Management of thyroid carcinoma
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Overview
The two most common forms of thyroid cancer, papillary and follicular thyroid cancer, together termed differentiated thyroid cancer (DTC), comprise the majority of thyroid cancers and have the best prognosis. Experts believe that DTC has increased in many places around the world over the past three decades, yet this has been associated with a significant fall in mortality rate in some countries. In our experience, we also found that the incidence of DTC is increasing in Bangladesh.

Epidemiology
Although thyroid nodules are extremely common, malignant lesions derived from thyroid epithelial cells are relatively rare. Clinically recognized thyroid carcinomas constitute less than 1% of all human malignant tumors. The annual incidence of thyroid cancer varies worldwide from 0.5 to 10 per 100,000 populations. It is the most common endocrine malignant lesion (90% of all endocrine cancers) and is responsible for more deaths than all other endocrine cancers combined. Exact incidence of thyroid cancer in Bangladesh is not known. One study at INM & Thyroid Clinic in IPGMR Dhaka reviewed 2629 Thyroid patients from January 1994 to June 1995, and found Thyroid carcinoma in 2.58%. The American Cancer Society estimates that 17,000 new cases of thyroid cancer are diagnosed annually in the United States and that 1,300 thyroid cancer-related deaths occur annually. Nevertheless, with appropriate treatment, the survival rate from thyroid cancer is very high. In the United States, an estimated 190,000 patients are thyroid cancer survivors, some for more than 40 years after diagnosis.

Etiology
Exact etiology of thyroid cancer is unknown. Radiation to head and neck and thorax in small doses in childhood is liable to induce thyroid cancer in later life. Irradiation of the cervical lymph node in Hodgkin's disease may predispose for thyroid malignancy in late life. Endemic goiter predisposes for Follicular carcinoma.

Classification of malignant thyroid tumors
Primary
- Follicular epithelium: differentiated
  - Papillary carcinoma
  - Follicular carcinoma
- Follicular epithelium: undifferentiated
  - Anaplastic carcinoma
- Parafollicular cells
  - Medullary carcinoma
- Lymphoid cells
  - Lymphoma

Secondary
- Metastatic carcinoma
- Local infiltration.

Though there are various types of thyroid cancer as seen in the above list, the present article will be dedicated in discussing management of Papillary and Follicular Carcinoma. There is difference of opinion among Surgeons about the extent of thyroid resection. Managing differentiated (papillary and follicular) thyroid carcinoma can be a challenge because there have been no prospective randomized trials of treatment. Results from randomized trials that are under consideration will not be available for many years given the typically prolonged course. This account for much of the disagreement in managing differentiated thyroid carcinoma.

Diagnosis
At the time of initial assessment, most patients with thyroid cancer have a palpable neck mass, either a primary intrathyroidal
tumor or metastatic regional lymphadenopathy. In some patients, however, the tumor may be clinically occult, and the impalpable lesion may first be recognized at the time of surgical intervention for presumed benign thyroid disease. Unfortunately, even thorough history taking and physical examination rarely allow the definitive diagnosis of thyroid cancer. The diagnosis of thyroid cancer necessitates cytological or histological confirmation. FNA biopsy is the most cost-effective method of distinguishing benign from malignant thyroid nodules preoperatively. The diagnosis of thyroid cancer must be substantiated by careful pathologic examination of surgically excised thyroid tissue. This verification is particularly important in cases of cellular follicular lesions described by cytologists as "suspicious" for follicular cell neoplasm (also known as follicular neoplasms or microfollicular lesions). For accurate diagnosis of follicular carcinoma, one must clearly demonstrate tumor invasion through the capsule of the nodule or tumor invasion of blood vessels (angioinvasion). This process requires multiple serial sections through the excised paraffin-fixed specimens and careful evaluation for the presence or absence of such microinvasion. Intraoperative frozen section is often inadequate for this purpose. Papillary thyroid carcinoma (PTC) constitutes 75 to 80% of cases of clinically recognized thyroid cancer and can often be diagnosed with confidence by FNA biopsy.

Prognosis and recurrence of differentiated thyroid carcinoma
In the NCDB (National Cancer Data Base, USA) study, the 10-year relative survival rates for patients with papillary and follicular were 93% and 85%, respectively. Although anaplastic thyroid carcinoma is uniformly lethal, most thyroid carcinoma deaths are from papillary and follicular carcinomas, which account for nearly 95% of all thyroid carcinoma cases.

Age, stage, and gender at diagnosis
Although many factors influence the outcome for patients with papillary and follicular thyroid carcinomas, the two most important and consistently demonstrable are patient age at the time of initial therapy and tumor stage.

A significant number of studies show that age is an important prognostic variable for cancer mortality. Thyroid carcinoma is more lethal after age 40, increasing in severity thereafter with each subsequent decade of life and rising dramatically after age 60. However, tumor recurrence rates show a remarkably different age pattern. Rates are highest (40%) before age 20 and after age 60. Recurrence for other ages is approximately half this rate. Children typically present with more advanced disease and have more tumor recurrences after therapy than adults, yet their prognosis for survival is good. Prognosis is less favorable in men than in women, but the difference is usually small.

Tumor variables affecting prognosis
Certain tumor features have a profound effect on prognosis. Perhaps the most important features are tumor histology, primary tumor size, local invasion, and metastases.

Histology
Although survival rates with typical papillary carcinoma are quite good, cancer-specific mortality rates vary considerably with certain histological subsets of tumors. A graver prognosis is associated with (1) anaplastic tumor transformation and tall-cell papillary variants, (2) columnar variant papillary carcinoma, (3) diffuse sclerosing variants. Follicular-variant papillary carcinoma, which is recognized by its follicular architecture and typical papillary cytology, does not appear to have a worse prognosis than the more common pure papillary lesions. Follicular carcinoma is typically a solitary encapsulated tumor that may be more aggressive than papillary carcinoma. It usually has a microfollicular histologic pattern. It is identified as cancer by follicular cell invasion of the tumor capsule and/or blood vessels. The latter has a worse prognosis than capsular penetration alone.
Primary tumor size
Papillary carcinomas smaller than 1 cm, termed "microcarcinomas," are typically found unexpectedly after surgery for benign thyroid conditions. Their recurrence and cancer specific mortality rates are near zero. Small (less than 1.5 cm) but clinically apparent papillary or follicular carcinomas almost never cause distant metastases. Fig 2: Papillary Carcinoma of Thyroid Furthermore, rates of recurrence after 30 years are one-third those associated with larger tumors and 30 year cancer-specific mortality is 0.4% compared to 7% for tumors 1.5 cm or larger. In fact, the prognosis for papillary and follicular carcinomas is incrementally poorer as tumors increase in size.

Local tumor invasion
Up to 10% of differentiated thyroid carcinomas grow directly into surrounding tissues, increasing morbidity and mortality. The invasion may be microscopic or gross and can occur with both papillary and follicular carcinomas. Recurrence rates are two times higher with invasive than noninvasive tumors. Up to one-third of patients with invasive tumors die of cancer within a decade.

Lymph node metastases
In one review, nodal metastases were found in 36% of 8,029 adults with papillary carcinoma, in 17% of 1,540 patients with follicular carcinoma, and in up to 80% of children with papillary carcinoma. An enlarged cervical lymph node may be the only sign of thyroid carcinoma. In these patients, multiple nodal metastases are usually found at surgery. The prognostic importance of regional lymph node metastases is controversial. Some studies find that the presence of regional lymph node metastases has no impact on recurrence or survival. Other studies find nodal metastases are a risk factor for local tumor recurrence and cancer specific mortality and correlate with distant metastases, especially if there are bilateral cervical or mediastinal lymph node metastases or if the tumor invades through the lymph node capsule. In one study, 15% of patients with cervical node metastases died of thyroid carcinoma while all patients without cervical node metastases survived. Another study of patients with distant metastases from papillary carcinoma who had cervical or mediastinal lymph node metastases had a significantly higher 30-year cancer-specific mortality (10%) than patients without metastases (6%).

Distant Metastases
Distant metastases are the principal cause of death from papillary and follicular carcinomas. Almost 10% of patients with papillary carcinoma and up to 25% of those with follicular carcinoma develop distant metastases. About half of these metastases are present at the time of diagnosis. The sites of reported distant metastases among 1,231 patients in 13 studies were lung (49%), bone (25%), both lung and bone (15%), and the central nervous system or other soft tissues (10%). Although some patients, especially younger ones, with distant metastases survive for decades, about half die within 5 years regardless of tumor histology. Even so, some pulmonary metastases are compatible with long-term survival.
Tumor staging and prognostic scoring strategies

Several staging and clinical prognostic scoring strategies use patient age over 40 as a major feature to identify cancer mortality risk from differentiated thyroid carcinoma. When applied to the papillary carcinoma data from the Mayo Clinic, four of schemes using age (EORTC/European Organization for Research and Treatment of Cancer, TNM/tumor characteristics, lymph node involvement, and distant metastatic lesions, AMES/age of patient, presence of distant metastatic lesions, and extent and size of the primary cancer, and AGES/patient age and tumor grade, extent, and size), were effective in separating low-risk patients, in whom the 20 year cancer-specific mortality was 1%, from high-risk patients, in whom the 20 year cancer-specific mortality was 30% to 40%. Incrementally metastasis, age, completeness resection, invasion, and (MAC'S) scores of less than 6; 6.99; 7 to 7.99; and 8+; the 20-year survival rates were progressively lower: 99%, 86%, 59%, and 24%, respectively. The American Joint Commission on Cancer (AJCC) TNM staging approach, which is perhaps the most widely used schemes, classifies tumors in all patient under age 45 as stage I and stage II (i.e., low risk), even those with distant metastases. Although, it has been widely verified to predict cancer mortality, TNM staging does not forecast the high number of recurrences that occur in patients diagnosed before age 20, which is true of all prognostic scoring systems that lend heavy weight to ages. In the Otolaryngology Department of Bangabandhu Sheikh Mujib Medical University at Dhaka we define low and high risk in following order. Here, in papillary carcinoma a low risk patient means a case which has got, a. age between 15 to 40 years, b. intrathyroidal growth, c. tumor size less than 4 cm. and d. no nodal or distant metastasis; and a high risk patient means a case having i. age below 15 year and over 40 years, ii. extra thyroid growth, iii. tumor size 4 cm. or more and iv. with nodal or distant metastasis. All follicular carcinoma are kept in high risk group irrespective of age of patient, extent & size of tumor and metastasis. The above criteria has a close similarity with NCCN (National comprehensive cancer network, USA) criteria in regard to papillary carcinoma but different to NCCNs low and high risk types, we categorize all follicular carcinoma as high risk ones.

Primary treatment-Papillary thyroid carcinoma (PTC)

No prospective clinical trials have clearly determined the "best treatment" of patients with PTC. In most cases, a preoperative diagnosis of PTC established by FNA allows appropriate surgical planning. Total ipsilateral thyroid lobectomy is generally thought to be the minimal surgical procedure for a unilateral, possibly malignant thyroid nodule. Unilateral total lobectomy may be an appropriate definitive procedure for patients with minimal thyroid cancers. Most surgeons agree that total thyroidectomy is the preferred operation for high-risk patients with PTC- as defined by the AMES, AGES, TNM EORTC, or MAGS classification system. For several reasons, however, opinions differ about the extent of thyroid resection for patients with low-risk PTC. Most of these patients have an
excellent prognosis as long as gross tumor is completely resected. One group of surgeons prefer total thyroidectomy where as other group prefer Lobectomy & Isthmusectomy. The arguments advanced in favor of total thyroidectomy are that PTC is often multifocal in origin and may spread throughout the thyroid by lymphatic drainage. Total thyroidectomy facilitates the postoperative use of 131I to ablate residual thyroid tissue and to identify and treat residual or distant tumor. After total thyroidectomy, Tg is a more sensitive indicator of residual disease. Whereas the proponents of Lobectomy & Isthmusectomy argue that total thyroidectomy has an increased chance of recurrent laryngeal nerve injury and hypoparathyroidism, contralateral disease is not clinically relevant, survival rate is nearly equivalent for low risk patients, 131I ablation and Thyroglobulin level estimation is not necessary for most patients. Lymph node metastatic lesions are present in about 40% of adult patients with PTC; where complete lymphadenectomy of Involved nodes is recommended. In children and young adults, clinical node involvement is more common. Nodal metastatic lesions increase the risk for subsequent nodal recurrences but have little effect on survival. Surgeons should remove all enlarged lymph nodes in the central and lateral neck areas. In the central neck, removal is essential because reoperations in this area are more difficult and are associated with a higher risk of complications. When enlarged nodes are identified in the lateral aspect of the neck, most surgeons perform an ipsilateral functional (modified radical neck) dissection and remove all the perijugular nodes from the clavicle to the hyoid, including the nodes along the spinal accessory nerve. During this operation, the spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle should be preserved. Prophylactic lateral neck dissection is not recommended, and radical neck dissections that result in loss of function are rarely indicated for patients with PTC unless direct muscle Invasion is present. We offer Lobectomy & Isthmusectomy for low risk PTC. Then thyroxine is prescribed for lifelong. The high risk PTC are offered total thyroidectomy. Additionally, Neck dissection and treatment /removal of metastases is offered when nodal or distant metastases are present. These are followed by radio iodine ablation & thyroxine. We found good results in relation to recurrence and mortality.

**Follicular cell carcinoma**

Most follicular cell neoplasms are large (2- to 5-cm), relatively soft, solitary thyroid nodules. Typically, FNA cytological findings are reported as "indeterminate or suspicious for follicular cell neoplasm". About 80% of follicular cell neoplasms are benign; larger follicular cell neoplasms are more likely to be malignant, especially in men and patients older than age 50 years. Unfortunately, follicular adenomas and carcinomas usually cannot be distinguished at the time of surgical intervention. Therefore, most surgeons recommend a total thyroid lobectomy with isthmusectomy for "follicular cell neoplasm." When the lesion is benign, no further therapy is needed. When the tumor is malignant, completion (total) thyroidectomy may be indicated to facilitate subsequent radioactive iodine (RAI) scanning and therapy. Risk group assignments classifies low and high risk cases of follicular carcinoma in a similar way to papillary one. Similar to papillary carcinoma, NCCN guide line advocate that the low risk follicular carcinoma should be treated by lobectomy with isthmusectomy; and high risk follicular carcinoma should be treated by total thyroidectomy. As mentioned earlier, we designate all follicular carcinoma as high risk class. And our way is to do total thyroidectomy in all cases of follicular carcinoma. This is followed by scanning, radio iodine ablation and thyroxine treatment. Ipsilateral lymph node metastatic lesions occur in only about 10% of patients with follicular thyroid cancer (FTC). When lymphadenopathy is extensive in a patient with a follicular neoplasm as determined by FNA cytology, the tumor is usually a follicular variant of PTC. Enlarged lymph nodes in the central neck area should be removed. A functional lateral neck dissection is indicated for patients with clinically palpable nodes.
Adjuvant therapy
Thyroid Hormone. The administration of supraphysiologic doses of thyroid hormone to suppress serum TSH in patients with Follicular Cell-Derived Cancer (FCDC) has been a mainstay of therapy for more than 40 years. Growth of FCDC cells depends on TSH; suppression of endogenous TSH is thought to deprive these cells of an important growth-promoting influence. Traditionally, the goal of levothyroxine therapy has been complete suppression of pituitary secretion of TSH.

Radioiodine remnant ablation
Many patients with FCDC receive RAI to ablate residual thyroid tissue postoperatively (RRA). RRA is defined as "the destruction of residual macroscopically normal thyroid tissue after surgical thyroidectomy." RRA is used as an adjunct to surgical treatment when the primary FCDC has been completely resected. This technique is contrasted with RAI therapy, in which larger doses of I are administered in an attempt to destroy persistent neck disease or distant metastatic lesions.

External irradiation
External irradiation is rarely used as adjunctive therapy in the initial management of patients with FCDC. It may be beneficial, however, in patients with poorly differentiated (higher histologic grade) tumors that do not concentrate RAI. It also may be considered in the postoperative management of patients with FCDC who have gross evidence of local invasion and who are presumed to have microscopic residual disease after primary surgical treatment.

Long-term follow-up
Diagnostic scanning
For whole-body scanning with Radioactive iodine, an increased serum TSH level (generally >25 microIU/mL) is necessary to thyroid cells to accumulate the radio-iodine. This state is usually accomplished by the withdrawal of thyroid hormone therapy. Newly advocated recombinant human TSH does not require withdrawal of thyroid hormone.

Thyroglobulin
Thyroid tissue is the only source of circulating Tg. Serum Tg levels may be high in thyrotoxicosis, thyroiditis, iodine deficiency, and benign thyroid adenomas as well as in thyroid cancer. Tg is a highly specific tumor marker for differentiated thyroid cancer and has a pivotal role in follow-up of patients with such cancers. After thyroidectomy and successful radioiodine ablation, serum Tg should be undetectable (generally, <2 ng/mL). After a unilateral lobectomy, serum Tg is usually less than 10 mg/mL during thyroid hormone therapy in the absence of metastatic disease.

Reference
3. MCE (American Association of clinical Endocrinologist) guidelines. Thyroid Carcinoma guidelines, Endocr Pract. 2001;7 (No.3)
5. NCCN (National comprehensive cancer network), Practice Guidelines in Oncology-v.1.2002, Thyroid Carcinoma