REVIEW ARTICLE

Management of Thyroid Cancer: A Brief Review of Selected Literature

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Introduction :

Carcinoma of thyroid gland is a quite common malignancy affecting the thyroid gland. Females are more likely to have thyroid cancer at a ratio of three to one[1]. Thyroid cancer can occur in any age group, although it is most common after age 30 and its aggressiveness increases significantly in older patients. The majority of patients present with a nodule on their thyroid, which typically does not cause symptoms[2].

There are five types of thyroid cancer some of which are much more common than others. The most common types of thyroid carcinoma are papillary and mixed papillary/follicular (~75%), and follicular and Herthele cell tumour (15%). Others are medullary (~ 7%), and anaplastic and lymphoma (3%)[1]. Papillary and follicular carcinoma of thyroid together termed as differentiated thyroid carcinoma (DTC), and have best prognosis. The prognosis of DTC are improving significantly over the past three decades all over the world and in our country as well with the radioiodine remnant ablation therapy and improved surgical clearance of diseased thyroid and its metastatic sites.[3]

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Epidemiology :

Thyroid swellings, also known as goitres, are common clinical problems throughout the globe and in Bangladesh as well. Swelling presenting in front of the neck due to thyroid disease ranges from invisible but palpable to huge one almost equal to the size of the head of the patient are seen. Exact incidence of thyroid cancer in Bangladesh is not known but an estimate of 2.58 % of 2,629 patients attending at the then Institute of Post-graduate Medicine and Research (IPGMR) from January 1994 to June 1995 were suffering from carcinoma thyroid [3]. In the United States, there are over 11,000 new cases of thyroid cancer diagnosed in each year and 19,000 patients are thyroid cancer survivors, some for more than 40 years after diagnosis. Thyroid cancer constitutes nearly 1% of all human malignant tumours[4]. The annual incidence is about 3.7 per 100,000 population[2,4].

Aetiology :

Exact aetiology of thyroid cancers is not known. Endemic goitres predisposing to follicular variant of differentiated thyroid carcinoma possibly occurs due to high TSH stimulation[5]. Treatment by radiation in childhood for diseases of head-neck and thorax are observed to induce papillary variant of thyroid malignancy in adult life. Malignant lymphoma can present in patients known to have autoimmune thyroiditis.[6]

Classification :

Classification of malignant thyroid tumours is detailed below[1,2,4]. Primary tumours of follicular cell origin may be differentiated or undifferentiated. Differentiated follicular cancers include papillary carcinoma and follicular carcinoma, and undifferentiated type include anaplastic variety of growth. Parafollicular cells give rise to medullary carcinoma and lymphoid cells to lymphoma. Secondary carcinomas may be metastatic or may be locally infiltrative (Table – I).

Table – I: Classification of malignant thyroid tumours

Nature of growth	Cells of origin	Type of cancer
Primary	Follicullar epithelium	Differentiated: Papillary carcinoma Follicular carcinoma Undifferentiated: Anaplastic carcinoma
	Parafollicular cells	Medullary carcinoma
	Lymphoid cells	Lymphoma
Secondary		Metastatic cancers Local infiltration

There may be mixed follicular variant of papillary and follicular with Hurthle cells types affecting the prognosis of thyroid malignancies.[6,7].

Diagnosis :

Diagnosis of thyroid neoplasm depends on clinical presentation and investigations[7,8]. The commonest presenting feature is a thyroid swelling, and a 5-year history is far from uncommon in differentiated thyroid malignancies[5]. Enlarged cervical nodes remaining inpalpable in the thyroid region may be a presentation of papillary carcinoma. Recurrent laryngeal nerve paralysis may be a presenting feature of locally advanced disease. Hard, irregular and infiltrating thyroid swellings are usually anaplastic growths.

There are differences between the papillary and follicular carcinoma. Follicular carcinoma has a male preference, less frequent lymph node metastasis, early and frequent capsular and vascular invation, high distant metastasis and there is recurrence with high mortality rate. Papillary carcinoma has got a high rate of nodal metastasis and local recurrence[4,5,8]. A number of risk factors have been identified which determine the prognosis of the differentiated thyroid carcinomas. On the basis of the age, tumour spread, size and histology, patients are classified as low risk and high-risk groups (Table - II). Patients in low risk group account for 90% of cases of differentiated carcinoma[6,7,8].

Table - II: Differentiated thyroid carcinoma: Risk group definitions[1]

Risk group	Description
Low risk group	Men of 40 years and younger, women of 50 years and younger, without distant metastasis. All older patients with intrathyroid papillary carcinoma, follicular carcinoma with minor capsular involvement, tumour less than 5 cm in diameter, no distant metastasis.
High risk group	All patients with distant metastasis. All older patients with extrathyroid papillary carcinoma, folliculer carcinoma with major capsular involvement, tumour 5 cm or larger.

Undifferentiated carcinoma occurring mainly in elderly women are extremely lethal tumours and presents with local infiltration and early lymphatic and vascular spread. These aggressive tumours are at times present with tracheal obstruction[1,2,6,7].

Medullary carcinoma are neural crest derived parafolliculer 'C' cell tumours incorporated in thyroid and present as primary thyroid tumour. High levels of serum calcitonin (>0.08ng/ml) are produced by many medullary tumours. Some tumours are familial affecting children and young adults, and accounting 10-20% of all cases[1,5,8]. Medullary carcinoma may occur in combination with adrenal phaeochromocytoma and hyperparathyroidism and the syndrome known as multiple endocrine neoplasia type 11a (MEN11a). Lymph node metastasis and blood born metastasis are very common[1,8].

Malignant lymphoma are diagnosed when thyroid is involved and often confused with anaplastic thyroid carcinoma[1,2,8,9,10].

Radiolabelled iodine (I^{131}) in low dose is taken up by the thyroid gland and shows the activity; if the thyroid swelling shows no activity of thyroid there is suspicion of tumour, 17-30% of which may be malignant[9]. For detection of metastasis and assessment of residue after surgery for ablation, radiolabelled iodine is of immense value.

Fine needle aspiration cytology (FNAC) has become established as an investigation of choice[1,2,4,6,8,10,11] to evaluate a thyroid swelling. It has excellent patient compliance, the procedure is simple and quick to perform, and may be done in an outpatient clinic. The procedure may easily be repeated. Thyroid malignancies that can be diagnosed by FNAC are papillary carcinoma, medullery carcinoma, anaplastic carcinoma and lymphoma. Follicular neoplasms, adenoma and carcinoma cannot be differentiated by cytology alone, it also depends on capsular and vascular invasion. There are very few false positives in FNAC in malignancies, but there is a definite false negative rate with respect to both benign and malignant neoplasms.

Histological confirmation remains the main tool for deciding the treatment protocol[1,2,5,6,8]. Papillary carcinoma can often be diagnosed by FNAC and it constitutes 70-85% of thyroid malignancies but for accurate diagnosis of folliculer carcinoma, one must clearly demonstrate tumour invasion through the capsule of the nodule or of blood vessels, which requires multiple serial sections of paraffin fixed specimen to be examined. Intraoperative frozen section is also inadequate for this purpose[4]. Postoperative serial section histopathology of the resected specimen remains the main and confirmatory diagnostic procedure.

Serum calcitonin level is an important tumour marker in follow up of medullary thyroid carcinoma[1,8]. Measurement of serum thyroglobulin is of value in follow up and in the detection of metastetic diseases after surgery of differentiated thyroid carcinoma[1,4,8].

Treatment :

Treatment options for thyroid carcinomas varies depending of the pathology of the tumour and its presentation.

Differentiated thyroid carcinoma: Modalities of treatment for differentiated thyroid carcinoma are surgery, radio-iodine ablation therapy and external radiotherapy[1,6,7,8]. There is continuing disagreement on the most appropriate operation for differentiated

thyroid carcinoma. There are two schools of thought, conservative approach is lobectomy with isthmusectomy in patients with unilateral thyroid disease, and radical approach is total thyroidectomy and surgery or radioablation of metastases in high risk group. In conservative approach, patients in low risk group are treated by lobectomy with isthmusectomy and are followed up at regular intervals, and if any recurrence or nodal metastasis appears then complete thyroidectmy with berry picking /radical neck dissection is done. Subsequent management remains to residual assessment and radio-iodine ablation of remnants, and life long total thyroxin supplement. The proponents for total thyroidectomy in low risk group believe that multiple foci may occur in the same lobe of the primary tumour or less commonly in other lobe also. But it must always be remembered that total thyroidectomy has higher risk of recurrent larygeal nerve palsy, and bilateral intervention is associated with of life long tracheostomy or risk of it and of hypoparathyroidism[8].

Total thyroidectomy and thyroxin replacement is done for low risk patients here and for high risk patients total thyroidectomy with nodal clearence by berry picking/modified neck dissection/radical neck dissection followed by residual radio-iodine ablation and thyroxin replacement. Distant metastasis requires external radiotherapy.

Undifferentiated thyroid carcinoma: Radiotherapy with adjuvant combination chemotherapy may provide a worthwhile period of palliation. Many of these aggressive tumours cause tracheal obstruction and require decompression [1,2,8].

Medullary carcinoma: Total thyroidectomy and resection of involved lymph nodes by a radical or modified radical neck dissection is the treatment of choice for medullary carcinoma of thyroid gland. Genetic screening is done to detect familial cases. Phaeochromocytoma needs to be excluded. Prophylectic thyroidectomy is recommended for those with positive family history especially if there is a rise in calcitonon level[8,9].

Malignant lymphoma: Lymphomas are treated by irradiation[1,8].

Prognosis :

Prognosis of thyroid carcinoma patients depends on a number factors: a) host factors like age and sex of the patients and b) tumour factors like tumour histology, primary tumour size, local invasion, metastasis–stage of the tumour[1,4,5,8].

Age is an important variable for thyroid cancer mortality. After the age of 40 carcinomas are more lethal and after 60 the lethality rises dramatically [1,8,11]. Prognosis of tumours in children are good with respect to survival though presentations are more advanced and recurrences are more after therapy[12]. Prognosis is favorable for women than men.

In general, prognosis of differentiated thyroid carcinoma is good, more so with the papillary thyroid carcinoma. In some histological types like anaplastic tumour transformation, columner variant of papillary carcinoma, diffuse sclerosing variants have graver prognosis[7]. Follicular carcinoma is more aggressive than papillary carcinoma and shows early tendency to capsular and vascular infiltration. It also causes a rapid and distal metastasis leading to a worse prognosis. Prognosis of differentiated carcinoma is

poorer as the tumour rapidly increases in size. Nodal metastasis is a risk factor for local recurrence and is associated with poorer prognosis. Distant metastasis is the principal cause of death for papillary and follicular carcinoma of thyroid. The sites of reported distant metstasis in decreasing order of frequency are lung, bone, central nervous system and other soft tissues[6,7,11].

Undifferentiated carcinomas are extremely lethal and survival after 1-2 years after presentation is most unusual. Prognosis of medullary carcinoma is excellent if the tumour is confined to the thyroid gland, and good as long as the metastases are confined to the cervical lymph nodes. It is poor once the blood born metastases are present.

Prognosis of lymphoma of thyroid is good if there is no involvement of cervical lymph nodes and worse if it is associated with generalized lymphadenopathy.[1,8,10]

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