CARCINOMA OF THYROID

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Abstract: Carcinoma of thyroid is a malignant tumour of thyroid commonly occurring in both young and old age patients. The most common presentation of thyroid carcinoma is a thyroid nodule, however clinical evaluation of a thyroid nodule for carcinoma is difficult because benign thyroid nodules are so prevalent and by contrast thyroid carcinoma is so uncommon. Surgical treatment is preferred first line treatment in all types of thyroid malignancy. The risk factors are assessed in patients with follicular carcinoma having solitary nodule. External beam radiation and chemotherapy have less prominent roles but some patients require post operative external irradiation or chemotherapy.

Key words: Solitary Nodule, Papillary Carcinoma thyroidectomy, External bean redio-therapy.

Carcinoma of thyroid is a malignant tumour of thyroid commonly occurring in both young and old age patients.

The diagnosis can easily be made clinically as any enlargement of thyroid gland or change in its size or shape becomes obvious. The lesion is usually diagnosed at early and well differen-tiated stage.

INCIDENCE

Carcinoma thyroid is the most common malignant endocrine tumour. It is a less common malignancy (1% of all malignancies).

The lifetime risk of having thyroid carcinoma is about 1%. It is 2-3 times more common in females. Although thyroid cancer can occur at any age, the peak incidence is 50-54 years in females and 65-69 years in males1. Its incidence has increased almost 240% between 1950 and 2000 in USA but its overall mortality has remained stable since 1973[2].

Only few patients with thyroid malignancy die from this disease. It is responsible for less than 1% cancer related deaths. Annual incidence is between 05-10/100,00 population.

CHARACTERISTICS OF A MALIGNANT THYROID NODULE

The nodules smaller than 1cm are almost always benign. These do not require biopsy whereas those more than 4cm in size are suspicious. Other characteristics are its firmness, fixity to adjacent structures, presence of enlarged lymph nodes in the neck, vocal cord paralysis (hoarse voice), dysphagia, rapid growth and clinical features of invasion

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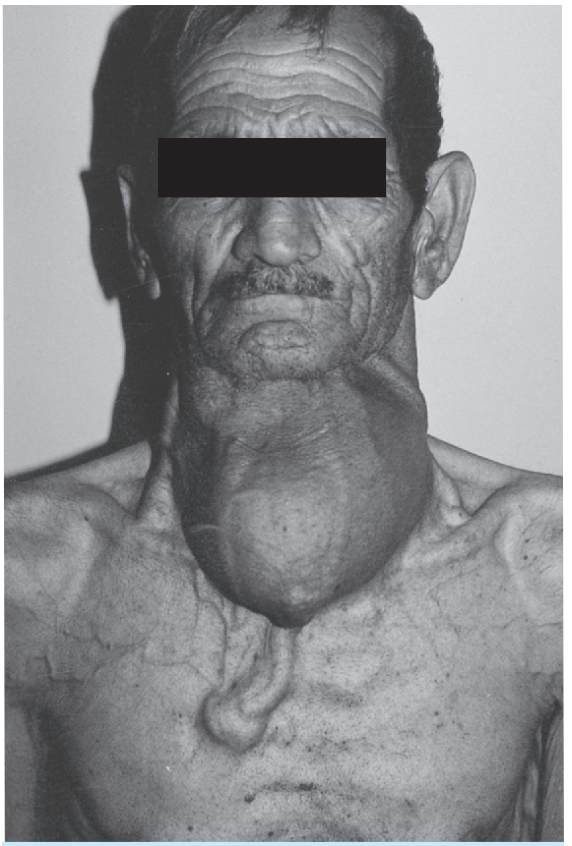
to adjacent structures.



Carcinoma thyroid (reterosternal extention) (superior vena caval syndrome)

Moreover the presence of central vascularity, microcalcifications and irregular borders on imaging studies are also suspicious.

The most common presentation of thyroid carcinoma is a thyroid nodule, however clinical evaluation of a thyroid nodule for carcinoma is difficult because benign thyroid nodules are so prevalent and by contrast thyroid carcinoma is so uncommon. However there are certain risk factors which increase the likelihood of a thyroid nodule to be malignant and these risk factors are:

Carcinoma of right lobe of thyroid

RISK FACTORS

AGE

Appearance of a new nodule in patients with less than 15 years and more than 60 years age.

SEX

Females are more prone to suffer from this disease.

IRRADIATION

History of irradiation to head and neck in the past is a common predisposing factor.

Exposure to ionizing radiation particularly during first two decades of life is an important predisposing factor. One third of these develop nodule and one third of these develop malignancy3.

Atom bomb survivors in Japan had an

increase risk.

FAMILY HISTORY

Positive family history of thyroid malignancy is a strong risk factor.

MEN-2

Multiple endocrine neoplasia type - 2 is a strong risk factor.

MISCELLANEOUS

- Hashimoto's thyroiditis.
- Nodular goitre.
- (PTC) oncogene is responsible for papillary thyroid carcinoma.
- RET proto-oncogene is also a major risk factor.

Recurrent laryngeal nerve palsy raises serious suspicions about malignant process involving the nerve.

Cervical lymphadenopathy may be the only clinical feature suggesting malignancy.

DIAGNOSIS OF THYROID CARCINOMA

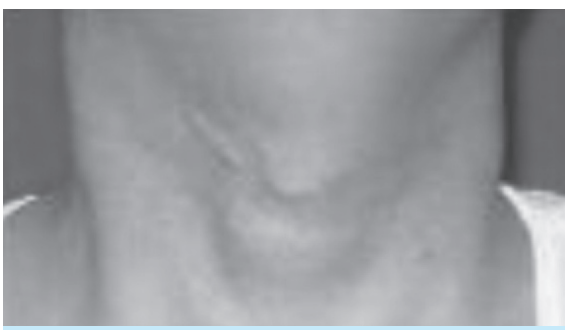
It requires good history and clinical examination. FNAC is a sensitive test for papillary, medullary and anaplastic carcinoma and one should not hesitate to repeat, if it is inconclusive in the presence of a strong clinical suspicion.

However it cannot differentiate between follicular adenoma and carcinoma which requires evidence of capsular or vascular invasion.

Patient should also have thyroid function tests, radioiodine or technicium scan, ultrasound of thyroid and neck. CT scan of neck is done if the nodule is fixed or there is retrosternal ex-tension.

Indirect laryngoscopy is performed, if there is any change in voice. The diagnosis is confirmed by FNAC or biopsy of the operated specimen. X-ray chest is essential to exclude metastasis in the chest.

Bomb blast causing irradiation



Carcinoma thyroid

Thyroid gland has greatest range of biologic behavior of the malignant phenotype.

Commonly following types of carcinoma thyroid are seen;

- Well differentiated thyroid carcinoma (WDTC) (Papillary, Follicular & Hurthle Cell Carcinoma).
- Anaplastic thyroid cancer.
- Medullary cell carcinoma.
- Lymphoma.

Papillary variety of differentiated thyroid carcinoma is the most common (80%) followed by follicular, medullary, hurthle cell and anaplastic4.

DUNHILL CLASSIFICATION

Well differentiated Thyroid Carcinoma (WDTC) 85%.

Anaplastic Thyroid Carcinoma (ATC) 15%.

Medullary Thyroid Carcinoma (MTC) 5-10%.
Lymphoma 5%.

WELLDIFFERENTIATED THYROID CARCINOMA (WDTC)

It is the most common type. It constitutes most of thyroid malignancies. It has following variants;

PAPILLARY CARCINOMA (60%)

It is the most common variant of carcinoma of thyroid. It is the least aggressive human cancer3. It accounts for 80% of thyroid carcinoma in patients under 40 years of age. It can occur at any age but is common in children and young adults Female to male ratio is 2:1.

It presents as a solitary or multi focal lesion within thyroid and may infiltrate into adjacent parenchyma with ill defined margins. The lesions are usually cystic but may have areas of calcification and fibrosis.

The surface has granular or papillary foci. The diagnosis is based on nuclear features and not the cell architecture. The nuclei contain fine dispersed chromatin giving an optically clear appearance. These are also called ground glass or Orphan Annie Nuclei.

The cytoplasmic invagination may give appearance of intra nuclear inclusions on cross section. Some tumours are predominantly follicular but even these behave biologically as papillary tumors due to nuclear features.

The neoplastic papillae have dense fibrovascular cores. These lesions often have concentrically calcified lesions called psammoma bodies. Foci of lymphatic permeation are seen in about 50% lesions and spread to adjacent lymph glands. Papillary carcinomas present as a mass in the neck, thyroid or cervical lymph glands. Lungs are a site of haemotogenous spread of these lesions in a minority of patients .

The prognosis of these patients is good (10 years survival is over 85%) but the prognosis is less favourable in elderly patients and with distant metastasis.

OCCULT CARCINOMA

Papillary carcinoma may present as an enlarged lymph node in the jugular chain with no palpable abnormality of the thyroid. The primary tumour may be no more than a few millimeters in size and is termed occult. Such primary foci of papillary carcinoma may also be discovered in thyroid tissue resected for other reasons, e.g. Graves disease. The term occult is now applied to all papillary carcinomas less than 1.5 cm in diameter. These have an excellent prognosis and are regarded as of little clinical significance.

FOLLICULAR CARCINOMA (15%)

It is the second most common differentiated thyroid carcinoma.

Follicular carcinoma is usually seen in older patients (peak incidence middle adult years).

Its incidence is higher in areas of iodine deficiency and nodular goiters. It may be grossly infiltrative or well circum-scribed. Larger lesions may infiltrate beyond the capsule of thyroid into soft tissues of the neck. Some of the lesions are formed of small follicles just like normal thyroid tissue, other lesions show less follicular differentiation. Some lesions show abundance of granular eosinophilic cytoplasm (Hurthle cells). Follicular carcinoma frequently presents as solitary thyroid nodule.

Differences between papillary and follicular carcinoma are as follows[5];

Differences between papillary and follicular carcinoma.

Factors	Papillary Carcinoma	Follicular Carcinoma
Male incidence	< 22%	> 35%
Multifocal	More	Rare
Capsular invasion	Unencapsu-lated	Encapsulated
Distant Metastasis	45%	75%
Recurrence Rate	19%	29%
Lymph node metastases	Common 35%	Rare 13%
Blood born metastases	Less common 40%	Common 60%
Local rec-curence after treatment	Common	less common 12%
Mortality Rate	Low 11%	High 24%

Extensive invasion of adjacent thyroid parenchyma makes the diagnosis obvious. Invasion may be limited to microscopic foci, vascular or capsular areas causing difficulty in differentiating from follicular adenomas.

Rarely these may be hyperfunctional. These metastasize via blood stream to lungs, bone and liver.

Regional nodal metastasis is uncommon. Well differentiated tumor responds well to radio active iodine (RAI). Thyroxine helps to suppress the endogenous TSH and keeps the lesion in control from further spread.

HURTHLE CELL CARCINOMA

It is also known as oxyphillic carcinoma. Although it is a variant of follicular carcinoma but carries poor prognosis.

It is similar to follicular carcinoma with the following differences;

- Loco-regional nodal metastasis occurs frequently.
- Metastasis is less likely to concentrate I131 so diagnostic I131 scans may be false negative.
- Radio therapy can be used to adjuvant for T4 lesions.

STAGING FOR WELL DIFFERENTIATED THYROID CARCINOMA (WDTC)

Patients with WDTC are assigned as "Low Risk" and "High Risk" patients by the two scale systems. One devised by the Mayo's clinic having two scales;

AGES scale:

(Age, Grade of tumour, Extent, Size)

MACIS scale:

(Metastasis, Age, Completeness of

resection, Invasion, Size).

The other devised by Lahey's clinic is as;

AMES scale:

Age, Metastases other than lymph nodes, Extent of disease, Sizes.

Based on above scale systems patients with WDTC are grouped into;

LOW RISK GROUP

Male of 40 years and younger or female 50 years and younger without distant metastasis. All older patients with ;

- Intra thyroid papillary carcinoma
- Follicular carcinoma with minor capsule invasion
- Tumor < 5 cm in diameter
- No distant metastasis

HIGH RISK GROUP

All patients with distant metastasis. All older patients with;

- Extra thyroid papillary carcinoma
- Follicular carcinoma with major capsule invasion
- Tumour > 5 cm in diameter

TNM STAGING OF THYROID CANCER

TUMOR

Tx	Primary cannot be assessed
T0	No evidence of primary
T1	Limited to thyroid, 1 cm or less
T2	Limited to thyroid > 1 cm but < 4 cm
T3	Limited to thyroid > 4 cm
T4	Extending beyond capsule, any size.

NODES

Nx	Cannot be assessed
N0	No regional node metastases
N1	Regional node metastases

METASTASES

Mx	Cannot be assessed
M0	No metastases
M1	Metastases present

Stage	Under 45 years	Over 45 years
I	Any T, Any N, M0	T1, N0, M0
II	Any T, Any N, M1	T2, N0, M0 or T3, N0, M0
III		T4, N0, M0 or Any T, N1, M0
IV		Any T, any N, M1
Only patients over 45years can suffer from stage III & IV disease5		

TREATMENT

WELL DIFFERENTIATED THYROID CARCINOMA

Two main modalities are available;

- Surgical
- Non Surgical

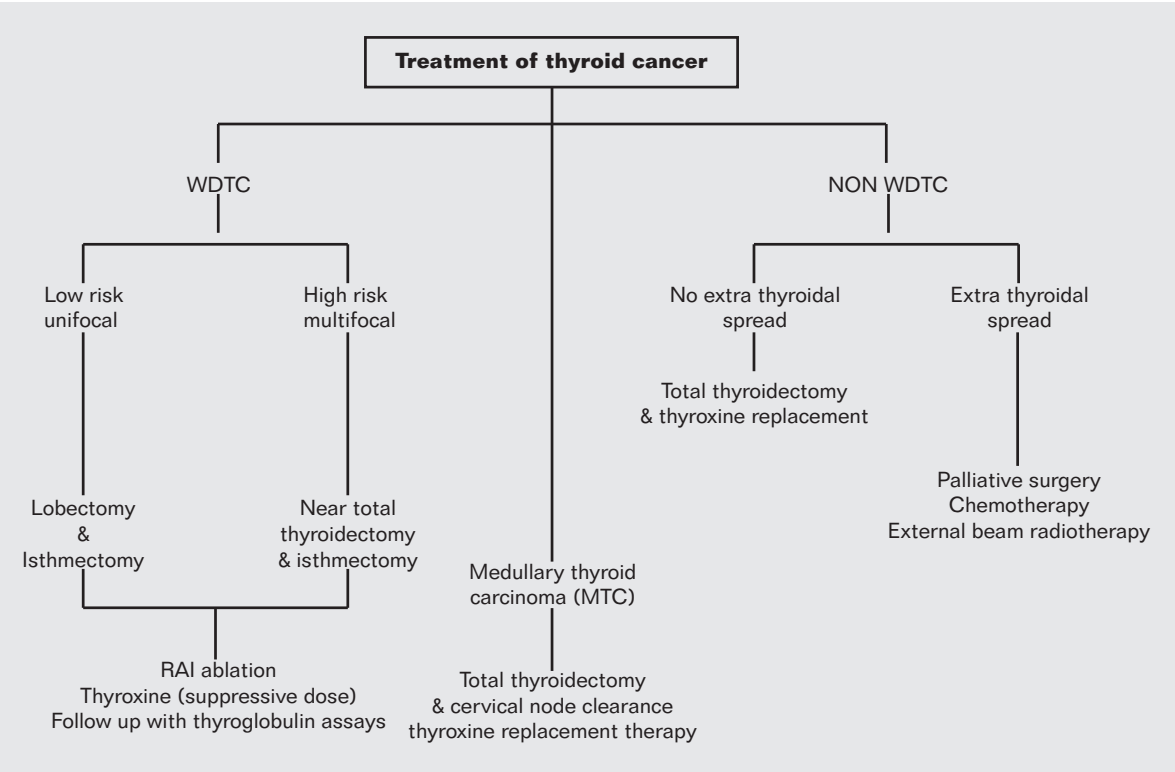
SURGERY

Surgical treatment is preferred first line treatment in all types of thyroid malignancy. The risk factors are assessed in patients with follicular carcinoma having solitary nodule. If the patient belongs to low risk group then the option is;

Lobectomy plus isthmusectomy for low risk group patients. The ultimate survival is the same between this procedure and total thyroidectomy in these patients.

Following features are assessed and debated for management;

- Extent of primary surgical resection.
- The need for and extent of regional lymph node dissection.
- Role of post operative Radio iodine Remnant Ablation (RRA) in follicular cell



differentiated carcinoma.

- Degree of thyrotrophin (TSH) suppression required in long term management of follicular cell differentiated carcinoma.

Total thyroidectomy with or without cervical lymph nodes dissection (Central lymph nodes dissection is performed in high risk patients if cervical lymph nodes are not palpable.

Ipsilateral modified radical neck dissection is performed if lymph nodes are palpable.1

However if final histopathology report shows aggressive variant disease (tall, columnar cell or poorly differentiated cells).

Total thyroidectomy or near total thyroidectomy for any patient with WDTC.

Patients with poorly differentiated carcinoma, multifocal disease, positive isthmus margins, cervical node enlargement or extra thyroidal extention should have completion total thyroidectomy.

Lobectomy is sufficient for tumors with no history of neck radiation, negative margins, no obvious enlargement of lymph nodes and small incidentally found < 1cm tumors.

LYMPH NODE SURGERY

Routine lymph node dissection in WDTC is not of any benefit. Cervical lymph node clearance is only indicated in WDTC with macroscopic nodal involvement.

NON SURGICAL TREATMENT

After surgery (total thyroidectomy) a diagnostic I131 or 1123 whole body scan is

done. If any uptake is detected it is ablated using 30-100 mci of 1123 some centres do straightway ablation without a diagnostic whole body scan and then perform post treatment whole body scan. These patients are given thyroxine (100-200mg) to suppress TSH levels just below the lower limit of normal range for lower risk patients and a greater level of suppression is required for high risk patients.

Radio iodine (I131) ablation and thyroxine suppression therapy.

External beam radiation and chemotherapy have less prominent roles but some patients require post operative external irradiation or chemotherapy.

T4 tumors are given adjuvant radiotherapy.

TREATMENT OF RECURRENT DISEASE

Surgery is the treatment of choice for loco-regional recurrence of differentiated carcinoma. The treatment options are surgery, I131 therapy with or without radiotherapy. Radiotherapy alone or tumor embolization or doxorubicin chemotherapy.

Four to six weeks after surgery TSH level is assessed. When it rises to 30 to 50 microunit /ml, I131 scan (2 - 5 mci) is repeated. If the tumor is papillary carcinoma and unresectable for any reason, I131 combined with external beam radiotherapy is used for tumors which concentrate I131 (as seen on I131 scan) whereas external beam radiotherapy alone for those which do not concentrate I131.

Radioiodine alone is used for loco-regional recurrence of unresectable follicular carcinoma and if it is not responsive to radioiodine radio-therapy can be tried.

If uptake by thyroid tissue is <01% and there is no metastasis, then thyroxin is given in suppressive dosage that is 100 to 200 microgram/day. The patient is followed up by serial serum thyroglobulin levels (normal range 01-35 µg/ltr).

Thyroglobulin level more than 50µg/ltr means residual or local recurrence.

Thyroglobulin level >100 µg/ltr means presence of distant metastasis.

If uptake of thyroid tissue is >1% then ablation of the residual thyroid tissue with 30 mci I131 is performed. Whole body scan is repeated to assess distant metastasis.

Ablative dosages of I131 is 75 - 100 mci is used for neck metastasis.

Ablative dose for distant metastasis is 150 - 200 mci.

Patient is given thyroxine in suppressive dosages after ablation. Follow up is done with serial thyroglobulin levels.

FOLLOW UP

The patients are followed up at 6-12 monthly intervals. Clinical examination, TSH, thyro-globulin (Tg) and I131 scan (exclude pregnancy before I131 scan) are performed.

Ultrasound CT/MRI or PET scans are also done in patients where thyroglobulin levels are high but I131 scan is negative.

The patients should be hypothyroid before I131 scan and thyroglobulin measurements (thyro-xine is with held for 4-6 weeks and TSH levels are assessed).

The other option is use of T3 for four weeks or using recombinant TSH without withholding thyroxine. Recombinant TSH is given I/M in a dose of 2mg per day followed by 4 mci of I131 on 3rd day. Then whole body scan and thyro-globulin levels are performed on 5th day.

PROGNOSIS OF DIFFERENTIATED THYROID CARCINOMA

Overall 10 years survival of papillary, follicular and Hurthle cell carcinoma is 93%, 85%, 76% respectively.

The patient related prognostic factors are age, sex and family history of thyroid cancer. It behaves more aggressively in males > 40 years of age and there is dramatic increase in mortality in patients who are above 60. It has got highest recurrence 40% in patients of less than 20 years and more than 60 years of age. Whereas in other age groups overall recurrence is 20%.

The tumor related prognostic factors are poor histologic picture (tall cell and columnar cell papillary carcinoma, invasion outside thyroid capsule and extensive vascular invasion), local tissue invasion lymph node involvements and distant metastasis (90% in lungs and pleura). There is a linear relationship between;

- Increase in size above 1.5 cm
- Tumor recurrence
- Mortality

PAPILLARY CARCINOMA WITH SOLITARY NODULE

Whether patient is low risk or high risk, total thyroidectomy is performed (as this tumor is multifocal). Follow up and adjuvant treatment plan is the same as for follicular carcinoma.

Total ipsilateral thyroid lobectomy is minimal surgical excision required for unilateral solitary malignant nodule (Less than 1 cm and confined with in the capsule and without metastasis or angio-invasion).

Total or near total thyroidectomy is performed for residual tissue ablation as it is a multifocal malignancy. Complete lymphadenectomy is done for involved nodes. Prophylactic lateral neck node dissection may not be performed.

FOLLICULAR OR HURTHLE CELL CARCINOMA

Most of follicular and Hurthle cell carcinomas are large, soft and solitary nodules. Approximately 80% of these are benign, larger lesions may be malignant specially in men over 50 years of age.

Total thyroid lobectomy and isthmusectomy is preferred in benign cases and if malignancy is confirmed total thyroidectomy is performed. It is followed by Radio Iodine Ablation of residual tumour.

Lymph node dissection is performed when palpable.

Suppressive doses of thyroxine are used.

Radio active I131 is used to ablate the residual thyroid tissue after complete thyroid resection.

FOLLOW UP

Thyroid hormone therapy is stopped for 6 weeks. Tri-iodothyroxine 25µG 2-3 times daily is given during first four weeks to minimize the period of hypothyroidism. The dose can be lowered for elderly and heart patients.

A low iodine diet is given 2-4 weeks before radio iodine scanning.

More than 90% of patients after total or near total thyroidectomy achieve a serum TSH concentration of more than 25µk/ml which is a necessary level for optimal scanning. Hypo-thyroidism symptoms are the biggest drawback of this investigation.

Thyroxine withdrawal is contraindicated in pat-ients with severe pulmonary or cardiovascular disease.

Higher doses of radio iodine are used for metastatic disease. Pregnancy is excluded before starting radio iodine. Post therapy scan is performed 4-10 days after the radio iodine treatment.

Thyroid hormone replacement therapy is restarted after treatment. Giant cell variety of undifferentiated thyroid malignancy is the most lethal and very few patient survive for more than three years after diagnosis3.

ANAPLASTIC THYROID CARCINOMA

Anaplastic thyroid carcinoma is the most aggressive human malignancy. It occurs in elderly patients in areas of endemic goitre.

These present as bulky mass which grows beyond thyroid capsule into adjacent struc-tures of neck. The cells are highly anaplastic (undifferentiated). These are large pleomor-phic giant cells, spindle cells with sarcomatous appearance of cells with a vague squamous appearance.

Some are small cells. Foci of papillary or follicular differentiation may be seen at many places. These grow widely and metastasis to distant sites is common. These tumors have very poor prognosis.

Total thyroidectomy is performed if extra thyroidal disease is detected although this situation is rare.

In patients with extra thyroidal spread, palliative surgery is offered as debulking and tracheostomy. Chemotherapy and external beam radiotherapy is also offered.

Most patients die within one year of diagnosis.

MEDULLARY THYROID CARCINOMA (MTC)6

It is the malignancy arising from C cells (para follicular cells). These produce calcitonin just like normal "C" cells.

Medullary carcinomas arise sporadically in about 80% of the cases. The remaining 20% occur in MEN syndromes IIa or IIb (multiple endocrine neoplasia) as familial tumors (Younger patients). The malignancy is always bilateral in these cases.

Some of these tumors may produce other polypeptide hormones such as Carcino Embryonic Antigen (CEA), Somatostatin, Serotonin and Vaso-active intestinal peptide (VIP).

Recently RET (proto-oncogene mutation) have been found in these tumors.

Peak age incidence is 5th and 6th decades of life.

These may arise as a solitary nodule or as multiple lesions in both lobes.

Familial cases are multi-centric larger lesions

contain areas of necrosis and hemorrhages. The tumor invades through the capsule.

The tumor is composed of polygonal to spindle shaped cells which may form nests, trabaculae and even follicles.

Anaplastic cells are also seen. Acellular amyloid deposits derived from altered calcitonin molecules are present in adjacent stroma in many cases. Areas of "C" cell hyperplasia are present in surrounding thyroid parenchyma.

These patients present with swelling in the neck and sometimes associated with dysphagia and hoarseness of voice .

Some present with diarrhoea due to VIP secretion. Screening of relatives for elevated levels of calcitonin or RET mutation help in early detection of disease. Raised serum level of calcitonin helps in diagnosis monitoring and follow up of the disease. Sporadic medullary thyroid carcinomas and those arising in patients with MEN IIb are aggressive and spread through blood stream and have 50% five year survival.

Total thyroidectomy is performed. Central node clearance from hyoid bone superiorly to innominate vein inferiorly.

There is no role of thyroxine suppression therapy although replacement thyroxine therapy can be given.

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