Cancer Association of South Africa (CANSA)

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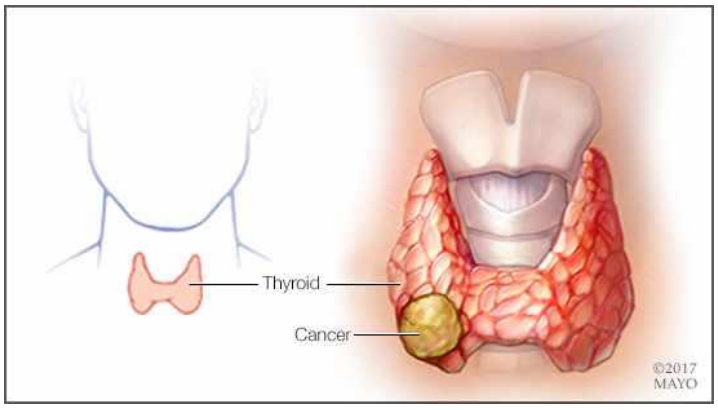
Fact Sheet on Medullary Thyroid Cancer

Introduction

Thyroid cancer occurs in the cells of the thyroid - a butterfly-shaped gland located at the base of the neck, just below the Adam's apple. The thyroid produces hormones that regulate one's heart rate, blood pressure, body temperature and weight.



[Picture Credit: Thyroid Cancer]

Although thyroid cancer is not common, rates seem to be increasing. Doctors think this is because new technology is allowing them to find small thyroid cancers that may not have been found in the past.

Most cases of thyroid cancer can be cured with treatment.

Medullary Thyroid Cancer

Medullary thyroid cancer is a form of thyroid carcinoma which originates from the parafollicular cells (C cells), which produce the hormone calcitonin. Medullary tumours are the third most common of all thyroid cancers and together make up about 3% of all thyroid cancer cases. Medullary Thyroid Cancer (MTC) was first characterized in 1959.

Approximately 25% of medullary thyroid cancer cases are genetic in nature, caused by a mutation in the RET proto-oncogene. This form is identified as familial medullary thyroid cancer (FMTC). When MTC occurs by itself it is termed sporadic medullary thyroid cancer (SMTC). When it coexists with tumours of the parathyroid gland and medullary component of the adrenal glands (pheochromocytoma), it is called Multiple Endocrine Neoplasia Type 2.

The survival for medullary thyroid cancer over 10 years is about 75 percent. Certain factors improve the outlook for medullary thyroid cancer. Among the most important are age and the stage of the cancer at diagnosis.

Younger individuals diagnosed with medullary thyroid cancer tend to have a better outlook. Individuals who are 40 or younger at diagnosis have five- and 10-year survival outlooks of 95 percent and 75 percent. For those

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older than 40, the 5- and 10-year survival outlooks are 65 percent and 50 percent, respectively. The prognosis declines drastically once the cancer advances and spreads to distant organs. Early diagnosis is key to having the most positive outlook for medullary thyroid cancer.

Incidence of Medullary Thyroid Cancer

The South African National Cancer Registry (2017) does not provide any information on the incidence of Medullary Thyroid Cancer. According to the National Cancer Registry (2017) the following number of cases of the thyroid gland was histologically diagnosed in South Africa during 2017. Histologically diagnosed means that a tissue sample (biopsy) was forwarded to an approved pathology laboratory where a specially trained pathologist confirmed a cancer diagnosis:

Group - Males 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	188	1:1 035	0,47%
Asian males	13	1:783	1,34%
Black males	48	1:2 555	0,35%
Coloured males	24	1:940	0,51%
White males	103	1:302	0,49%

Group - Females 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	559	1:506	1,34%
Asian females	41	1:225	3,18%
Black females	205	1:1 035	1,05%
Coloured females	73	1:387	1,56%
White females	240	1:136	1,41%

The frequency of histologically diagnosed cases of cancer of the thyroid gland in South Africa for 2017 was as follows (National Cancer Registry, 2017):

Group - Males 2017	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	5	13	26	32	41	42	25	4
Asian males	0	3	1	4	3	1	1	0
Black males	2	2	10	7	14	8	4	1
Coloured males	1	1	4	5	3	6	2	2
White males	2	7	11	16	21	`27	18	1

Group - Females 2017	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	9	54	114	118	113	77	58	16
Asian females	1	6	13	10	6	3	2	0
Black females	4	18	37	50	40	26	21	9
Coloured females	1	7	18	13	12	11	8	3
White females	3	23	46	45	55	37	27	4

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Risk Factors for Medullary Thyroid Cancer

Risk factors identified for Medullary Thyroid Cancer include:

- Tobacco use – directly linked to quantity
- Personal history of goitre
- Personal history of thyroid nodules
- Personal history of non-thyroid cancer
- Menarche after 14 years of age
- First full-term pregnancy before 20 years of age
- Oral contraceptive use

Torresan, F., Mian, C., Cavedon, E. & Iacobone, M. 2019.

BACKGROUND: The improvement in outcome of sporadic medullary thyroid carcinoma (MTC) during the last decades remains controversial, even if a trend toward a better prognosis has been recently proposed. This study was aimed to determine the time trend cure and survival rates in sporadic MTC according to the use of systematic preoperative calcitonin screening.

METHODS: Retrospective analysis of 178 sporadic MTC patients operated between 1980 and 2017 was performed. The impact of prognostic factors on cure and survival following the introduction of routine preoperative calcitonin screening in 2001 was evaluated according to the year of surgery.

RESULTS: Since 2001, a significant decline of node-positive tumors (from 56.1 to 34.7%) and advanced stage at diagnosis (stage III/IV from 56.1 to 34.7%) occurred, with a concomitant significant increase in cure rate (64.5% vs 38.6%; $p = 0.0012$) and survival ($p < 0.05$). At univariate analysis, the cure was achieved more frequently in more recently operated patients (64.5% vs 38.6%; $p = 0.0012$), in disease staging I/II (86.5% vs 13.5%; $p < 0.0001$), in patients undergoing preoperative calcitonin screening (63.8% vs 23.5%; $p < 0.0001$) and in the absence of lymph node metastases (86.5% vs 13.5%; $p < 0.0001$). At multivariate analysis, only preoperative calcitonin screening and stage at diagnosis turned out to be significant independent prognostic factors for cure and survival.

CONCLUSION: The outcome of sporadic MTC improved in the new millennium; diagnosis was achieved earlier, at a less advanced stage. Routine preoperative calcitonin screening may have contributed to improve cure and survival rates.

Signs and Symptoms of Medullary Thyroid Cancer

Medullary thyroid cancer is a rare type of thyroid cancer. The first sign of it is usually the appearance of a painless lump in the front of a person's neck. If caught early, this cancer is often very treatable. MTC starts in specialised thyroid cells known as parafollicular cells, or C cells. These C cells release a hormone called calcitonin, which controls the levels of calcium in a person's blood.

Unlike other types of thyroid cancer, MTC can sometimes run in families. When a person inherits MTC from a parent, it is known as familial medullary thyroid cancer (FMTC). Around 75% of MTC cases are sporadic, which mean that the individual with the condition did not inherit it from a parent.

Because MTC tends to develop slowly, people in the early stages of the disease usually have no symptoms. For this reason, early diagnosis of MTC is not common.

When symptoms do appear, they typically consist of a painless lump in the front of a person's neck or throat. This lump corresponds with the cancerous mass of cells that is growing inside the thyroid.

Common symptoms of MTC can include:

- swelling in the neck near the thyroid gland, which corresponds to enlarged lymph nodes
- cough, sometimes producing blood

- difficulty swallowing, sometimes causing pain
- shortness of breath
- difficulty breathing, because of a narrowing of the airways

If the condition progresses, symptoms may become more severe, and people can also experience other signs. These may include:

- a large mass in the neck
- pain in the neck, jaw, or ear
- choking sensations

People with cancer that has spread to the nerves that control the vocal cords may also experience hoarseness or changes in their voice. In the advanced stages of MTC, high levels of calcitonin produced by the tumour can cause diarrhoea and flushing.

Diagnosis of Medullary Thyroid Cancer

A diagnosis of thyroid cancer is usually made by a fine needle aspiration (FNA) biopsy of a thyroid nodule, or after the nodule is surgically removed. Patients in whom the results of an FNA biopsy (or histopathology) are suggestive or indicative of MTC should be further evaluated with measurement of the proteins calcitonin and carcinoembryonic antigen (CEA) in the blood, which are typically elevated in patients with MTC. These tests are useful to confirm the diagnosis of MTC which can help ensure the surgeon plans the correct surgery, and also serve as tumour markers during long-term follow-up to detect any remaining disease or recurrence of the cancer.

Lorenz, K., Machens, A., Siebolts, U. & Dralle, H. 2020.

"Improvements in preoperative diagnostic modalities in conjunction with highly sensitive calcitonin assays, ultrasound and functional imaging modalities and differentiated genetic testing for detection of hereditary forms, have enabled detection and resection of medullary thyroid carcinoma at an increasingly earlier stage. These developments open up possibilities to deescalate primary surgery adapted to these stages and avoid surgical overtreatment in locally limited tumor growth: thus, promoting a shift from routinely recommended total thyroidectomy with bilateral central lymph node dissection in favor of limited unilateral thyroid resection. Prerequisites for limited thyroid resection include clinical evidence that the tumor is sporadic, unifocal and confined to the thyroid. Corresponding calcitonin levels should also indicate that a biochemical cure will be achieved after unilateral resection. A decisive structural prerequisite for such a limited concept is the low threshold availability of intraoperative frozen section analysis that reliably detects and evaluates a medullary thyroid carcinoma and can assess a breach of the thyroid capsule and desmoplasia with certainty."

Treatment of Medullary Thyroid Cancer

The best treatment for Medullary Thyroid Cancer (MTC) is surgery. The goal of surgery is to completely remove all disease at the first operation.

After surgery, blood levels for calcitonin and CEA should be monitored routinely, usually every 6 months to a year. If calcitonin and CEA levels rise above the immediate post-operative level, a neck ultrasound and computed tomography (CAT) scan, should be performed to look for recurrent disease. If there is recurrent disease, then another operation may be needed.

Master, S.R. & Burns, B. 2020. Medullary thyroid cancer. ***In***: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan. 2020 Nov 16.
"Medullary thyroid cancer is a tumor arising from the parafollicular cells, or C cells, of the thyroid gland. Medullary thyroid cancer produces calcitonin, and elevated calcitonin levels are an essential feature of this tumor. It is derived from the medullary C cells that are of neural crest origin. Recent advances in molecular pathogenesis and genetic testing has led to risk stratification of the patients and identification of molecular targets for therapy. Prophylactic thyroidectomy is recommended for patients with mutations that put them at high risk. Various tyrosine kinase inhibitors are approved for use in progressive, metastatic medullary thyroid cancer."

Shete, J., AlSaleh, K., Safwat, R., Bedair, A., ElSherify, M., Hussein, A., Nazeeh, M. & Mohanty, A. 2020.
Introduction: Medullary thyroid cancers (MTC) constitute about 5% of all thyroid cancers. The 10-year overall survival (OS) rate of patients with localized disease in thyroid for this pathology is 80% to 90% which is comparable with differentiated thyroid cancers, figures drop to 75% for cases with nodal metastases. Only 20% of patients with distant metastases at diagnosis survive for 10 years. In metastatic disease there are variations with smoldering less active disease to progressive active disease. Surgery is cornerstone of the management with total thyroidectomy and nodal dissection as main treatment. Adjuvant treatment with radiotherapy is case selective, varies from case to case. The management of residual, recurrent disease is possible re-surgery with external beam radiation therapy. The development of targeted therapy has brought in a major advantage in management of metastatic disease. Two drugs -vandetanib and cabozantinib- have been approved for use in metastatic MTC. The optimum management in this group of patients is a challenge and long-term use of TKI needs to be balanced with monitoring side effects of TKI and dose adjustments of TKI.
Materials and methods: A retrospective review of cases with diagnosis of medullary thyroid cancers treated or registered at Kuwait Cancer Control Center was conducted. The data of patients registered between 1987 till 2017 was analyzed. The data was collected and analyzed using SPSS (version 20) software program. For analysis we considered date of surgery as the date of diagnosis. Final state of disease along with emphasis on prognostic factors was correlated with Kaplan Meyer survival curves.
Results: There were total 31 cases out of which 15(48.4%) were male and 16(51.6%) females. The median age at presentation was 51.6 years (range-28years-77years). MEN syndrome was diagnosed in 6(19.4%) patients. Staging revealed Stage I - 7/31 (22.58%), Stage II-3/31(9.67%), Stage III-7/31(22.58%), Stage IVA (nonmetastatic) -12/31 (38.70%), Stage IVC (metastatic) - 2/31 (6.45%). Total thyroidectomy and central compartment neck dissection was optimum surgery (29%). Total thyroidectomy with central compartment neck dissection and unilateral neck dissection was done in 38.7% patients, comprehensive neck dissection and total thyroidectomy was done in 32.2% patients. External beam radiotherapy (EBRT) with conformal or IMRT technique was used in 13 out of 31 patients. One patient was treated for bony metastasis with palliative intent. Four patients were treated by TKI for metastatic disease or at progression. Median follow up was 79 months. Median overall survival was 93 months. Median progression free survival irrespective of stage was 62 months. At the end of 5 years 61% patients were alive irrespective of stage of disease. Due to the small sample size and natural history of advanced MTC the observed p-value for several pathological variables in relation with survival was not significant.
Conclusion: Stage I and stage II cases of our study did well and were all alive and disease free till our last follow up. EBRT in our cohort of patient did not revealed any added benefits in survival. The use of TKI in metastatic disease was associated with many issues including availability of drug. Elevated serum calcitonin and CEA levels in absence of measurable disease should be dealt cautiously.

Rowell, N.P. 2019.
OBJECTIVE: In order to clarify the role of external beam radiotherapy in the management of medullary thyroid cancer (MTC), a systematic review was undertaken.

PATIENTS AND INTERVENTIONS: Patients with MTC of any stage receiving radiotherapy, either as adjuvant postoperative treatment or as primary treatment for unresectable disease.
DESIGN: Electronic searching Medline and ProQuest databases for randomised or non-randomised studies. A risk of bias assessment (ROBINS-I) was carried out for each study.
MAIN OUTCOME MEASURES: Overall survival, rates of locoregional recurrence, locoregional relapse-free survival.
RESULTS: There were no randomised studies. Twenty-seven non-randomised studies were identified. Within four cohort studies, radiotherapy had no significant effect on overall survival. Within one prospective and 22 retrospective studies (of approximately 1200 patients), radiotherapy similarly had no consistent effect on overall survival but there was evidence that radiotherapy reduces the risk of locoregional relapse, particularly in those with nodal involvement, extrathyroidal extension or residual disease. In a meta-analysis of patients within four studies, radiotherapy reduced the risk of locoregional relapse by at least 38%. Evidence supports the use of doses of 60 Gy or greater and an interval between surgery and radiotherapy of less than two months. Thirteen of 63 patients (21%) treated for unresectable disease achieved a complete response. Acute morbidity was observed in relation to difficulty swallowing, xerostomia and skin reactions. Late morbidity was infrequent with a low incidence of xerostomia.
CONCLUSIONS: Radiotherapy should be considered for those at high risk of locoregional relapse, in particular those with nodal involvement, extrathyroidal extension or residual disease (microscopic or macroscopic).

Wang, X., Li, C., Huang, L., Shui, C.Y., Liu, W., Cai, Y.C., Sun, R.H., Zhou, Y.Q., Jiang, J., Wang, W. & Zeng, D.F. 2019.
Objective: To review and summarize recent update on preoperative diagnostic criteria, treatment and postoperative follow-up for medullary thyroid carcinoma.
Methods: The relevant literatures and guidelines about medullary thyroid carcinoma were analysed and summarized.
Results: In the early stages of the disease radical surgery still dominated. Ultrasound results suggested that prophylactic lateral neck dissection was required for patients with high risk factors or high levels of carcinoembryonic antigen and calcitonin need prophylactic. Early hereditary medullary carcinoma could receive prophylactic thyroidectomy based on RET gene test results. Advanced progressive medullary thyroid carcinoma could be treated with palliative surgery, molecular targeted drugs and chemotherapy.
Conclusions: The prognosis of medullary thyroid carcinoma is poor and lymph node metastasis is easy to occur early. The extent of initial operation should be enough. Locally advanced or distant metastatic medullary thyroid carcinoma can be treated with palliative surgery, molecular targeted drugs and chemotherapy.

Beukhof, C.M., Brabander, T., van Nederveen, F.H., van Velthuysen, M.F., de Rijke, Y.B., Hofland, L.J., Franssen, G.J.H., Fröberg, L.A.C., Kam, B.L.R., Visser, W.E., de Herder, W.W. & Peeters, R.P. 2019.
BACKGROUND: For progressive metastatic medullary thyroid carcinoma (MTC), the available treatment options with tyrosine kinase inhibitors result in grade 3-4 adverse events in a large number of patients. Peptide Receptor Radionuclide Therapy (PRRT), which has also been suggested to be a useful treatment for MTC, is usually well tolerated, but evidence on its effectivity is very limited.
METHODS: Retrospective evaluation of treatment effects of PRRT in a highly selected group of MTC patients, with progressive disease or refractory symptoms. In addition, a retrospective evaluation of uptake on historical ^{111}In-DTPA-octreotide scans was performed in patients with detectable tumor size > 1 cm.
RESULTS: Over the last 17 years, 10 MTC patients were treated with PRRT. Four out of 10 patients showed stable disease at first follow-up (8 months after start of therapy) whereas the other 6 were progressive. Patients with stable disease were characterized by a combination of both a high uptake on ^{111}In-DTPA-octreotide scan (uptake grade ≥ 3) and a positive somatostatin receptor type 2a (SSTR2a) expression of the tumor by immunohistochemistry. Retrospective evaluation of historical ^{111}In-DTPA-octreotide scans of 35

non-treated MTC patients revealed low uptake (uptake grade 1) in the vast majority of patients 31/35 (89%) with intermediate uptake (uptake grade 2) in the remaining 4/35 (11%).
CONCLUSIONS: PRRT using ^{177}Lu-octreotate could be considered as a treatment in those patients with high uptake on ^{111}In-DTPA-octreotide scan (uptake grade 3) and positive SSTR2a expression in tumor histology. Since this high uptake was present in a very limited number of patients, this treatment is only suitable in a selected group of MTC patients.

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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