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Thyroid nodule core needle biopsy — current approach

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Abstract

Fine needle aspiration biopsy (FNAB) guided by ultrasonography is routinely used to identify thyroid nodules prior to surgery. Although FNAB has great diagnostic accuracy and safety, it is limited by its relatively low diagnostic accuracy in follicular lesions, such as non-diagnostic or atypia of unclear significance (AUS)/follicular lesion of uncertain significance (FLUS). Additional diagnostic tests are required to overcome these challenges in evaluating thyroid nodules. Thyroid nodules can now be diagnosed with spring-activated single- or double-action needles following the introduction of core needle biopsy (CNB). CNB has the ability to address the limitations of FNAB by obtaining a sizeable tissue sample with more details on the histological structure supporting the capsule and fewer non-diagnostic effects brought on by the absence of follicular cells. Compared to repeated FNAB, CNB has been demonstrated to produce fewer ambiguous results, such as non-diagnostic or AUS/FLUS results. The Korean Endocrine Pathology Thyroid CNB Working Group issued its first set of guidelines for "Pathology Reporting of Thyroid Core Needle Biopsy" in 2015. In 2017, the Korean Society of Thyroid Radiology (KSThR) published "Core Needle Biopsy of Thyroid: 2016 Consensus Statement and Recommendations from the Korean Society of Thyroid Radiology". The main objectives of thyroid CNB are to detect individuals with thyroid illness who require surgery and to obtain a significant number of thyroid lesions with low morbidity. **(Endokrynol Pol 2023; 74 (6): 591–600)**

Key words: *thyroid nodule; core needle biopsy; FNAB; ultrasound*

Introduction

To diagnose thyroid nodules before surgery, fine needle aspiration biopsy (FNAB) guided by ultrasound is frequently employed [1]. Due to its excellent diagnostic accuracy and low complication rate, FNAB has replaced large-core needle biopsy as the go-to diagnostic method for thyroid nodules over the past 40 years. The primary clinical use of FNAB is to exclude surgically required malignant tumours, hence minimizing needless procedures [2]. The relatively low diagnostic accuracy in follicular lesions, such as non-diagnostic or atypia of undetermined significance (AUS)/follicular lesion of uncertain significance (FLUS), limits this approach despite its excellent diagnostic accuracy and safety [3]. Recurrent FNABs may result from certain FNAB-related restrictions. To overcome these obstacles in the evaluation of thyroid nodules, additional diagnostic tests are needed [3, 4].

With the development of core needle biopsy (CNB), thyroid nodules can now be diagnosed using spring-activated single- or double-action needles. Furthermore, broad application of high-resolution US provides precise diagnosis and reduction of CNB-related consequences in head and neck disorders. When carried out by a professional, CNB is secure, well-tolerated, and has a low incidence of problems [5]. Low rates of severe and mild complications and no procedure-related deaths have been established by several large-scale studies [6, 7].

By getting a substantial tissue sample with more information about the histological structure underpinning the capsule and fewer non-diagnostic effects brought on by the lack of follicular cells, CNB offers the potential to overcome the limitations of FNAB. CNB has been shown to give less inconclusive outcomes than repeated FNAB, including non-diagnostic or AUS/FLUS results [8]. The potential use of CNB as a primary diagnostic tool for the management of thyroid nodules has also been described in several recent studies [9, 10].

For patients with thyroid nodules, a multidisciplinary strategy using FNAB and CNB is necessary to enhance quality of life and produce better results. To enable the best possible therapy of patients with thyroid nodules, standardized recommendations are required. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), developed in 2007, serves as the foundation for the language used to describe thyroid FNAB cytology globally, and 2017 saw the release

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Table 1. *Summary of consensus statement and recommendations*

Category	Statement of understanding and recommendations
Indication	1. CNB may be an alternative to FNAB in the evaluation of thyroid nodules in selected cases.
Device and procedure	2. Modern CNB devices, particularly 18–21 gauge, spring-activated, cored needles are recommended for the procedure.
	3. Patients with a tendency to bleed, for example those taking anticoagulants, or who have disorders affecting the coagulation cascade, should be thoroughly evaluated and any problems corrected prior to CNB.
	4A. CNB should be performed by experienced radiologists under US guidance.
	4B. Manual compression of the biopsy site should be performed for 20–30 minutes immediately after the procedure.
Clinical results	5. CNB can be used as an alternative for thyroid nodules with non-diagnostic cytology in previous FNAB.
	6. CNB can be used as an alternative for thyroid nodules with atypia (follicular lesion) whose significance cannot be determined in previous FNAB.
	7A. CNB has advantages in distinguishing encapsulated follicular neoplasm from non-neoplastic nodule.
	7B. CNB cannot distinguish follicular thyroid carcinoma from follicular adenoma.
	8. CNB can be used as an alternative to FNAB for calcified thyroid nodules.
	9. CNB can achieve low rates of non-diagnostic and imprecise results for initially detected thyroid nodules. However, the use of CNB as a first-line diagnostic tool for these nodules is unclear based on the available evidence.
	10A. CNB can be used as an alternative to FNAB in patients with clinical and radiological features of uncommon malignancies (anaplastic carcinoma, lymphoma, or medullary carcinoma).
	10B. CNB can be used as an alternative for thyroid nodules with US-cytology mismatch in previous FNAB.
Complications	11. CNB is safe, well tolerated, and has a low incidence of complications when performed by experienced radiologists.

CNB — core needle biopsy; FNAB — fine needle aspiration biopsy; US — ultrasound

of TBSRTC's second edition [11]. The first guideline for "Pathology Reporting of Thyroid Core Needle Biopsy" was released by the Korean Endocrine Pathology Thyroid CNB Working Group in 2015 [12]. "Core Needle Biopsy of Thyroid: 2016 Consensus Statement and Recommendations from the Korean Society of Thyroid Radiology (KSThR)" was released in 2017 by the KSThR [13].

The Korean Thyroid Association (KTA) Practice Guide Committee has assembled a team to create useful CNB guidelines for the diagnosis and treatment of thyroid nodules in conjunction with recent developments in diagnostic, classification, and management guidelines of thyroid nodules [14]. The indications, patient preparation, biopsy procedure, complications, specimen preparation, and pathology reporting are all covered by this recommendation (Tab. 1).

CNB Indications

Most thyroid guidelines advise using FNAB as the initial thyroid nodule biopsy. CNB is therefore viewed as an auxiliary tool [11–14]. Atypia of unknown relevance and previous nondiagnostic FNAB results are 2 of the most commonly acknowledged indications for CNB in the literature. Due to the aspiration of acellular or few-cellular material, calcified nodules and degenerating nodules are frequently underdiagnosed by FNA (Fig. 1). With CNB, insufficient cellular nodules can be identified as particular disease entities [10, 15]. The CNB Guidelines were released by KSThR in 2017 and include several recommendations as well as the potential use of CNB for thyroid nodules with nondiagnostic or ambiguous FNAB results [13].

The National Cancer Institute (NCI) asserts that circumstances when the FNAB procedure is "inadequate" may benefit from US-guided CNB employing contemporary needles [16]. Additionally, CNB is recommended for use in patients with malignant thyroid tumours like lymphoma, anaplastic cancer, medullary cancer, and metastases, according to the American Association of Clinical Endocrinologists (AACE), American College of Endocrinology (ACE), Associazione Medici Endocrinologi (AME), British Thyroid Association (BTA), and KSThR [13, 17]. Previously nondiagnostic FNAB results, prior AUS/FLUS, and CNB have been recommended as the next diagnostic procedure for clinically suspected uncommon thyroid cancers [12–17], based on the data now available. Also, the "Recommendations of the Polish Scientific Societies and the National Oncological Strategy" guide for the diagnosis and treatment of thyroid cancer was published in 2022. In this comprehensive guide, in addition to the NCCN and ATA guidelines, the results of prospective studies are recommended. It has also been stated that CNB can be used as an alternative to FNAB in the diagnosis of thyroid cancer and provides a wide range of histological material for immunohistochemistry. In the same guideline,

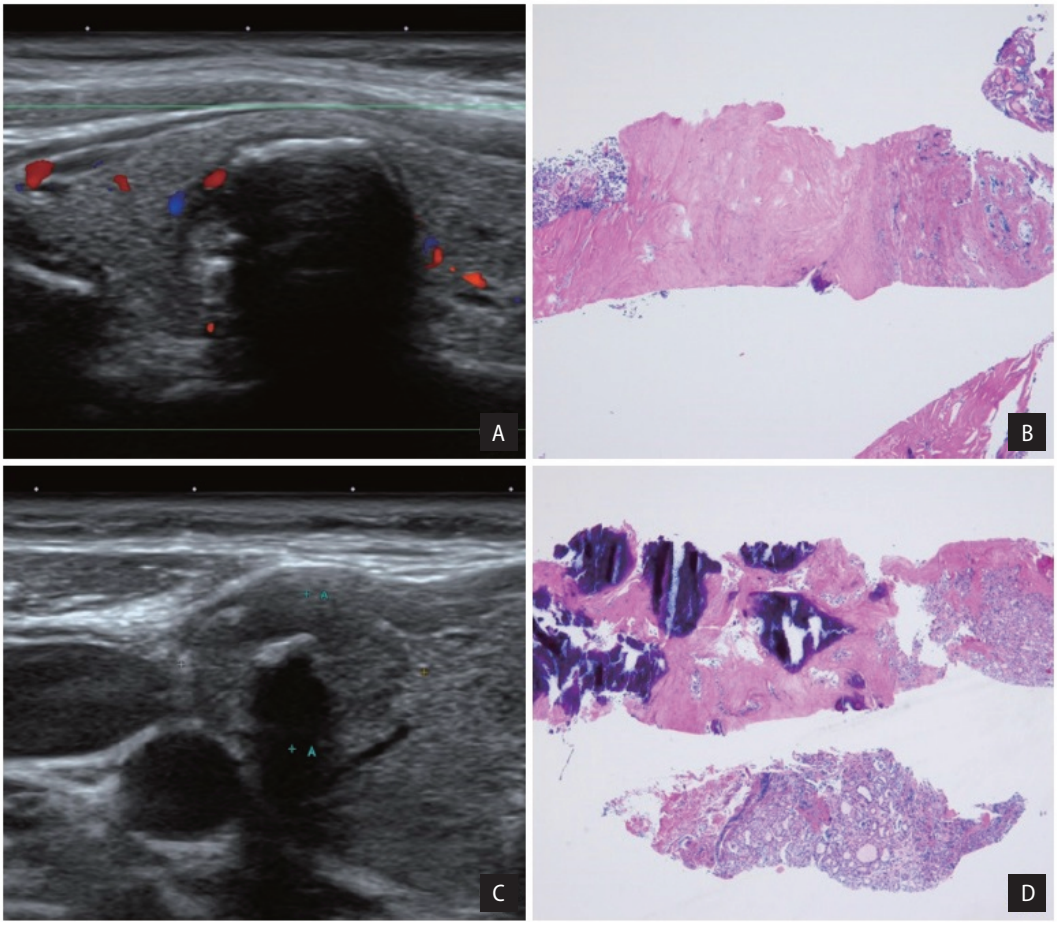

Figure 1. *Core needle biopsy (CNB) samples from thyroid nodules and non-diagnostic fine needle aspiration cytology were compared. A well-defined, hypoechoic solid nodule with calcified edges is shown in the ultrasound (US) findings of Case 1 (***A***), and (***B***) the fine needle aspiration biopsy (FNAB) examination of the nodule reveals inadequate cellular and sclerotic nodules (H&E staining, 40×);* **C.** *An ultrasound scan from Case 2 reveals a 1.5 cm solid nodule that is poorly defined, hypoechoic, and has macrocalcifications;* **D.** *In CNB, there is noticeable calcified sclerosis and focal follicular proliferative lesions (H&E staining, 40×)*

it was also suggested that CNB could be an alternative to excisional biopsy in the diagnosis of anaplastic carcinoma and lymphoma, and in differentiating inflammatory tumours and thyroid metastases [18].

Patient preparation for CNB

First, consent should be sought with full disclosure of all pertinent facts regarding the CNB technique and any side effects. A screening blood test for coagulation is frequently not required, but medication-related side effects (such as bleeding tendency with medications like warfarin, heparin, aspirin, or clopidogrel) should be assessed. Aspirin and clopidogrel should be stopped for 7–10 days, warfarin for 3–5 days, and heparin for 4–6 hours before CNB, according to KSThR recommendations [13]. Following CNB, it is advised to begin taking aspirin, clopidogrel, warfarin at night, and heparin 2 hours later. The termination of anticoagulant therapy should be carefully discussed with the prescribing physician due to the clinical relevance of anticoagulant therapy. Shorter-acting heparin can be briefly made from warfarin. Fasting before the CNB surgery is not advised for most patients [12–14].

Planning the CNB procedure

With grey scale US and colour Doppler US, the nodule's features, size, location, and vascularization should be assessed prior to the surgery. Bleeding during CNB can be reduced with careful colour Doppler US monitoring of nodular vascularity. Based on the data gathered from the pre-procedural US, the CNB approach path is chosen [13]. The trans-isthmic technique is regarded as the most suitable of the 4 accessible options, including lateral, longitudinal, and oblique. The size of the sampling notch is affected by the nodule's size and position (Fig. 2). Under US supervision, CNB should be carried out by skilled radiologists to improve safety and diagnostic precision [13, 19].

Figure 2. *Dark grey arrows denote the sample notch and the stylet on the needle of core needle biopsy (CNB)*

Core biopsy device and preparation

For large-core needle biopsy in the past, huge diameter needles like 14 G (gauge) were utilized. CNB pins that have recently been released feature a smaller bore (typically 18–21 G) and spring-activated parts [19]. Without US guidance, large-core needle biopsy is not advised for thyroid nodules [13, 20].

For thyroid nodules, KSThR has recommended optimal CNB needle conditions. It is recommended that a short needle length (less than 10 cm) be used to start, because the thyroid gland is a superficial organ. Second, the thickness of the sample is determined by the pinhole. Less normal tissue is harmed by finer needles, but less tissue is harvested [13]. Even though some publications mention the use of 16–22 G needles, thyroid nodules are typically treated with 18–21 G needles today [13, 19, 21]. The following specifications are usual for CNB needles used to treat thyroid nodules: diameter, 18–21 G; needle length, 6–10 cm; shot length, 1.1–2.0 cm. However, there is no proof that the needle thickness, complication rate, and diagnostic precision are related. Also, the length of the stylet, or the depth of penetration, can be selected based on the size of the nodule, typically 1–2 cm [13]. Two needles, a stylet, and a cutting cannula make up a CNB needle. The stylet's (inner needle) tip is around 2 mm long and has a sharp bevel to cut through tissue and a sample notch to hold the tissue being collected. The external component utilized to cut the tissue is a cutting cannula (external needle) [13, 19].

According on their mode of operation, core biopsy devices are classified as automated or semi-automatic. Because both the inner and outer needles are spring activated, the automated needle is referred to as a double-action device. This kind of needle fires the inner needle using a spring, which can more readily penetrate hard, calcified, or fibrous tissue [13]. However, it might be more prone to harming nearby tissue or blood vessels. Because the spring is only actuated once — first the stylet is manually inserted, then the spring-activated needle — the semi-automatic needle is known as a single-action needle. Despite the fact that the operation using the semi-automatic needle is dangerous, because the doctor must manually press the stylet into the tissue, it is still comparatively safe. The needle thickness and sample notch length both affect how much tissue is extracted [20–22]. On the other hand, a guide needle or coaxial needle is a different needle that helps and aids in the simple inter-needle transit of the central needle to the target. When doing many biopsies in the same area, it offers a clear method of operation and can increase accuracy and productivity. However, because it is larger than the matching biopsy needles in size, the needle route is wider [13, 23].

Sampling techniques for CNB

Under US supervision, core needle biopsy should be carried out by skilled radiologists. The selection of the optimum CNB needle type and access route through pre-procedural US evaluation is also crucial to increase safety and diagnostic accuracy [13]. Although there is no set standard technique for thyroid CNB, the KSThR suggests particular techniques for efficient and secure treatments. One of the most crucial elements in CNB security is experience. Less skilled practitioners may struggle to locate the needle under US, potentially increasing the risk of problems. Less experienced operators should be overseen by more experienced operators when performing CNB procedures [13, 14, 17].

There are 2 choices for needle guidance during US-guided CNB: free-hand and US-guided needle device. The KSThR manual advises use of the free-hand approach because it provides practitioners more latitude in selecting the puncture spot and modifying the route while performing the treatment (particularly for specialists) [13]. Because it offers more flexibility and enables radiologists to choose the puncture spot and modify the path while doing the procedure, the free-hand method is frequently advised [22].

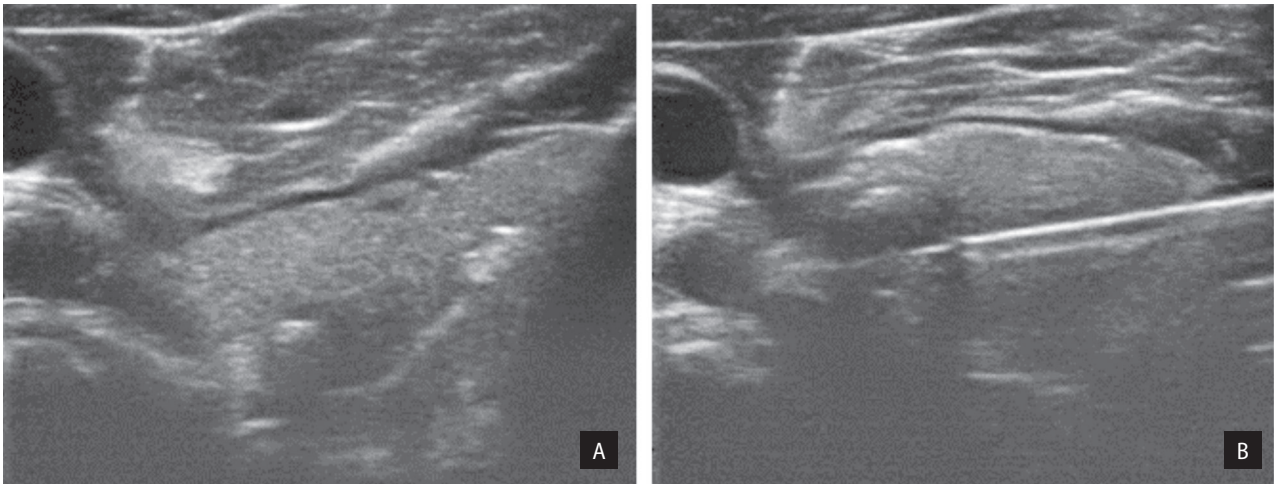

Figure 3. *In the thyroid US image.* **A.** *the stylet is manually moved gently in the direction of the nodule behind the right lobe;* **B.** *Inserting the needle, if necessary, causes the nodule to be elevated. The stylet is adjusted to point in a safer direction before the firing direction is altered, and the cutting cannula is then discharged*

Greyscale and colour Doppler US should be used to assess the nodule's size, position, characteristics, and vascularization prior to the surgery. To reduce sampling of healthy tissue, it is advised that a needle be chosen with a sample notch length close to the nodule diameter [19, 20].

Under local anaesthetic, the patients lie supine along the approach path. It is advised that local anaesthetic be applied with 1% lidocaine using a finer needle along the route [13]. Throughout the process, US monitoring should be used to monitor the full length of the needle. To avoid vessel damage and guarantee the safety of the surgery, complete vessel mapping along the approach route (from the skin to the nodule) is essential [13, 17]. A wrist motion is desirable for quick and effective needle passage through the epidermis and thyroid capsule after vascular mapping using colour Doppler US (Fig. 3).

Without making a skin incision, the skin incision can be performed successfully by using the entry hole made by the needle or by puncturing the skin directly with the umbilical needle and quickly snapping the wrist. Throughout the operation, the CNB needle's whole length should be observed, and it should remain perpendicular to the axis of the US probe. A vertical approach to the needle should be avoided because it is impossible to see the entire length of the needle with US during the process [17]. The appropriate number of biopsy samples is debatable. At least 2 core samples with a nodular tissue and a capsule have been recommended in the past for nodules with unknown cytology [23]. The length of the core sample is also crucial because a longer core sample requires fewer biopsies. Additional risks that could result from multiple biopsies should be taken into account while doing CNB operations [24].

Most crucially, throughout the CNB procedure, the complete length of the needle and needle tip must be delivered. The tip of the needle should be inside the thyroid capsule, away from any large vessels that would be in the projected firing path. Additionally, the cutting cannula and stylet can both be shot [25]. When a successful technique is applied, the specimen notch's position can be changed to find the best biopsy site after the stylet has been fired. Numerous studies have recommended obtaining nodule tissue, the nodule-parenchyma border (and/or visible capsule), and normal thyroid parenchyma [20–25]. When utilizing a double-action CNB needle, it is important to make sure that the needle's entire length (including the tip) is displayed as a single plane before firing the stylet, and that the expected travel distance of the stylet is correctly assessed before firing. Nodules found in dangerous areas need to be thoroughly examined. The sample notch may be adjusted precisely using the single-action needle, which is safer [13].

Thyroid nodules hardly ever show significant fibrosis or hard calcifications. To successfully sample such hard nodules, a double-action biopsy needle works better [24]. For several CNBs, a guiding (coaxial) needle is helpful. In this method, the guide needle is positioned near to the nodule surface, and the biopsy needle is introduced through the skin through its lumen. Following the CNB, the tissue sample can be visually assessed to determine whether more samples are required. The ability to visually assess the acquired tissue is a key benefit of CNB versus FNAB. The normal thyroid parenchyma is visible to the naked eye as soft, blood-red tissue. The majority of tumours resemble solid, fibrous tissue, especially when they are solid. The tissue of calcifications is milky white in colour [13, 19].

The obtained tissue should be quickly fixed in formalin following visual inspection. One or two biopsy samples are usually enough for a reliable histological diagnosis of thyroid nodules. An additional biopsy should be taken into consideration if visual evaluation reveals that the sample size is insufficient. It is advised that tissue samples be collected from various parts of the nodule to represent all of the nodule's regions if a nodule has heterogeneous components on US [19, 23, 24]. If there is a problem, such as bleeding, further sampling may be postponed. Following the biopsy, manual compression should be performed for 20–30 minutes [23–25].

Complications related to core needle biopsy

According to the KSThR or NCI guidelines, when carried out by skilled radiologists, CNB is safe, well-tolerated, and linked with a low incidence of problems. Because CNB is carried out under real-time US direction, serious difficulties seem to be uncommon. Up to 4.1% of reported complications and 1.9% of serious complications have been documented [7, 21]. Infection, haemoptysis, oedema, vasovagal response, dysphagia, and haematoma are some of the consequences of CNB that have been documented [13, 14, 24]. Few severe and mild problems [4/6,169 (0.06%) and 49/6,169 (0.79%), respectively] and no procedure-related deaths or sequelae have been observed in a sizable single-centre study (6687 thyroid nodules in 6169 patients). An expert with understanding of anatomy, anatomical variances, and probable difficulties should conduct CNB to prevent complications [2, 13, 14].

CNB is frequently linked to discomfort and pain. The level of pain and the complication rate can be decreased with US guidance and the use of small 18–21 G needles (typically 18 G) [13]. Numerous investigations that examined the pain and tolerability of FNAB and CNB came to the same conclusion [26, 27]. According to a recent study, patients who received FNAB versus CNB did not significantly differ in their overall satisfaction scores 2 weeks after the CNB operation [27].

The most frequent thyroid CNB consequence is a vascular injury-related haemorrhage, which has been shown to occur up to 3.9% of the time, which is comparable to FNAB (1–6.4%) [12, 14]. Small-artery injury-induced parenchymal oedema is frequently accompanied by haemorrhage and discomfort. These vascular injuries are typically treated by simple compression without the use of medicine [13]. Haematomas have been observed on a few occasions, particularly as a serious side effect following CNB [14, 28]. After the biopsy, manual compression should be done for 20 to 30 minutes to reduce the likelihood of these problems and delayed haematomas [14].

An uncommon but severe side effect of thyroid CNB is voice alteration brought on by direct or indirect damage to the recurrent laryngeal nerve from haemorrhage or oedema. According to a systematic review, the incidence of both permanent and temporary voice changes following thyroid CNB was, respectively, 0.0013% (2/14.818) and 0.034% (5/14.818) [2]. The recurrent laryngeal nerve palsy brought on by haemorrhage or oedema typically resolves on its own. To prevent causing direct damage to the recurrent laryngeal nerve, it is crucial to perform the procedure under US direction [13]. For recurrent laryngeal nerve injuries or damage to the trachea, oesophagus, or both, the lateral-medial route is significantly riskier [7]. Because of the thyroid's extensive lymphatic drainage, abundant vascularization, and high iodine content, abscess formation is an uncommon complication following CNB. Therefore, it is not advised that prophylactic antibiotics be administered before or after CNB [13, 14].

After ruling out the pharyngoesophageal or oesophageal diverticulum, CNB is recommended in the case of a nodule at the posteromedial margin of the thyroid gland [14]. Coughing or haemoptysis result from direct tracheal damage. Haemoptysis spontaneously clears up without the need for hospitalization [13, 14, 20]. When the needle point is pushed too far through the thyroid capsule, damage to extrathyroidal tissue, such as vessels, muscles, or vertebrae, may result. After damage to the perithyroidal vertebral artery and vein, an arteriovenous fistula has been linked to tinnitus, a rare consequence [29]. Dysphagia and vasovagal response are potential side effects that may improve with conservative therapies. After CNB of thyroid nodules, there have been no reports of tumour seeding [30]. Radiologists need to be aware of a wide range of issues and how to prevent them to perform US-guided CNB safely and effectively. The risk-benefit ratio of CNB should be evaluated, as well as US-based thyroid and perithyroidal anatomical experience, including arteries and nerves [13, 14], to prevent and limit difficulties.

Pathology request form

The patient sample ID, patient's name, date of birth, unit number, or medical record number, name of the requesting clinician and the clinician performing the procedure, site and site of the lesion, number of biopsy nuclei, US imaging findings, and pertinent clinical history should all be included in the CNB request form.

Preparation and processing of CNB samples

For a subsequent pathological diagnosis, appropriate tissue processing and histological staining processes are crucial. Biopsy specimens should be handled carefully because they are delicate. As soon as thyroid gland biopsy tissues are removed, biopsy cores should be quickly fixed with 10% neutral buffered formalin (NBF) to prevent sample loss and tissue folding (equivalent to 4% formaldehyde to prevent autolysis and rot). This is done by wrapping the cores in gauze or filter paper that has been moistened with saline or fixative. To prevent cell lysis and loss of cell identity when studied under a microscope, compression of the biopsy specimen should be avoided. The sample should be wrapped in wet saline gauze and kept chilled until it has been treated with an appropriate fixative if a fixative cannot be applied in a timely manner. With 10 mL of fixative per gram of tissue, the formalin solution to tissue ratio should be at least 10:1 [31].

The appropriate volume of 10% NBF in clinical practice should be 15–20 times the volume of the sample. The sample size affects fixation time. The tiny biopsy material must typically be exposed for at least 5 hours to receive an adequate fixation period with 10% NBF [32]. Nevertheless, procedures could vary amongst laboratories. Factory outcomes that are poor and unsatisfactory can be caused by incomplete or subpar tissue fixation. Each sample should be placed into a container that can be closed [31, 32]. It is possible to do standard haematoxylin-eosin staining on sections taken from formalin-fixed, paraffin-embedded tissue blocks, as well as supplementary tests such custom staining, immunohistochemistry, and molecular testing.

Post-thyroid CNB pathology reporting

Usually, CNB can only make a histological diagnosis to distinguish between malignant and benign nodules. It is less likely that pathological findings are misinterpreted when there is excellent communication between pathologists and doctors, thanks to a categorical reporting system for CNB. Korean pathologists frequently adopt the first edition of "Pathology Reporting of Thyroid Core Needle Biopsy", which was issued by the Korean Endocrine Pathology CNB Working Group in 2015 [12]. A recent study in China demonstrated the clinical objectivity, applicability, and value of the thyroid CNB pathology reporting system for the pathological diagnosis of thyroid nodules [33]. In the 2022 "Recommendations of the Polish Scientific Societies and the National Oncological Strategy" the importance of pathology reporting is detailed with up-to-date information. In light of the updated information, this guide focuses on the diagnosis of thyroid cancer and providing effective treatment [18].

Thyroid CNB pathology should be associated with clinical and US imaging findings. Biopsy results should be reviewed with surgery and pathology units after surgery. A categorical reporting system for CNB provides effective communication between pathologists and clinicians that reduces the possibility of misinterpretation of pathology results. The 6 original general categories were retained in the 2019 revision. To communicate clearly, the pathology report of thyroid CNB begins with a general diagnostic category. The 6 general diagnostic categories are shown in Table 2. Subcategorization is often informative, especially in diagnostic categories III and IV. A brief microscopic description of the biopsy specimen may be informative but should not be used alone to communicate the diagnosis. Standardized terms for diagnostic categories should be used. The numeric code alone should not be used without the diagnostic category term. Recommendations associated with malignancy risk and each general category are not required, but they can be provided based on their own CNB-histology correlations or published studies [18].

Non-diagnostic or inadequate diagnosis

When the volume of the biopsy specimen and the number of follicular cells are too few to provide a reliable diagnosis and the specimen does not accurately reflect the lesion's US imaging findings, this category is employed. The type of thyroid lesion, the radiologist's experience, and the procedure used during the biopsy may all affect the adequacy of the specimen. There is no agreement on the bare minimum number or volume of follicular components needed for a good biopsy specimen; hence, this diagnosis is arbitrary. As a result, the report needs to describe why the sample is not accurate or sufficient. Any CNB sample, however, should not be discounted as non-diagnostic or insufficient simply because it contains unusual cells.

Benign

All benign thyroid and nonthyroidal conditions fall under this heading. Based on the precise lesion diagnosis, a CNB specimen can be categorized as benign. Benign follicular nodules, Hashimoto's thyroiditis, subacute granulomatous thyroiditis, parathyroid lesions, benign neurogenic tumours, benign lymph nodes, or other benign lesions are a few examples of possible samples. Nodular hyperplasia (adenomatoid nodule), colloid nodules, Graves' disease-associated nodules, nodular Hashimoto's thyroiditis, and a subset of follicular adenomas are all examples of benign follicular nodules. Although benign in most cases,

Table 2. *Diagnostic categories of thyroid core needle biopsy (CNB)*

I	Non-diagnostic or underdiagnosed
	Only adjacent non-tumour thyroid tissue
	Extra thyroid tissue only (e.g. skeletal muscle, mature adipose tissue)
	Cellular sample (e.g. acellular fibrotic tissue, acellular hyalinized tissue, cystic fluid only)
	Only blood clot
	Other
II	Benign lesion
	Benign follicular nodule
	Hashimoto's thyroiditis
	Subacute granulomatous thyroiditis
	Non-thyroid lesion (e.g. parathyroid lesions, benign neurogenic tumours, benign lymph node)
	Other
III	Indeterminate lesion
	IIIa. Indeterminate follicular lesion with nuclear atypia
	IIIb. Indeterminate follicular lesion with structural atypia
	IIIc. Indeterminate follicular lesion with nuclear and structural atypia
	IIId. Indeterminate follicular lesion with Hurthle cell changes
	IIIe. Indeterminate lesion, not otherwise specified
IV	Follicular neoplasia
	IVa. Follicular neoplasm, traditional type
	IVb. Follicular neoplasm with nuclear atypia
	IVc. Hurthle cell neoplasm
	IVd. Follicular neoplasm, not otherwise specified
V	Suspicion of malignancy
	Papillary thyroid carcinoma, medullary thyroid carcinoma, poorly differentiated thyroid carcinoma, metastatic carcinoma, lymphoma, etc. suspicious lesion
VI	Malignancy
	Papillary thyroid carcinoma, poorly differentiated thyroid carcinoma, anaplastic thyroid carcinoma, medullary thyroid carcinoma, lymphoma, metastatic carcinoma, etc.

degenerating nodules frequently exhibit worrisome US findings and non-diagnostic or ambiguous cytological results [34].

The CNB of the nodule shows haemorrhagic materials in the early stage, stromal fibrosis and hyalinization with chronic inflammatory cells infiltrating in the middle stage after the regression of bleeding, and paucicellular dense hyalinized stroma in the late stage [14, 34]. By contrasting the histological characteristics of the follicular cells in both the central and peripheral regions present in the CNB sample, atypia status can be ascertained. Patients with Hashimoto's thyroiditis frequently develop benign Hurthle cell lesions, which can mirror their malignant counterparts [14].

Indetermined lesion

The significance of the cytological atypia and histological development patterns in this group is questionable, and they are insufficient to place the patient in another diagnostic category. "Indeterminate lesion" in diagnostic category III is represented by "AUS" or "FLUS" in the TBSRTC. Some pathologists prefer the term "AUS" while others prefer the term "indeterminate lesion" when describing category III in the histological diagnosis of CNB specimens [12, 25].

When a follicular proliferative lesion exhibits focal nuclear atypia, such as nuclear enlargement with pale chromatin, uneven nuclear membrane, and nuclear furrows against a background of mostly benign-appearing follicles, a category III diagnosis is warranted. Nuclear atypia, histological development patterns, cell type, and other histological traits should be used to further classify category III. Because subclassification suggests distinct histological characteristics and a risk of cancer in thyroid nodules [12]. Nuclear atypia subclassifies papillary thyroid cancer as a possibility that should be

ruled out, whereas structural atypia does not rule out follicular neoplasm.

Follicular neoplasia

In CNB and FNAB, the term "follicular neoplasia" is used to cover neoplastic lesions with follicular proliferative pattern [cellular nodular hyperplasia, follicular adenoma, noninvasive follicular thyroid neoplasm (NIFTP) with papillary-like nuclear features, follicular carcinoma, follicular variant of papillary carcinoma, follicular variant of medullary carcinoma] [1]. The terms "follicular neoplasm" and "suspicious for follicular neoplasm" are not used interchangeably in the TBSRTC and are not meant to denote the 2 distinct interpretations separately. Based on the existence of a fibrous capsule and microscopic characteristics that are distinct from the surrounding thyroid parenchyma, the histological diagnosis of "follicular neoplasm" in a CNB specimen is made. Follicular cells in this group do not exhibit the typical nuclear characteristics linked to papillary cancer.

For the CNB specimen's follicular neoplasm to be diagnosed, a well-formed fibrous capsule must be found. The fibrous capsule, which isolates the tumour cells from the surrounding thyroid tissue, is made up of fibrous connective tissue. When the tumour fibrous capsule is detected in a CNB test, the growth patterns of a follicular neoplasm may be microfollicular, normofollicular, solid, or trabecular. Follicular carcinoma and follicular adenoma require inspection of the complete tumour capsule for diagnosis, which CNB cannot do [35].

Suspicion of malignancy

When the histological findings strongly imply malignancy but are insufficient or suspect for a conclusive diagnosis of malignancy, the diagnosis of "suspicious malignancy" is established. This type of lesion may be suspect for lymphoma, papillary thyroid carcinoma, medullary thyroid carcinoma, poorly differentiated thyroid carcinoma, metastatic carcinoma, or other thyroid cancers. Low cellularity or insufficient sample are frequent causes of diagnostic ambiguity in the current category.

The results should be regarded as papillary carcinoma when a follicular proliferative lesion with nuclear characteristics of papillary carcinoma exhibits capsular invasion in CNB specimens. It should be understood as a follicular neoplasm with nuclear atypia in the absence of capsular invasion [14]. But when a fibrous capsule or neighbouring non-lesional tissue is absent from the CNB specimen, which mostly exhibits a follicular growth pattern and nuclear characteristics of papillary carcinoma, the data are best interpreted as suggestive for papillary carcinoma.

The diagnosis of CNB specimens suspected of being cancerous is made easier by ancillary immunohistochemistry or molecular tests. A galectin-3, HBME1, cytokeratin-19, or CD56 immunostaining panel can help in the detection of lesions that could be papillary thyroid cancer. To improve diagnostic precision, combinations of at least 2 immunostaining markers are advised [35]. The diagnosis of papillary cancer is strongly supported by BRAF V600E mutations found by genetic testing or immunohistochemistry for the BRAF VE1 antibody [36]. The presence of positive immunostaining for calcitonin in the CNB material can support the diagnosis of medullary thyroid cancer. Immunophenotyping investigations are used to confirm the lymphoma diagnosis in a CNB sample [12–14].

Malignancy

Most thyroid cancers, with the exception of follicular carcinoma and Hurthle cell carcinoma, have conventional histological characteristics and can be identified as cancers on a CNB specimen. Papillary thyroid cancer, poorly differentiated carcinoma, medullary thyroid carcinoma, anaplastic thyroid carcinoma, lymphoma, and metastatic carcinoma are among the diagnoses that fall under the category of thyroid malignancies.

Conclusions

To overcome the problems with FNAB for diagnosing thyroid nodules, US-guided CNB is an alternative method. The major goals of thyroid CNB are to get a significant number of thyroid lesions with low morbidity and to identify thyroid disease patients who need surgery. Current practical guidelines provide a standardized system for pathology reporting of CNB specimens as well as clinical recommendations for effective thyroid CNB.

Authorship contributions

Conception and design: E.K., M.J., and H.K. Acquisition of data: E.K., M.J., and H.K. Analysis and interpretation of data: E.K., M.J., and H.K. Drafting the article: E.K., M.J., and H.K. Revising it critically for important intellectual content: E.K., M.J., and H.K. Final approval of the version to be published: E.K., M.J., and H.K.

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Conflict of interests

The authors declare that they have no competing interests.

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Informed consent

All patients included in this study gave written informed consent to participate in this research. Because human data were available, the Declaration of Helsinki was adhered to throughout the study.

References

1. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. Thyroid. 2017; 27(11): 1341–1346, doi: 10.1089/thy.2017.0500, indexed in Pubmed: 29091573.
2. Ha EJu, Lim HK, Yoon JH, et al. Korean Society of Thyroid Radiology (KSThR) and Korean Society of Radiology. Primary Imaging Test and Appropriate Biopsy Methods for Thyroid Nodules: Guidelines by Korean Society of Radiology and National Evidence-Based Healthcare Collaborating Agency. Korean J Radiol. 2018; 19(4): 623–631, doi: 10.3348/kjr.2018.19.4.623, indexed in Pubmed: 29962869.
3. Bongiovanni M, Spitale A, Faquin WC, et al. The Bethesda System for Reporting Thyroid Cytopathology: a meta-analysis. Acta Cytol. 2012; 56(4): 333–339, doi: 10.1159/000339959, indexed in Pubmed: 22846422.
4. Yoo C, Choi HJ, Im S, et al. Fine needle aspiration cytology of thyroid follicular neoplasm: cytohistologic correlation and accuracy. Korean J Pathol. 2013; 47(1): 61–66, doi: 10.4132/KoreanJPathol.2013.47.1.61, indexed in Pubmed: 23483732.
5. Novoa E, Gürtler N, Arnoux A, et al. Role of ultrasound-guided core-needle biopsy in the assessment of head and neck lesions: a meta-analysis and systematic review of the literature. Head Neck. 2012; 34(10): 1497–1503, doi: 10.1002/hed.21821, indexed in Pubmed: 22127851.
6. Ha EJu, Baek JH, Lee JH, et al. Complications following US-guided core-needle biopsy for thyroid lesions: a retrospective study of 6,169 consecutive patients with 6,687 thyroid nodules. Eur Radiol. 2017; 27(3): 1186–1194, doi: 10.1007/s00330-016-4461-9, indexed in Pubmed: 27311538.
7. Paja M, Del Cura JL, Zabala R, et al. Core-needle biopsy in thyroid nodules: performance, accuracy, and complications. Eur Radiol. 2019; 29(9): 4889–4896, doi: 10.1007/s00330-019-06038-6, indexed in Pubmed: 30783787.
8. Cao H, Kao RH, Hsieh MC. Comparison of core-needle biopsy and fine-needle aspiration in screening for thyroid malignancy: a systematic review and meta-analysis. Curr Med Res Opin. 2016; 32(7): 1291–1301, doi: 10.1185/03007995.2016.1170674, indexed in Pubmed: 27010079.
9. Suh CH, Baek JH, Choi YJ, et al. Efficacy and safety of core-needle biopsy in initially detected thyroid nodules via propensity score analysis. Sci Rep. 2017; 7(1): 8242, doi: 10.1038/s41598-017-07924-z, indexed in Pubmed: 28811482.
10. Hong MJi, Na DG, Kim SJ, et al. Role of core needle biopsy as a first-line diagnostic tool for thyroid nodules: a retrospective cohort study. Ultrasonography. 2018; 37(3): 244–253, doi: 10.14366/usg.17041, indexed in Pubmed: 29113031.
11. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. J Am Soc Cytopathol. 2017; 6(6): 217–222, doi: 10.1016/j.jasc.2017.09.002, indexed in Pubmed: 31043290.
12. Jung CK, Min HS, Park HJ, et al. Korean Endocrine Pathology Thyroid Core Needle Biopsy Study Group. Pathology Reporting of Thyroid Core Needle Biopsy: A Proposal of the Korean Endocrine Pathology Thyroid Core Needle Biopsy Study Group. J Pathol Transl Med. 2015; 49(4): 288–299, doi: 10.4132/jptm.2015.06.04, indexed in Pubmed: 26081825.
13. Na DG, Baek JH, Jung SoL, et al. Korean Society of Thyroid Radiology (KSThR) and Korean Society of Radiology. Core Needle Biopsy of the Thyroid: 2016 Consensus Statement and Recommendations from Korean Society of Thyroid Radiology. Korean J Radiol. 2017; 18(1): 217–237, doi: 10.3348/kjr.2017.18.1.217, indexed in Pubmed: 28096731.
14. Jung CK, Baek JH, Na DG, et al. 2019 Practice guidelines for thyroid core needle biopsy: a report of the Clinical Practice Guidelines Development Committee of the Korean Thyroid Association. J Pathol Transl Med. 2020; 54(1): 64–86, doi: 10.4132/jptm.2019.12.04, indexed in Pubmed: 31964112.
15. Choi YJ, Baek JH, Suh CH, et al. Core-needle biopsy versus repeat fine-needle aspiration for thyroid nodules initially read as atypia/follicular lesion of undetermined significance. Head Neck. 2017; 39(2): 361–369, doi: 10.1002/hed.24597, indexed in Pubmed: 27704650.
16. Baloch ZW, Cibas ES, Clark DP, et al. The National Cancer Institute Thyroid fine needle aspiration state of the science conference: a summation. Cytojournal. 2008; 5: 6, doi: 10.1186/1742-6413-5-6, indexed in Pubmed: 18394201.
17. Gharib H, Papini E, Garber JR, et al. AACE/ACE/AME Task Force on Thyroid Nodules. American Association Of Clinical Endocrinologists, American College Of Endocrinology, and Associazione Medici Endocrinologi Medical Guidelines For Clinical Practice For The Diagnosis and Management Of Thyroid Nodules — 2016 Update. Endocr Pract. 2016; 22(5): 622–639, doi: 10.4158/EP161208.GL, indexed in Pubmed: 27167915.
18. Jarząb B, Dedecjus M, Lewiński A, et al. Diagnosis and treatment of thyroid cancer in adult patients - Recommendations of Polish Scientific Societies and the National Oncological Strategy. 2022 Update [Diagnostyka i leczenie raka tarczycy u chorych dorosłych - Rekomendacje Polskich Towarzystw Naukowych oraz Narodowej Strategii Onkologicznej. Aktualizacja na rok 2022]. Endokrynol Pol. 2022; 73(2): 173–300, doi: 10.5603/EP.a2022.0028, indexed in Pubmed: 35593680.
19. Na DG, Kim Jh, Sung JY, et al. Core-needle biopsy is more useful than repeat fine-needle aspiration in thyroid nodules read as nondiagnostic or atypia of undetermined significance by the Bethesda system for reporting thyroid cytopathology. Thyroid. 2012; 22(5): 468–475, doi: 10.1089/thy.2011.0185, indexed in Pubmed: 22304417.
20. Baek JH. Current status of core needle biopsy of the thyroid. Ultrasonography. 2017; 36(2): 83–85, doi: 10.14366/usg.17018, indexed in Pubmed: 28301922.
21. Park KT, Ahn SH, Mo JH, et al. Role of core needle biopsy and ultrasonographic finding in management of indeterminate thyroid nodules. Head Neck. 2011; 33(2): 160–165, doi: 10.1002/hed.21414, indexed in Pubmed: 20848434.
22. López JI, Zabala R, Del Cura JL. Histological diagnosis of thyroid disease using ultrasound-guided core biopsies. Eur Thyroid J. 2013; 2(1): 29–36, doi: 10.1159/000343825, indexed in Pubmed: 24783036.
23. Hahn SY, Shin JH, Oh YL. What Is the Ideal Core Number for Ultrasonography-Guided Thyroid Biopsy of Cytologically Inconclusive Nodules? AJNR Am J Neuroradiol. 2017; 38(4): 777–781, doi: 10.3174/ajnr.A5075, indexed in Pubmed: 28154123.
24. Suh CH, Baek JH, Lee JH, et al. The Role of Core-Needle Biopsy as a First-Line Diagnostic Tool for Initially Detected Thyroid Nodules. Thyroid. 2016; 26(3): 395–403, doi: 10.1089/thy.2015.0404, indexed in Pubmed: 26651390.
25. Chung SR, Baek JH, Choi YJ, et al. The Role of Core Needle Biopsy for the Evaluation of Thyroid Nodules with Suspicious Ultrasound Features. Korean J Radiol. 2019; 20(1): 158–165, doi: 10.3348/kjr.2018.0101, indexed in Pubmed: 30627031.
26. Jeong EJi, Chung SR, Baek JH, et al. A Comparison of Ultrasound-Guided Fine Needle Aspiration versus Core Needle Biopsy for Thyroid Nodules: Pain, Tolerability, and Complications. Endocrinol Metab (Seoul). 2018; 33(1): 114–120, doi: 10.3803/EnM.2018.33.1.114, indexed in Pubmed: 29589393.
27. Jin Kim H, Koon Kim Y, Hoon Moon J, et al. Thyroid core needle biopsy: patients' pain and satisfaction compared to fine needle aspiration. Endocrine. 2019; 65(2): 365–370, doi: 10.1007/s12020-019-01973-2, indexed in Pubmed: 31203562.
28. Harvey JN, Parker D, De P, et al. Sonographically guided core biopsy in the assessment of thyroid nodules. J Clin Ultrasound. 2005; 33(2): 57–62, doi: 10.1002/jcu.20092, indexed in Pubmed: 15674833.
29. Bergeron M, Beaudoin D. Simple core-needle biopsy for thyroid nodule, complicated tinnitus. Eur Thyroid J. 2014; 3(2): 130–133, doi: 10.1159/000360985, indexed in Pubmed: 25114877.
30. Shah KSV, Ethunandan M. Tumour seeding after fine-needle aspiration and core biopsy of the head and neck--a systematic review. Br J Oral Maxillofac Surg. 2016; 54(3): 260–265, doi: 10.1016/j.bjoms.2016.01.004, indexed in Pubmed: 26837638.
31. Thavarajah R, Mudimbaimannar VK, Elizabeth J, et al. Chemical and physical basics of routine formaldehyde fixation. J Oral Maxillofac Pathol. 2012; 16(3): 400–405, doi: 10.4103/0973-029X.102496, indexed in Pubmed: 23248474.
32. Hewitt SM, Lewis FA, Cao Y, et al. Tissue handling and specimen preparation in surgical pathology: issues concerning the recovery of nucleic acids from formalin-fixed, paraffin-embedded tissue. Arch Pathol Lab Med. 2008; 132(12): 1929–1935, doi: 10.5858/132.12.1929, indexed in Pubmed: 19061293.
33. Xiong Y, Yan L, Nong L, et al. Pathological diagnosis of thyroid nodules based on core needle biopsies: comparative study between core needle biopsies and resected specimens in 578 cases. Diagn Pathol. 2019; 14(1): 10, doi: 10.1186/s13000-019-0786-4, indexed in Pubmed: 30711008.
34. Ren J, Baek JH, Chung SR, et al. Degenerating Thyroid Nodules: Ultrasound Diagnosis, Clinical Significance, and Management. Korean J Radiol. 2019; 20(6): 947–955, doi: 10.3348/kjr.2018.0599, indexed in Pubmed: 31132820.
35. Basolo F, Macerola E, Poma AM, et al. The 5 edition of WHO classification of tumors of endocrine organs: changes in the diagnosis of follicular-derived thyroid carcinoma. Endocrine. 2023; 80(3): 470–476, doi: 10.1007/s12020-023-03336-4, indexed in Pubmed: 36964880.
36. Alshenawy HA. Utility of immunohistochemical markers in diagnosis of follicular cell derived thyroid lesions. Pathol Oncol Res. 2014; 20(4): 819–828, doi: 10.1007/s12253-014-9760-3, indexed in Pubmed: 24659044.
37. Crescenzi A, Guidobaldi L, Nasrollah N, et al. Immunohistochemistry for BRAF(V600E) antibody VE1 performed in core needle biopsy samples identifies mutated papillary thyroid cancers. Horm Metab Res. 2014; 46(5): 370–374, doi: 10.1055/s-0034-1368700, indexed in Pubmed: 24570209.