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THYROID CANCER DIAGNOSIS AND TREATMENT

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ABSTRACT

Background: The common tumor of the endocrine glands is thyroid cancer. According to the American Cancer Society, in 2023, there will be 43,720 new cases of thyroid cancer in the country, and there will be 2120 mortality due to it. Is the 13th most common cancer overall and its prevalence continue to increase. Is a malignant tumor arising from the cells of thyroid parenchyma. Clinically it is variable, from, slowly progressing indolent tumors to more aggressive tumors with high mortality rates Thyroid cancer exists in various forms, including papillary, follicular, medullary, and anaplastic. Papillary thyroid cancer is the commonest one. If thyroid cancer identified earlier so it can be treated effectively. Surgery, radioactive iodine therapy, and molecularly targeted medicines using tyrosine kinase inhibitors are all a component of the therapy. As a result, the guidelines for the management of thyroid cancer and nodules are presented in this review, with an emphasis on diagnosis, treatment, and follow-up.

INTRODUCTION

An essential endocrine gland located anterior to the trachea is the thyroid gland. It is made up of two wing-like lobes joined by an isthmus, and it is typically not perceptible when examined physically. It secretes hormones that control body temperature, basal metabolic rate, blood pressure, and heart rate. "Thyroid gland cancer is segregating into types that are formed from neuroendocrine cells and those that are derived from follicular cells" (medullary thyroid cancer). About 95% of thyroid cancer cases are follicular cell-derived, and will be referred to as thyroid cancer ".[10]

Thyroid tumor is one of the common cancers, both developing & developed countries are affecting by it, incidence of it was 600,000 new cases diagnosed per year.[1-2] The number of people diagnosed with thyroid cancer has been increase in the past 3 decades.[3]. This increase in cases could be attributed to overdiagnosis[4] brought on by widespread use of imaging tests as well as improved pathologic examination of thyroid materials that resulted in the early discovery of malignancy. [5]
Commonly discovered thyroid nodules are typically benign. [6] A thyroid nodule is a proliferation of cells in the thyroid gland. About 5% of identified nodules are malignant; PET scan is sensitive for malignant nodules with a 33% risk for malignancy. [7, 8] so detected nodules are important from clinical aspect to exclude risk of thyroid cancer. Nodules that measure more than 1 cm only need to be appraised, except when there are other risk factors which raise the possibility of cancer. They encompass a previous exposure to radiation to the head and neck, a family history of thyroid disease or cancer, lymphadenopathy, female sex, and an ultrasound finding that suggests cancer. [3, 7]

Diagnosis

A serum thyroid-stimulating hormone (TSH) level should be a first step in any newly detected thyroid nodule.[7] A TSH level measuring can make differentiation between functional and nonfunctional nodules, as hyperactive nodules are infrequently malignant. [10] Though, if a TSH is subnormal, representing a hyperactive gland, the next step is a nuclear imaging study, to see if the nodule is hyperfunctioning (appear hot in the scan), isofunctioning (appear warm), or nonfunctioning (cold) in comparison with the thyroid tissue surrounding it. No cytological investigation is needed if the nodule is hot or warm. Cytological investigation utilize fine-needle aspiration (FNA) is recommended for nonfunctioning nodules. In non-functioning nodules and glands affected by Hashimoto's thyroiditis, a FNA is done if the TSH increase or even normal, because the higher incidence of malignancy.[7]
Fine needle aspiration is used for detecting of malignant nodule.[11, 12] The indications for FNA are:1-** size of thyroid nodule; FNA perform for nodules larger than 10 mm[13, 14, 15], except in cases have elevated risk factors [15] or in presence of doubtful ultrasound elements. [13] also done in nodules measuring more than 5 mm with doubtful ultrasound element s, even in a patient without high risk factors. It done selectively in thyroid nodular lesion less than 5 mm according to risk factors and experience of radiologist.
2-** number of lesion; solitary nodular lesion are regard as more malignant than multiple nodules. Though, cases with multiple nodular lesions do not have a lower risk of malignancy comparing to those with single nodular lesion. [16, 17] So, the ultrasound features of isolated nodule regard as guideline for doing FNA or not.
3-** Interval growth; it mean that a nodule increase in volume more than a 50% or a 20% become more in at least two dimensions with a solid portion grow more than 2 mm in a mixed nodules.[15]
4-** ultrasound features.
A- Internal content of nodules: cystic nodule is a benign nodule contains echogenic dot with comet tail artifacts (these comet tail represent microcrystals inside colloid cysts).
B- Solid nodules with size greater than 10mm or more than 15mm with mixed echoic nodules with some variation in the size.[13]
c- Echogenicity: hypoechogenicity is an ultrasound finding associated with malignancy, and most of malignant thyroid nodule appears as hypoechoic nodule.[18, 19, 20]
d- Calcification: A specific ultrasound features that suggests malignancy is microcalcification .[21, 22]
e- Margin: Microlobulated, infiltrative, irregular margins regarded as suspicious features.[23]
f- Shape: A taller nodule has been regarded a suspicious feature.
g- Vascularity: Intranodular vascularity regarding as suspicious features. Newly, Moon et al. proved that benign nodules have greater blood flow than malignant nodules, making this characteristic useless for differentiating nodules.[24] produced a study on 1,083 nodules with color Doppler ultrasound .
As the number of suspicious ultrasound features raises then risk of malignancy also rise as in figure below:

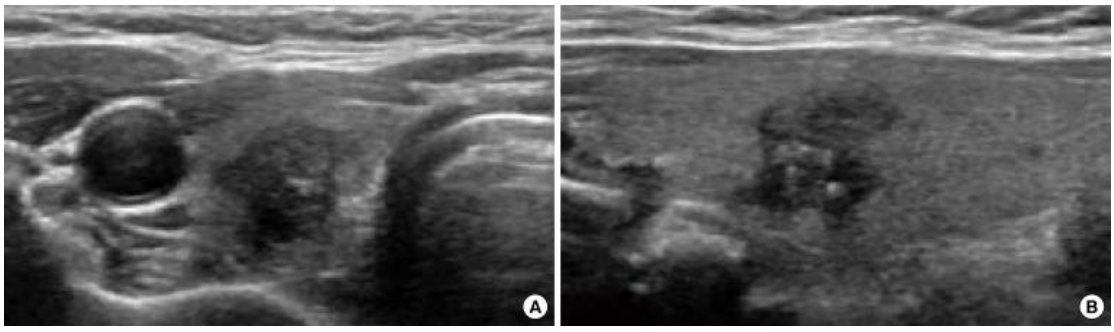

Fig Ultrasonography of papillary thyroid cancer. (A) Trensverse and (B) longitudinal images showed a hypoechoic nodule measure 1 cm with an irregular margin and internal microcalcifications in the right thyroid gland.[23]

Thyroid Cancer and Staging

Histologically the cancer is diagnosed and grouped into four types. Papillary cancer is commonest type about 70% to 80% of thyroid carcinoma .[7, 9] Papillary type grow and metastasize slowly so it is the least aggressive type of cancer, the site of adenocarcinoma form from multifocal papillary and follicular elements.

Follicular thyroid carcinoma represents 14% of thyroid cancers, is more offensive than papillary cell type, it is linked to iodine deficiency.[7] Hürthle-cell carcinoma is a follicular carcinoma variant which is managed like follicular carcinoma.

Medullary thyroid carcinoma, it arises from non-thyroid cells which are normally present in thyroid gland, account for 3% of their cancers and is often associated with multiple endocrine neoplasia type II. Excess calcitonin produces by medullary carcinoma, considered a useful tumor marker.[7,]

Anaplastic thyroid carcinoma is the dangerous type of thyroid carcinoma represents about 2% of thyroid cancers; it is aggressive involving adjacent lymph nodes early in course of disease and also metastasized distally.

From Clinical point, thyroid cancer can be classified into two groups: (1) well-differentiated tumor (papillary and follicular type), and (2) poorly differentiated tumor (medullary and anaplastic type).

Preoperative staging perform after a diagnosis, which affect the patient's treatment course and their prognosis. A preoperative neck ultrasound performs for assessment of other lobe of thyroid gland and regional lymph nodes, to exclude metastasis. Cross-sectional imaging using CT scan and magnetic resonance imaging (MRI) for evaluation spread of tumor to nearby structures[25] and for regional or distant metastases[26]. The American Joint Committee on Cancer (AJCC) stage thyroid cancer according to Tumor, Node, and Metastasis (TNM) classification system[9]

Treatment

Treatment includes surgery, radioactive iodine (^{131}I) therapy, and tyrosine kinase inhibitors. Treatment options base on the type and stage of the cancer. Treatment options as recommended by the NCI. [3] As shown in table (1)

Table 1

Treatment protocol for Thyroid Cancer by NCI

Papillary and follicular thyroid cancer stage I and II
If tumor more than 1 cm so total thyroidectomy If tumor less than 1 cm so lobectomy
Papillary and follicular thyroid cancer stage III
Surgical removal of thyroid gland with removal of pathological lymph nodes and any extrathyroid extension.

After thyroidectomy use ^{131}I ablation if the tumor shows isotope uptake and if ^{131}I uptake is minimal so use external beam radiation therapy.

Papillary and follicular cancer stage IV: metastatic deposits which show isotope uptake can be removed uses ^{131}I
If patient have localized lesion which is not responding to ^{131}I can utilized external beam radiation therapy.
If localized metastasis mainly symptomatic one and not responding must ^{131}I so better resected surgically.

Medullary thyroid cancer

Total thyroidectomy proceeded by external beam radiation therapy for cancer recurrence.
In case of metastatic tumor so use palliative chemotherapy

Anaplastic thyroid cancer

Tracheostomy if needed; if restricted to small region, total thyroidectomy
If tumor cannot be removed surgically so use external beam radiation therapy.
Chemotherapy: doxorubicin plus cisplatin

Surgery

Primary tumors removed either by hemithyroidectomy, with or without removal of isthmus; near-total thyroidectomy or total thyroidectomy in cases that the tumor size more than 1 cm to 2 cm.[27] Since the rate of the multifocal spreading of thyroid tumor is high, so all the gland must remove to reduce the risk for malignancy in the remaining tissue.[28]
Complication of surgery include: 1-hypocalcemia, 2- adhesion which result from an extensive lymph nodes dissection, and multiple cervical region exploration, 3- recurrent laryngeal nerve injury in few cases. Bilateral recurrent laryngeal nerve palsy was a rare complication. 4- postoperative hemorrhage[29]

Radioactive Iodine Ablation

^{131}I has play a noteworthy part in the management of thyroid cancer from 1946.[30] ^{131}I utilized together with thyroidectomy to remove the thyroid gland completely and postoperatively to eliminate any remaining cancer. American Thyroid Association guideline use ^{131}I ablation for cancer extent more than 4 cm, extrathyroidal extension and metastases, and or tumors associated with high-risk features, such as vascular invasion and aggressive histologies.[31] Alternatively, the guidelines do not suggest removal of unifocal or multifocal tumors less than1 cm lacking high-risk properties.

Tyrosine Kinase Inhibitors

A patient whose cancer does not take up iodine, a different treatment decision is recommended. Various genetic alterations seen which involve tyrosine- kinase signaling pathways, involving the protein kinase genes (*R E T, R A F,* or *R A S*), that cause activation of the tyrosine- kinase domain.[32] The epidermal growth factor receptor–activated cascade is connected with the *R E T/R A S/R A F* pathway, which result in the productions of vascular endothelial growth factor and its receptor. Drugs affecting these pathways could have an important role in controlling the progress of the disease.

These drugs are:
1- **Vandetanib**: this drug used for patients with unresectable, progressive, locally metastatic medullary thyroid cancer, which approved by FDA in 2011, it targets *RET, EGFR,* and VEGF receptor
2- **Cabozantinib**: The FDA approved in 2012, the second drug in this group, utilized for similar indication to vandetanib, depend on the groundwork of the Efficacy of XL184 in Advanced Medullary Thyroid Cancer(EXAM) trial.[33]
3- **Sorafenib.** Is third drug in this group which approved by FDA in 2013. It is a multikinase inhibitor of *RET* and *BRAF* V600E mutation, VEGF receptors 2 and 3. It was use for the treatment of differentiated thyroid cancer which are locally recurrent or metastatic or ^{131}I-refractory cases.

External Beam Radiation Therapy

In advanced cases or inoperable thyroid tumor is used for palliative treatment. Mainly in patients aged above 45 years with excessive extrathyroidal extension and a possibility of residual disease through operation. Also utilized in cases which are not responding to ^{131}I therapy .[7]

Conclusion

Thyroid neoplasm constitutes about 3.8% of malignant tumor cases in the United States.[9] The treatment of thyroid malignancy and its prognosis base on the tumor variety and its stage at the time of diagnosis. Total thyroidectomy raises survival rates and reduced recurrence rates. The use of 131I has in the treatment option play an essential adjuvant role in thyroid cancer treatment. Tyrosine-Kinase Inhibitors used for the treatment of advanced cases. These lines of treatment have lowered the mortality rate.

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