	ND	Yes	Persistent	<16	No uptake	None	16	Alive
37	53	M	0	Yes	1282	Inadequate	Yes	None	40	No uptake	None	12	Alive
38	43	M	12	Yes	3076	Inadequate	Yes	None	<16	No uptake	None	58	Alive
39	31	F	1	None	858	ND	Yes	None	1008	No uptake	None	61	Alive
40	39	F	1	None	10 400	ND	Yes	Persistent	1000	Local uptake	None	74	Alive

†In months at presentation to our institution. ‡Normal calcitonin levels – up to 50 pg/mL. §Reports classified as (i) diagnostic of MTC (ii) inadequate sampling and (iii) suspicious of malignancy. F, female; FNAC, fine-needle aspiration cytology; M, male; MTC medullary thyroid carcinoma; NC, not checked; ND, not done.

**Table 2.** Mode of clinical presentation in patients with medullary thyroid carcinoma

Clinical presentation	No. patients	Percentage
Goitre with lymphadenopathy	12	30
Solitary thyroid nodule	7	17.5
Isolated goitre	7	17.5
Isolated cervical lymph node enlargement	6	15
Pheochromocytoma	5	12.5
Familial screening	1	2.5
Mode of presentation unclear from medical records	2	5

one family. This family was screened for genetic markers by sending the blood samples to a reference laboratory abroad. The results showed a mutation common to both MEN 2 and Familial MTC. The four members of this family were labelled as familial MTC as there were no other manifestations of MEN 2 even after 40 years of age. A child in that family was found to have an increased serum calcitonin and prophylactically underwent a total thyroidectomy.

On analysing, the duration of symptoms before presentation ranged from 3 months to 10 years; the mean duration was 24 months and the median was 12 months.

Thirty-nine patients underwent surgery. The commonest surgical procedure that was carried out was a total thyroidectomy and central/lateral neck dissection – in 82.5% of the patients. The details of the initial surgical procedure carried out are given in Table 3. The extent of neoplastic involvement of the thyroid on histopathology showed that most of the patients (77.5%) had either both lobes of the thyroid being involved or the tumour invaded the adjacent lymph nodes. The remaining (22.5%) had tumour confined to one lobe of the thyroid. Surgical re-exploration was required in 9 of the 40 patients (for persistent hypercalcaemia) of whom 7 are well on follow up; one was lost to follow up and one has died. The incidence of postoperative hypocalcaemia was 25% in our series.

Seventy-five per cent of our patients received adjuvant therapy of one type or another, the decision to do so being made on an individualized basis by a team of endocrinologists, surgeons, physicians of nuclear medicine and radiotherapists during the weekly interdepartmental meeting. Half of our patients received

**Table 3.** Details of the surgical procedure carried out

Surgery carried out	No. patients	Percentage
Total thyroidectomy and neck dissection	26	65
Initial hemithyroidectomy followed by total thyroidectomy with neck dissection	7	17.5
Initial hemithyroidectomy followed by total thyroidectomy without neck dissection	1	2.5
Total thyroidectomy without neck dissection	3	7.5
Hemi-thyroidectomy	1	2.5
Total thyroidectomy with neck dissection and tracheostomy	1	2.5
Not operated	1	2.5

radiotherapy for residual disease, either alone or in combination with <sup>131</sup>I metaiodobenzylguanidine (MIBG), radioiodine (<sup>131</sup>I) or chemotherapy. The details of adjuvant therapy given are noted in Table 4.

Preoperatively, the calcitonin measurements were carried out in 15 of the 40 patients (37.5%) and all the values were increased. When the calcitonin levels were assessed postoperatively, they remained persistently increased in 73% of the patients. Postoperative <sup>131</sup>I MIBG scanning was carried out in 24 patients on at least one occasion. Seven of these patients had low postoperative calcitonin levels and negative uptake on <sup>131</sup>I MIBG scanning. In 16 patients with persistent hypercalcaemia the <sup>131</sup>I MIBG uptake was positive in 10 and negative in 6, indicating a positivity of 62%. The calcitonin report was not available in one patient. Of the 10 patients with positive uptake, 6 showed uptake in the thyroid bed and in 4 patients there was pooling in the lungs. Four of these patients underwent therapeutic MIBG ablation.

## DISCUSSION

Medullary thyroid carcinoma is an uncommon malignancy. Although it constitutes 3–10% of thyroid malignancies, it is responsible for more than 13% of the deaths attributable to thyroid malignancy.<sup>2,3</sup> MTC appears to be much less common in our country. Over 20 years we identified 40 patients with the diagnosis of MTC. This works out to be approximately two cases per year. Previous series suggest that there are ~80 new patients diagnosed with differentiated thyroid cancers every year at our institution.<sup>4</sup> Therefore, medullary carcinoma constitutes only ~2.5% of the thyroid malignancies seen in our institution. The reason for the relative rarity of MTC might be related to the inadequacy of familial screening in our country where people travel large distances to seek tertiary health care.

In 1961 Sipple first described an association of thyroid carcinomas with pheochromocytoma.<sup>5</sup> Subsequently, the genetic basis of MTC was identified and the benefit of early detection of tumour in genetically susceptible individuals has been shown.<sup>6</sup> Twenty-five per cent of patients in this series had a genetic basis for the disease. In India the only other series on MTC was able to show only two patients among 234 (1%) to have a genetic basis of the disease.<sup>7</sup>

There is generally a female preponderance (1.5:1) in most reported series of patients with MTC although in our series there was a male preponderance.<sup>8,9</sup> This could indicate a referral bias or bias in health-seeking behaviour. This is consistent with the observations from another large series from India where the M:F ratio

**Table 4.** Details of the nature of adjuvant therapy given for patients

Adjuvant therapy given	No. patients	Percentage
None	10	25
RAI alone	5	12.5
External beam radiotherapy	9	22.5
Ablative doses of MIBG alone	1	2.5
EBRT with RAI	9	22.5
EBRT with MIBG ablation	2	5
EBRT with chemotherapy	1	2.5
MIBG with RAI	1	2.5
Only chemotherapy	2	5

EBRT, external beam radiotherapy; MIBG, metaiodobenzylguanidine; RAI, radioactive <sup>131</sup>I therapy.

was 1:0.45.<sup>7</sup> The mean age of presentation in most series varies from 45 to 55 years and our series showed a lower mean age of 41 years and a median age of 38.5 years.<sup>2,9,10</sup>

### Clinical presentation

The proportion of patients presenting with a painless thyroid swelling was 65% in our series, which is in keeping with published work in the developed world.<sup>11</sup> Less commonly, compressive symptoms are described in the published work.<sup>12</sup> We did not have any patient who presented with dysphagia or hoarseness. Systemic symptoms of diarrhoea and flushing would increase the suspicion of MTC in patients with thyroid swellings;<sup>13</sup> however, none of our patients had these symptoms at the time of presentation. Preoperative calcitonin levels have been available in our centre from the mid-1990s. All patients (15 of 40) in whom preoperative measurements of calcitonin carried out had increased values, contrasting with the description in the published work that basal calcitonin levels may remain normal in more than 10–54% depending on the stage of disease.<sup>14</sup>

### Surgery

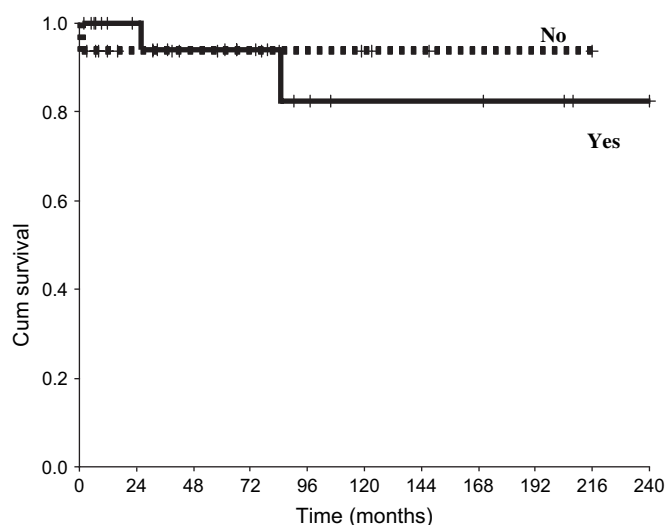
When the diagnosis of MTC was made preoperatively, all patients underwent mandatory radiological and biochemical screening to rule out the presence of associated pheochromocytoma. In 20% of patients the diagnosis of MTC was a histological surprise as it was not suspected preoperatively. In a good number of patients (12.5%) MTC was discovered after the diagnosis of pheochromocytoma was established. The commonest surgical procedure was a total thyroidectomy with central neck dissection. A few of the patients did not undergo central neck dissection and surgery was limited to a total thyroidectomy. Of the five patients who did not undergo central compartment neck dissection, one had a prophylactic thyroidectomy and one was lost to follow up after hemithyroidectomy. In 20% of patients where the diagnosis of MTC was a surprise following hemithyroidectomy (for a suspicious nodule), a completion thyroidectomy was carried out along with a central compartment lymph node dissection. One patient required tracheostomy because of significant tracheal infiltration at the time of surgery, although he had no preoperative compressive symptoms. Extensive thyroid surgery resulted in one-fourth of patients developing postoperative hypocalcaemia, which is much higher than the incidence of hypocalcaemia (~3%) among patients with differentiated carcinoma (Aravindan Nair *et al.*, pers. comm., 2003). In a few of patients (22%) disease was localized to one lobe of the thyroid on pathological examination.

### Postoperative follow up

Postoperative calcitonin levels were increased in 73% of patients in our series. Based on the presence of persistently increased calcitonin levels in many patients, a search by clinical and radiological imaging showed either a node or residual tissue. Of the nine patients who underwent re-exploration, four had evidence of a recurrent MTC. There is evidence that central compartment and/or lateral neck dissection can decrease the chances of re-exploration and regional disease recurrence<sup>13</sup>. However, because this information was available only in the early part of this decade, ~10% of patients without clinical evidence of lymph nodal involvement underwent total thyroidectomy without neck dissection.

The benefit of adjuvant therapy is controversial. External beam radiotherapy (EBRT) has been reported to have higher control rate in the neck, but with no improvements in the overall survival rates.<sup>15,16</sup> The usual protocol at our institution following adequate surgical intervention (total thyroidectomy with central neck lymph node dissection and sometimes lateral neck dissection) is to carry out an <sup>131</sup>I MIBG scan and if there is a positive uptake to consider <sup>131</sup>I MIBG ablative therapy for those who can afford it. The positivity of <sup>131</sup>I MIBG scan in identifying the source of persistent hypercalcaemia in our series was much better than that reported in published work. We had a detection rate of 62% compared with 11% quoted there<sup>17</sup>. However, <sup>131</sup>I MIBG ablative therapy is expensive and most of our patients with positive uptake could not afford it. It has been suggested that EBRT has some benefit if there is residual disease that is not excisable and more than 50% of our patients received this therapy. The other option remaining is radioiodine (<sup>131</sup>I) ablation, which was also used in a few patients. There were early reports of some benefit from the indirect scatter radiations when the residual thyroid tissue in proximity to tumour cells take up <sup>131</sup>I, but this rationale is not universally accepted and most authorities report no benefits from <sup>131</sup>I therapy.<sup>18</sup> Quite a few patients received a combination of adjuvant therapies.

One of the problems faced by clinicians while managing patients with MTC is the persistently increased calcitonin levels in the blood even after adequate surgery. This implies that probably there are some occult microscopic foci of MTC in the body. However, attempts to identify these foci on follow-up visits both by a meticulous clinical examination and imaging of the neck and mediastinum are often not rewarding. The follow up of these patients was in an era before positron emission tomography was available in India. The follow up of more than 50% of patients are being carried out for more than 5 years and 15% for more than 10 years. This further confirms that the long-term prognosis in patients with MTC is reasonable. However, persistent hypercalcaemia was associated with a poorer prognosis (Fig. 1), which was not statistically significant.



**Fig. 1.** Survival curves for patients with persistent postoperative hypercalcaemia compared with those with normal postoperative calcitonin levels (time in months).  $P = 0.901$ . Yes, persistent postoperative hypercalcaemia; No, no postoperative hypercalcaemia.

## CONCLUSIONS

In our series, MTC accounts for 2.5% of thyroid carcinomas. There is a small male preponderance. Serum calcitonin as a diagnostic test has a good sensitivity. It needs to be checked in any patient giving a family history of thyroid cancer or when the fine-needle aspiration cytology of the thyroid shows atypical features unlike that of a differentiated neoplasm. Persistently increased levels of serum calcitonin is an important concern following adequate surgical intervention. However, in our series often imaging for occult foci of the tumour is negative and many of these patients do well on follow up even when the calcitonin is markedly increased. In our series <sup>131</sup>I MIBG Scan had a better positivity than what is reported in published work. Persistent postoperative hypercalcaemia was associated with a poorer prognosis, which was not statistically significant.

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