Comentary

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Current Status of Approach to Thyroid Nodules

Tiroid Nodüllerine Yaklaşımda Güncel Durum

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The prevalence of thyroid nodules (TNs) in the community is high, and the rate of detection of TNs by using high-resolution ultrasonography (US) is approximately 60%. Less than 5% of TNs are malignant (1). TNs are seen approximately 4 times more frequently in women than in men. The prevalence of palpable TNs in areas without iodine defficiency is approximately 5% in women and 1% in men. The rate of thyroid cancer is two times higher in men than in women (4% vs. 8%) (2). In a screening study conducted with randomly selected individuals in the population, TNs were detected more frequently in women and the elderly (3). It is very important to distinguish between benign and malignant nodules. Clinical evaluation and US should be performed in palpable TNs (4). Physical examination alone may reveal 5% to 7% of TN. Ultrasound shows a prevalence of 20% to 76% in the same population, and this is in line with autopsy findings (2).

People with TN are usually euthyroid. Most patients are asymptomatic, but the absence of symptoms does not rule out malignancy. Less than 1 percent of TNs cause hyperthyroidism or thyrotoxicosis. If spontaneous bleeding into the nodule has occurred, patients may complain of a feeling of pressure or pain in the neck. When any nodule is detected; history of goiter, family history of thyroid carcinoma and autoimmune thyroid diseases such as Hashimoto's thyroiditis and Graves' disease, family history of polyposis (Gardner syndrome), hypothyroidism or hyperthyroidism should be questioned.

TNs can be solitary, multinodular, or cystic (5). TNs can also be classified as adenoma, carcinoma, cyst, colloidal nodule, and inflammatory nodules. The most common TN type with a low risk of malignancy is colloids. Most follicular adenomas are benign, but some may have features of follicular carcinoma. About 5% of microfollicular adenomas are proven to be follicular cancer. Thyroiditis may also present as a nodule. Thyroid carcinoma usually presents as a solitary palpable TN. The most common type of malignant TN is papillary carcinoma (6).

A TN is a lesion within the thyroid gland that is radiologically different from the surrounding thyroid parenchyma. Some palpable lesions may not have obvious radiological features. TNs can be solid or liquid. TNs that are detected in imaging studies performed for other reasons and that are not-palpable are called incidental nodules or "incidentalomas". There is no difference in malignancy risk between non-palpable nodules and sonographically confirmed palpable nodules of the same size.

Generally, nodules larger than 1 cm are considered clinically significant and are evaluated because they have malignant potential. Although rare, lymphadenopathy and nodules smaller than 1 cm with clinical symptoms may also cause morbidity and mortality, therefore they should be evaluated with advanced imaging techniques. The widely accepted view is that TNs smaller than 1 cm do not need to be investigated invasively for malignancy.

The clinical significance of TNs is due to the risk of development of thyroid cancer, which occurs in 7-15% of patients, depending on age, gender, radiation exposure, family history, and other factors. The generally accepted view is that most nodules are at low risk for malignancy, and even if malignancy is diagnosed, it can be successfully treated to a large extent (3).

High-resolution US, sensitive thyroid-stimulating hormone (TSH) assays, and fine needle aspiration biopsy (FNAB) are used together with clinical findings to detect the features of the TN. Thyroid scintigraphy is not required for diagnosis in most of the

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patients, but can be used to detect functional autonomy in iodine deficient soils in patients with low serum TSH or multinodular thyroid gland. Serum TSH measurement is the first laboratory test to detect thyroid function. Afterwards, measurement of free thyroxine (FT4) and free triiodothyronine (FT3) levels, and thyroid peroxidase antibodies (TPOAbs) may be requested. Measurement of unstimulated serum calcitonin should only be performed when medullary thyroid cancer (MTC) is suspected based on FNAB results or the patient's history (4).

1- **Measurement of serum thyrotropin level:** During the initial evaluation of a patient with a TN, serum thyrotropin level should be measured. If the serum TSH level is below normal, a radionuclide thyroid scan should be performed. If serum TSH level is normal or elevated, radionuclide scanning should not be performed as the initial imaging evaluation.

2- **Serum thyroglobulin level:** Routine measurement of serum thyroglobulin (Tg) level is not recommended for the initial evaluation of TNs. Serum Tg levels may be elevated in most thyroid diseases and measuring its level is a low-sensitivity and non-specific test for thyroid cancer.

3- **Serum calcitonin level:** Routine measurement of serum calcitonin level is not recommended for the initial evaluation of TNs. If the unstimulated serum calcitonin level is higher than 50-100 µpg/mL, it is significant for the diagnosis of MTC. There are studies showing that calcitonin measurement from the FNAB material of TN may be helpful in the preoperative evaluation of patients with moderately elevated basal serum calcitonin level (20-100 µpg/mL).

4- **18F-Fluorodeoxyglucose positron emission tomography scan (18FDG-PET**): Focal 18FDG-PET uptake in a sonographically confirmed TN is significant for thyroid cancer risk, and FNAB is recommended for nodules larger than 1 cm. Extensive 18FDG-PET uptake with sonographic and clinical signs of chronic lymphocytic thyroiditis does not require further imaging or FNAB.

5- **Thyroid sonography:** Thyroid sonography, including examination of cervical lymph nodes, should be performed in all patients with known or suspected TN. Thyroid US is widely used to assess the risk of malignancy in TN and to help decide whether FNAB is indicated. AACE/ACE/AME guidelines recommend that the position, shape, size, border, content, echogenicity and vascular status information of TN be included in US reports (3,7).

When evaluating the thyroid parenchyma with ultrasound, homogeneity or heterogeneity of the thyroid gland, size of the gland, size, location and sonographic characteristics of any nodule, presence or absence of suspicious cervical lymph nodes in the central or lateral compartments are evaluated. The report should note the size of the nodule in three dimensions and its location (for example, the right upper lobe) and all of the sonographic characteristics, including the structure of the nodule (solid, cystic ratio or spongy), echogenicity, borders, vascularity, presence and type of calcifications. The pattern of sonographic features and the size of the nodule provide important information in the decision of FNAB.

Thyroid ultrasound is an important imaging modality used to evaluate TNs. Thyroid sonography, including examination of cervical lymph nodes, should be offered in all patients with known or suspected TNs. US can provide information about dimensions, vascularity, structure and parenchymal changes and detect lesions as small as 2 mm. It is widely used to avoid unnecessary use of invasive procedures and to differentiate benign and malignant lesions (2).

The FNAB can be performed with palpation if diagnostic US confirms the presence of a solid nodule corresponding to the palpable nodule. When clinically indicated, it is preferred to perform FNAB under ultrasound guidance in the evaluation of TNs. FNAB is the most accurate and cost-effective method for evaluating TNs. Retrospective studies have shown that US-guided FNAB procedure has lower rates of both non-diagnostic and false-negative cytology compared to palpation. US-guided FNAB should be preferred, especially in deeply located, difficult to palpate or posteriorly located nodules that are not larger than 1 cm, are not palpable, have non-diagnostic cytology in the previous biopsy, have mixed or cystic components. Cystic or spongy lesions are considered to pose a low risk for malignancy, and if they are larger than 2 centimeters, they are either monitored or biopsied (2,3).

If a cyst is large and symptomatic, aspiration and ethanol ablation may be considered as therapeutic interventions. If aspiration is performed, it should be evaluated cytologically. When TNs are detected, sonographic evaluation of the anterior cervical lymph node compartments (central and lateral) is required. If US detects cervical lymph nodes sonographically suspicious for thyroid cancer, FNAB of the suspected lymph node should also be performed. Microcalcifications, cystic appearance, peripheral vascularity, hyperechogenicity and round shape are features suggestive of malignancy in lymph nodes. Lymph nodes with these features usually require histopathological evaluation (7).

The ATA guideline provides the following recommendations for the US findings of TNs, the estimated risk of malignancy, and the decision whether to perform FNAB (3).

A. High suspicion (**risk of malignancy >70%-90%**), FNAB recommended

A solid hypoechoic nodule or a solid hypoechoic component of a partial cystic nodule together with microlobulated, infiltrative irregular borders, microcalcifications, the length of the nodule being longer than the width, marginal calcifications, and the presence of one or more of the signs of extrathyroidal extension are risk factors for malignancy. A nodule with these sonographic features is likely to be papillary thyroid cancer (PTC). Nodules with a pattern of high suspicion and greater than 1 cm in size should undergo diagnostic fine-needle biopsy to rule out or confirm malignancy. However, in the absence of extrathyroidal spread, metastatic cervical lymph nodes, or evidence of distant metastases, micropapillary thyroid cancers (<1 cm) usually have a slow course,

although this may depend on the age of the patient. The patient's age and preference can alter the decision-making process.

B. Moderate suspicion **(risk of malignancy 10-20%)**, FNAB is recommended.

Hypoechoic solid nodule with regular borders without microcalcification, longer nodule length than width, and extrathyroidal extension finding constitute this group. This appearance has the highest sensitivity (60-80%) for PTC but a lower specificity than the previous high suspicion pattern, and FNAB should be considered for these nodules ≥1 cm to rule out malignancy.

C. Low suspicion **(risk of malignancy 5%-10%)**, FNAB is recommend if >1.5 cm

There are isoechoic and hypoechoic solid nodules which do not have microcalcification, irregular border, a shape where the neck is longer than the width and evidence of extrathyroidal extension, or there are cystic nodules with eccentric solid areas. Only about 15-20% of thyroid cancers on ultrasound are iso- or hyperechoic, and these are usually PTC or the follicular variant of follicular thyroid cancers (FTC). Less than 20% of these nodules are partially cystic. Therefore, these appearances have a lower probability of malignancy and those less than 1.5 cm in size can be followed up.

D. Very low suspicion **(≤3),** consider FNAB if it is >2 cm, follow-up without FNAB is possible.

Spongy or partial cystic nodules that do not have sonographic characteristics described in low, moderate, or high suspicion samples have a low malignancy risk (<3%). If FNAB is to be performed, the nodule should be at least 2 cm in size. For nodules smaller than 2 cm, observation without FNAB may also be considered.

E. Benign **(≤1%)**, FNAB is not recommended

Completely cystic nodules are unlikely to be malignant and diagnostic fine needle biopsy is not indicated. If a cyst is large and symptomatic, aspiration is performed and ethanol ablation may be added in appropriate cases. If aspiration is performed, it should be done in cytological examination (3).

In the cytological evaluation of the material obtained by using FNAB, the **Bethesda classification** is used, which classifies the lesions into 6 main categories with different characteristics. The Bethesda system defines six diagnostic categories, and cancer risk estimation is made in each category based on literature review and expert opinion. These categories are (1) non-diagnostic/unsatisfactory, (2) benign, (3) atypia/follicular lesion of undetermined significance (AUS/FLUS), (4) follicular neoplasm/suspicious follicular neoplasm (FN/SFN) category including Hurthle cell neoplasm/suspicious Hurthle cell neoplasm, (5) suspected malignancy (SUSP), and (6) malignancy (3).

In the Bethesta classification;

1- Non-diagnostic category represents an inadequate sample with an insufficient number of follicular cells. 2- Benign, normal thyroid tissue showing adenomatous or multinodular goiter nodules, common conditions include adenomatous nodules, Hashimoto's thyroiditis, and subacute granulomatous thyroiditis. 3- Follicular lesion of undetermined significance (FLUS) or atypia of undetermined significance (AUS): the lesions that cannot be determined to be benign are in this category. AUS includes lesions with nuclear atypia and lesions with extensive oncocytic changes, although not sufficient to be classified as a Hurthle cell neoplasm. FLUS includes a combined microfollicular and macrofollicular pattern. 4-Follicular neoplasm or suspicious follicular neoplasm includes microfollicular or cellular adenomas. Because the FNAB samples only a portion of the nodule, surgical excision is required to determine whether the microfollicular lesion is benign or malignant. Microfollicles are defined, colloid is absent or insufficient, and cells are more numerous than in macrofollicular nodules. 5- Suspicion of malignancy: It includes lesions with uncertain malignant features for thyroid cancer. 6-Malignancy: The cytology will differ according to the different types of possible thyroid malignancies. In papillary cancers, microscopy shows large cells with ground glass cytoplasm, prominent nucleoli, and intranuclear cytoplasmic inclusions. In medullary cancer microscopy shows scattered cells with eccentrically displaced nuclei and slightly granular cytoplasm often structured as a teardrop. Anaplastic cancer shows marked pleomorphism, peculiar giant cells, and spindle cells.

How should a surgeon who sees the cytological evaluation in the Bethesda classification interpret these results and what should he do? Non-diagnostic biopsies (Bethesda 1) are considered cytologically inconclusive. If insufficient follicular tissue is obtained, the absence of malignant cells should not be interpreted as a negative biopsy. The FNAB is usually repeated in 4 to 6 weeks. Patients with benign nodules (Bethesda 2) such as macrofollicular and colloid adenomas, nodular goiter, and Hashimoto's thyroiditis are usually followed up without surgery. Initially, periodic US monitoring at increasing intervals of 12 to 24 months is preferred. If US shows highly suspicious findings, FNAB should be repeated within 12 months despite a benign initial biopsy. For nodules with indeterminate cytology (Bethesda 3 and 4), the approach varies with institutional practice. Some institutions take an additional FNAB sample for molecular testing, while other centers repeat the FNAB 6 to 12 weeks later. A radionuclide scan may also be obtained if repeated aspirations show only structural atypia. For nodules in the Bethesda V category with suspected malignancy, treatment should include surgery. Molecular markers should not be used. Bethesda 6 includes papillary cancer, medullary thyroid cancer (MTC), thyroid lymphoma, anaplastic cancer, and metastatic cancer to the thyroid. In these patients, surgery is the appropriate method. [2]

Patients with a solitary nodule larger than 1 cm in multiple nodules should be evaluated in the same way. Each nodule larger than 1 cm carries an independent risk of malignancy and therefore requires a separate FNAB from each nodule.

Sonographic patterns should be considered for FNAB. The guideline recommends annual US and FNAB follow-up in patients with benign FNAB and nodules with high suspicion on US. In this group, patients with nodules with low or moderate suspicion on US can be followed up at 12-24 month intervals. If an increase in size (more than 20% increase in two different diameters or 50% increase in volume) or new suspicious nodule formation is detected during follow-up, FNAB should be applied again. US follow-up is not required in patients with nodules who have undergone two FNABs and have benign cytological results.[7]

As a result, most of the TNs seen quite frequently in the community are benign nodules. Close follow-up is important to detect cancerous nodules. The follow-up protocol should be made in accordance with the guidelines and this should be determined according to the risk status of each patient.

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