IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 16, Issue 9 Ver. VIII (September. 2017), PP 93-98
www.iosrjournals.org

Thyroid Cancer: Clinicalmanifestations, Diagnosis and Therapy

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Abstract:*Thyroid cancer (TC) affects more women than men and those of Asian descent. Environmentalexposure to ionizing radiation from natural and artificial sources plays a significant role. Genetic causes include endocrine neoplasia type 2, particularly of the rare medullary form of the disease. Initial symptom is enlarged nodule, pain, changes in voice due to involvement of laryngeal nerve. Hyperthyroidism or hypothyroidism may be associated with a large or metastatic well differentiated tumor. Physical examination, ultrasound, and fine needle aspiration cytology confirms a definitive diagnosis.TCs are classified according to their histological characteristics, i.e. Papillary(75% to 85%),follicular(10% to 20%),medullary(5% to 8%),poorly differentiated and anaplastic thyroid cancer(< 5%).Other TCs include thyroid lymphoma, squamous cell carcinoma and sarcoma of thyroid. Thyroidectomy is initial step in treatment. Radioactive iodine-131 is used in papillary or follicular thyroid cancer for ablation of residual thyroid tissue and external radiation is used when is unressectable. Prognosis of TC is related to the type of cancer and the stage at time of diagnosis. Early diagnosis have better outcome.*

Keywords:*Thyroid cancer, Nodule, Radiation exposure, FANC*

Date of Submission: 15 -09-2017 Date of acceptance: 23-09-2017

I. Introduction

Thyroid cancer that develops from the tissues of the thyroid gland[1].It is a disease in which cells grow abnormally and have the potential to spread to other parts of the body[2].Worldwide as of 2015 .2 millionpeople have thyroid cancer[3].In 2012,298,000 new cases occurred[4].Thyroid cancer, in 2010,resulted in 36,000 deaths globally up from 24,000 in 1990[5].Thyroid cancer accounts for less than 1% of cancer cases in the UK.Around 2,700 were diagnosed with thyroid cancer in the UK in 2011, and around 370 people died from the disease in 2012[6].In 2015,it resulted in 31,900 deaths. It most commonly occurs between the ages of 35 and 65[7].Women are affected more often than men[7,rpt].Those of Asian descent are more commonly affected[8].Rates have increased in the last few decades which is believed to be due to better detection[4].Risk factors include radiation exposure at a young age, having an enlarged thyroid, and family history[1,9].Obesity may be associated with a higher incidence of thyroid cancer, but this relationship remains the subject of much debate[10].Symptoms can include swelling or lump in the neck[1].Cancer can also occur in the thyroid after spread from other locations, in which case it is not classified as thyroid cancer[8].0ther clinically related conditions include thyroid neoplasm [11],thyroid lymphoma[12],poorly differentiated thyroid cancer[13],and thyroid nodule[14].Diagnosis is often based on ultrasound and fine needle aspiration [1].Treatment options may include surgery, radiation therapy including radioactive iodine,chemotherapy,thyroidhormone, targeted therapy, and watchful waiting[1].Screening people without symptoms and at normal risk for disease is not recommended as of 2017[15].The paper reviews the clinical presentation, diagnostic criteria, and current therapy of thyroid cancer.

II. Clinical Manifestations and Contributory Factors

Most often the first symptom of thyroid cancer is a nodule in the thyroid region of the neck[16].However, many adults have small nodules in their thyroid, but typically under 5% of these nodule are found to be cancerous. Sometimes the first sign is an enlarged node. Later symptoms that can be present are pain in the interior region of the neck and changes in voice due to an involvement of the laryngeal nerve [16].Thyroid cancer is usually found in a euthyroidpatient, but symptoms of hyperthyroidism or hypothyroidism may be associated with a large or metastatic well-differentiated tumor[16].

Contributory Factors:Thyroid cancers are thought to be related to a number of environmental and genetic predisposing factors, but significant uncertainty remains regarding their causes. Environmental exposure to ionizing radiation from both natural background sources and artificial sources is suspected to play a significant role, and there are significant increased rates of thyroid cancer in those exposed to mantle field radiation for lymphoma, and those exposed to iodine-131 following the Chernobyl[17],Fukushima, Kystym,andWind scale nuclear disaster[18,19].Thyroiditis and other thyroid diseases also predispose to thyroid cancer[20,18].Genetic causes include multiple endocrine neoplasia type 2 which markedly increases rates, particularly of the rare medullary form of the disease[21].

III. Diagnostic workout

After a thyroid nodule is found during a physical examination, a referral to an endocrinologist or a thyroidologist may occur. Most commonly an ultrasound is perfumed to confirm the presence of a nodule and assess the status of the whole gland. Measurement of thyroid stimulating hormone and ant-thyroid antibodies will help decide if there is a functional thyroid disease such as Hashimoto's thyroiditis present, a known cause of a benign modular goiter[22].Measurement of calcitonin is necessary to exclude the presence of medullary thyroid cancer.Finally, to achieve a definitive diagnosis before deciding on treatment, a fine needle aspiration cytology(FNAC) test is usually performed and reported accordingly to the Bethesda system[22].Ali and associates in a series of 300 patients with thyroid nodule, advocated that the FNAC is highly accurate and diagnostic of thyroid disease[23].In adults without symptoms screening for thyroid cancer is not recommended[24].

Thyroid cancer and its classification: Thyroid cancers can be classified according to their histological characteristics. Frequent variants can be distinguished (distribution over various subtypes may show regional variation):[25].a).Papillarythyroid cancer(75% to 85% of cases[26]-often in young females-excellent prognosis.May occur in woman with familial adenomatous polyposis and in patients with Cowden syndrome.
b)Newly classified variant non-invasive follicular thyroid neoplasm with papillary-like nuclear features is considered an indolent tumor of unlimited biologic potential[26]
c).follicular thyroid cancer (10% to 20% of cases.)-occasionally seen in patients with Cowden syndrome [26].
d).Medullary thyroid cancer(5% to 8 % of cases)-cancer of the perifollicularcells, often part of multiple endocrine neoplasia type 2[26,27].e). Poorly differentiated thyroid cancer[26]f).Anaplastic thyroid cancer(less than 5% of cases is not responsive to treatment and can cause pressure symptoms [26].g).Miscellaneous thyroid cancers: Thyroid lymphoma, Squamous cell thyroid carcinoma, and Sarcoma of thyroid. Follicular and papillary types can be classified as "differentiated thyroid cancer [28,].These types have a more favorable prognosis than the medullary undifferentiated types [29].

Thyroid cancer staging: Thyroid cancer staging is the process of determining the extent of the development of a cancer. The TNM {tumor,node,and metastases)[30] staging system is usually used to classify stages of cancers but not of brain. Staging include stage MI, stage N1a,stage N1b,stage T1a, and stage T1,T2,T3, stage T4a,and stage T1b.

Detection of metastases of thyroid cancer can be performed with a full body scintigraphy using iodine-131[31].

IV. Therapy

Thyroidectomy and dissection of central neck compartment is initial step in treatment of thyroid cancer in majority of cases [16].Thyroid-preserving operation may be applied in cases, when thyroid cancer exhibits low biological aggressiveness(e.g.well-differentiatedcancer, no evidence of lymph node metastases, low MIB-1 index,no major genetic alteration like BRAF mutations, RET/PTC rearrangements,p53 mutations etc) in patients younger than 45 years[32].If the diagnosis of well-differentiated thyroid cancer(e.g.papillary thyroid cancer) is established or suspected by FNA the surgery is indicated, whereas watchful waiting surgery is not recommended in any evidence-based guidelines[32].Watchful waiting reduces over diagnosis and overtreatment of thyroid cancer among old patients[33].Radioactive iodine-131 is used in patients with papillary or follicular thyroid cancer for ablation of residual thyroid tissue after surgery and for treatment of thyroid cancer[34].Patients with medullary, anaplastic, and most Hurthle cell cancers do not benefit from this therapy[16].External radiation may be used when is unresectable,when it occurs after resection or to relieve pain from bone metastases[16].Sorafenib and sunitinib, approved for other indications show positive promise for thyroid cancer are being used for some patients who do not qualify for clinical trials[35]Numerous agents are in phase-11 clinical trials and XI,1984.184 has started a phase III trial[35].

V. Disease outcome

Disease outcome or prognosis of thyroid cancer is related to the type of cancer and the stage at the time of diagnosis. For the most common form of thyroid cancer, papillary, the overall prognosis is excellent. Indeed, the increased incidence of papillary thyroid carcinoma in the recent years is likely to increased and earlier

diagnosis. The argument against early diagnosis and treatment is based on the logic that many small thyroid cancers (mostly papillary) will not grow or metastasized.(that is, will never cause any symptoms, illness, or death for the patient, even if nothing is ever done about the cancer).Including these over diagnosed cases skews the statistics by lumping clinically significant cases in apparently harmless cases[36].

Thyroid cancer is incredibly common with autopsy studies of people dying from other causes showing that more than one-third of older adults technically have thyroid cancer, which is causing no harm [36].It is easy to detect nodules that might be cancerous, simply by feeling the throat, which contributes to the level of over diagnosis .Benign(non-cancerous) nodules frequently co-exist with thyroid cancer, sometimes, it is a benign nodule that discovered but surgery uncovers an incidental small thyroid cancer. Increasingly small thyroid nodules are discovered as incidental findings on imaging(CT scan, MRI, ultrasound) performed for another purpose; very of these people with accidentally discovered, symptoms-free thyroid cancers will ever have any symptoms, and treatment in such patients has the potential to cause harm to them, not to help them [36,37].Thyroid cancer is three times more common in women than in men, but according to European statistics, the overall relative 5-year survival rate for thyroid cancer is 85% for females and 74% for males [38,39].There are challenges with decision making and prognostication in thyroid cancer. While there is general agreement that stage 1 or stage 11 papillary, follicular or modularly cancer have a good prognosis, it is not possible when evaluating a small thyroid cancer to determine which one will grow and metastasize and which will not. As a result, once a diagnosis of thyroid cancer has been established (most commonly by fine needle aspiration),it is likely that a total thyroidectomy will be performed [40].This drive to earlier diagnosis has also manifest itself on the European continent by use of serum calcitonin measurement in patients with goiter to identify patients with early abnormalities of the parafolicullar or calcitonin-producing cells within the thyroid gland. As multiple studies have demonstrated the finding of an elevated serum calcitonin is associated with finding of a medullary thyroid carcinoma in as high as 20% of cases [24].

Fortunately for those with metastatic thyroid cancer, the last 5 years has brought a renaissance in thyroid cancer treatment. The identification of some molecular or DNA abnormalities for thyroid cancer has led to the development of therapies that target molecular defects. The first of these agents to negotiate the approval process is vandetanib, a tyrosine kinase inhibitor that targets the RET proto-oncogene 2 subtypes of the vascular endothelial growth factor receptor [41].Prognosis is better in younger people than olderones [39].

VI. Clinically Related Thyroid Diseases

Clinically related thyroid diseases include poorly differentiated thyroid cancer, thyroid lymphoma,thyroid neoplasm and thyroid nodule.

Poorly differentiated thyroid cancer (PDTC) is malignant neoplasm of follicular cell origin showing intermediate histological patterns between differentiated and undifferentiated thyroid cancer[13].Diagnosis of PDTC is mainly on histological features,(a)presence of small cells with round nuclei and scat cytoplasm with diffuse solid pattern,(b)round or oval nests (insulae) or trabeculae,(c)solid growth and presence of micro follicles, some of which contain dense colloid(d)extra thyroidal extension and blood vessel invasion,(e) foci of necrosis, and(f) larger than 5 cm in greatest diameter at diagnosis[13].Clinically PDTC affects predominantly females about 55 years of age, and both local and distant, lung, bone and brain is affected[13].

Thyroid lymphoma is a rare malignant tumor constituting 1% to 2% of all thyroid malignancies and less than 2% of lymphomas. Thyroid lymphomas are classified as non-Hodgkin's B-cell lymphomas in a majority of cases, although Hodgkin's lymphoma of the thyroid has also been identified [12].Clinical manifestations are similar to other thyroid lesions, thyroid lymphoma affects predominantly female over 70 years of age with a history of Hashimoto's thyroiditis.Thus,Hashimoto thyroiditis is considering as risk factor for thyroid lymphoma development. The thyroid lymphoma manifests as rapidly enlarging neck mass causing respiratory difficulty. On physical examination, patients usually exhibit a firm thyroid and lymphadenopathy [12].Frequently associated symptoms are painless neck mass, hoarseness, dysphagia and signs of tracheal compression[12].

Diagnosis, treatment and prognosis: Thyroid lymphoma shows a diagnostic and therapeutic challenge in many cases, because some manifestation patterns are similar to(Anaplastic thyroid carcinoma ATC).Performance of FNAB has helped to distinguish these two entities preoperatively[12].The combined modality therapy is the most common approach for the initial treatment of thyroid lymphomas. The CHOP regimen (cyclophosphamide,doxorubicin,vincristine and prednisone) has been shown high effectiveness for many types of lymphoma. However, it is suggested to perform radiation therapy only for MALT(mucosal-associated lymphoid tissue) resulting a 96% complete response, with only 30% relapse rate. Surgical treatment might be performed for patients with thyroid lymphoma in addition to chemotherapy and radiation, particularly for MALT lymphomas[12].Staging of lymphoma from stage IE- to 4E depending on the location of the lymphoma[12].Outcome(prognosis) of lymphoma patients are advance age of the tumor, large size(> 10cm) as

well as spreading to mediastinum.The overall survival for primary thyroid lymphoma is 50% to 70%, ranging from 80% in stage IE to less than 36% in stage IIE and 4E in 5 years [12].

Thyroid neoplasm is a neoplasm or tumor of the thyroid. It can be benign tumor such as thyroid adenoma [11] ,or it can be a malignant neoplasm(thyroid cancer),such a papillary, follicular, medullary or anaplastic thyroid cancer[42].Most patients are 25 to 65 years of age when first diagnosed. Women are more affected than men[42].In 2010, in U.S.44,670 reported cases and 1,690 deaths[43].Of all thyroid nodules discovered only 5% are cancerous and under 3 percent of those result in fatalities[43].Diagnosis with blood tests, an ultrasound and nuclear scan. Patients are also tested for hyperthyroidism and hypothyroidism, two conditions that often arise from an abnormally functioning thyroid gland [43].Thyroid adenoma is benign neoplasm of the thyroid. Thyroid nodules are very common and round 80 percent of adults will have at least one by the time they reach 70 years of age. Approximately 90 to 95 percent of all nodules are found to be benign [43].Nearly 80 percent of thyroid cancer is papillary and about 15 percent is follicular, both types grow slowly and can be cured if caught early. Medullary thyroid cancer makes about 3 percent of this cancer. Anaplastic is the most deadly and makes up 2 percent. This type grows quickly and is hard to control [43].Other thyroid malignancies include thyroid lymphoma, various types of thyroid sarcoma, smooth muscle tumors, teratoma, squamous cell thyroid carcinoma and other rare types of tumors[44].

Treatment of thyroid nodule depends on, size of nodule, age of the patient, type of thyroid cancer, and whether or not it has spread to other areas in the body If the nodule is benign, patients may receive thyroxine therapy to suppress thyroid-stimulating hormone and should be reevaluated in 6 moths[43].However, if the benign nodule is inhibiting the patient's normal functions of life; such as breathing, speaking, or swallowing the thyroid may need to be removed[43].If the nodule is malignant or has indeterminate cytological features, it may require surgery[43].A thyroidectomy is a medium risk surgery that can result complication if not performed correctly. Problems with voice, nerve or muscular damage, or bleeding from the lacerated blood vessel are rare but serious complications can occur. After removing the thyroid, the patient must be supplied with a replacement hormone for the rest of their life. Radioactive iodine-131 is used in patients with papillary or follicular thyroid cancer for ablation of residual thyroid tissue after surgery and for treatment of thyroid cancer. Patients with medullary.anaplastic, and most Hurthe cell cancers do not benefit from this therapy[43].External radiation may be used when cancer is unresectable, when it recurs after resection, or to relieve pain from bone metastasis[43].

Thyroid nodules are nodules (raised areas of tissue or fluid)which commonly arise within an otherwise normal thyroid gland[14].They may be hyperplasia or a thyroid neoplasm, but only a small percentage of the latter are thyroid cancers. Small, asymptomatic nodules are common, and many people who have them are unaware [45].But nodules that grow larger or produce symptoms may eventually need medical care. Goiters may have nodules or be diffuse [45].Frequently clinical symptoms include abnormal growths of thyroid tissues are located at edge of the thyroid gland and can be felt as a lump in the throat. When they are large, they can sometimes be seen as a lump in the front of the neck. Sometimes a thyroid nodule presents as a fluid-filled cavity called a thyroid cyst. Often solid components are mixed the fluid. Thyroid cysts most commonly result from degenerating thyroid adenomas, which are benign, but they occasionally contain malignant solid components [46].Diagnosis mainly by physical examination by endocrinologist.Ultrasound is performed to confirm the presence of nodule, and assess that status of the whole gland. Measurement of thyroid hormone and anti-thyroid antibodies will help decide if there is a functional thyroid disease such as Hashimoto's thyroiditis present, a known cause of a benign nodular goiter[47].Blood tests measuring thyroid stimulating hormone(TSH),and the thyroid hormones thyroxine(T4) and triiodothyronine(T3)[47].Fine needle biopsy(FNB) is performed to determine whether the nodule is malignant[48].The report may be done according to the Bethesda System of Reporting Thyroid Cytopathology[49,50].

The blood tests may be accompanied by ultrasound imaging of the nodule to determine the position, size and texture and to assess whether the nodule may be cystic (fluid filled).Also suspicious findings in a nodule are hypoechoic. Irregular borders, microcalcifications, or very high levels of blood flow within the nodule. Less suspicious findings in benign nodules include, hyperechoic, comet tail artifacts from colloid, no blood flow in the nodule and a halo,or smooth border[51].A thyroid scan using a radioactive iodine uptake test can be used in viewing the thyroid. A scan using iodine-123 showing a hot nodule, accompanied by a lower than normal TSH,is strong evidence that nodule is not cancerous, as most hot nodules are benign [52].Only a small percentage of lumps in the neck are malignant(around 4-6.5%),and most thyroid n nodules are benign colloid nodules[53].

Miscellaneous nodule: Solitary thyroid nodules are common in females yet more worrisome in males. Other associations with neoplastic nodules are family history of thyroid cancer and prior radiation to the head or neck. Most common cause of solitary thyroid nodule is benign colloid nodules and second most common cause is follicular adenoma [54].Radiation exposure to the head and neck may be for historic indications such as tonsillar and adenoid hypertrophy, "enlarged thymus", acnevulgaris,or current indications such as Hodgkin

lymphoma.Children living near Chernobyl power plant the catastrophe of 1986 have experienced a 60 fold increase in the incidence of thyroid cancer. Thyroid cancer arising in the background of radiation is often multifocal with a high incidence of lymph node metastasis and has a poor prognosis [54].Symptoms include voice hoarseness, rapid increase in size, compressive symptoms (such as dyspnea or dysphagia) and appearance of lymphadenopathy. Diagnostic workout include TSH, and FNAC, and imaging, ultrasound and radioactive

scanning [55,56].Thyroid scan indicate,85% of nodules are cold nodules, and 5-8% of cold and warm nodules are malignant[57],and 5% of nodules are hot. Malignancy is virtually non-existent in hot nodules [58].

VII.Conclusions

Thyroid cancer is prevalent worldwide with high mortality. Environment and genetic significant factor.Diagnosis is based on ultrasound and FNAC.Thyroidectomy, dissection, and radioactive active iodine-131for ablation of thyroid residual tissue. External radiation for unresectable cases. Early detection and treatment has better prognosis.

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*Murtaza Mustafa. "Thyroid Cancer: Clinicalmanifestations, Diagnosis And Therapy." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) , vol. 16, no. 09, 2017, pp. 93–98.