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Pathological diagnosis of general rules for the description of thyroid cancer by Japanese Society of Thyroid Pathology and Japan Association of Endocrine Surgery

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Abstract. The Japanese Society of Thyroid Pathology and the Japan Association of Endocrine Surgeons developed the eighth edition of the General Rules for the Description of Thyroid Cancer (GRDTC) in December 2019. This article describes the pathological diagnosis of the GRDTC, which has been improved through repeated revisions based on the experience of Japanese pathologists and translated into English to introduce the Japanese diagnostic standard to foreign countries. In this edition of the GRDTC, the histopathological classification and descriptions differ in some respects from those of the fourth edition of the World Health Organization (WHO) classification as revised in 2017. For example, the GRDTC does not adopt the concept of borderline lesions (FT-UMP, WDT-UMP, and NIFTP) of the WHO, taking into consideration the popular histological criteria accepted by Japanese pathologists. The cytological reporting system of the GRDTC was partly modified from the Bethesda system in 2015. It has an additional cyst fluid category separated from the unsatisfactory category that has been demonstrated to be useful in Japan. This translated edition makes it easy to submit Japanese clinicopathological studies of thyroid tumors in an international journal. We also wish to contribute to the improvement, standardization, and globalization of the pathological diagnosis of thyroid tumors.

Key words: the General Rules for the Description of Thyroid Cancer (GRDTC), the World Health Organization (WHO), Thyroid tumors, Pathological diagnosis, Cytology

THE PATHOLOGICAL classification of general rules for the description of thyroid cancer (GRDTC) [1] has been improved through repeated revisions based on the experience of Japanese pathologists, although it fundamentally follows an international standard. In the eighth edition, the histological classification of the pathological diagnosis was partly changed according to the revised World Health Organization (WHO) classification in 2017 [2]. The Japanese classification of GRDTC does not adopt the concept of borderline lesions (FT-UMP, WDT-UMP, and NIFTP) of the WHO, considering the popular histological criteria accepted by Japanese pathologists, and a detailed commentary is described to establish consistency between the two classifications. For the

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E-mail: hkamma@ks.kyorin-u.ac.jp
Abbreviations: PTC, papillary (thyroid) carcinoma; FTC, follicular (thyroid) carcinoma; FTA, follicular (thyroid) adenoma; WDTC, well-differentiated thyroid carcinoma; PDTC, poorly differentiated (thyroid) carcinoma; ATC, anaplastic (thyroid) carcinoma; MTC, medullary (thyroid) carcinoma; HTT, hyalinizing trabecular tumor; GRDTC, General rules for the description of thyroid cancer (8th edition); WHO, WHO classification (4th edition); FT-UMP, follicular tumor of uncertain malignant potential; WDT-UMP, well-differentiated tumor of uncertain malignant potential; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features.

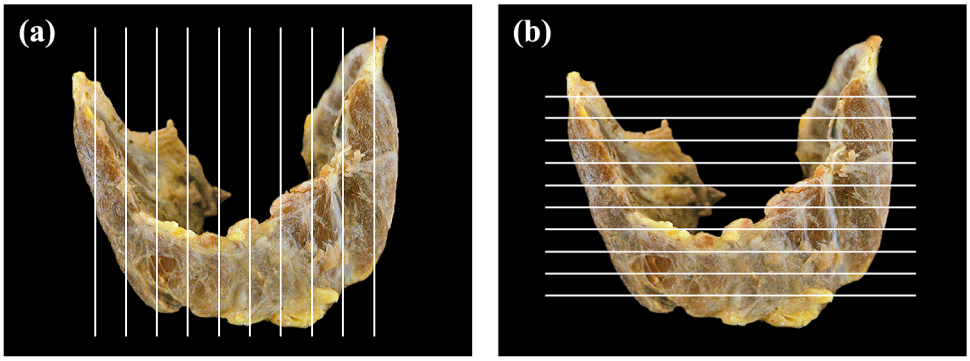

Fig. 1 (a) Sagittal section. (b) Horizontal section.

definition of poorly differentiated carcinoma, the standard of the previous WHO classification is used instead of the restrictive Turin standard. In contrast, an encapsulated angioinvasive subtype is added to follicular carcinoma according to the WHO classification.

The reporting system for cytological diagnosis followed the previous edition of the GRDTC. The GRDTC system was partly modified from the Bethesda system in 2015 [3] and it has been demonstrated to be useful in Japan.

We wish to contribute to the improvement, standardization, and globalization of the pathological diagnosis of thyroid tumors for all pathologists, physicians, and researchers engaged in thyroid cancer.

Handling of the Thyroid Excision Specimen

Fixation

Surgically-removed thyroid specimens are immediately immersed in a fixative (neutral buffered, 10% formalin solution). If the specimen is a large mass, it could be carefully cut before fixation to avoid disturbing the pathological examination.

Incision

The fixed thyroid gland is cut in a sagittal section (Fig. 1a) and sliced every 3–5 mm. It could be cut in a horizontal section (Fig. 1b) to examine the lesions in relation to the surrounding tissues and in comparison with the radiologic images.

Gross examination and cutting

The sectioned surfaces, property and border of tumors should be inspected carefully in the surrounding tissues and strap muscles, and appropriate sites are cut as specimens of enough number (Fig. 2).

1) Calcified lesions should not be cut forcibly, but are divided, if possible. The calcified specimens are placed in a decalcifying agent and cut after decalcification. It is undesirable to place the entire excised thyroid gland in a decalcifying agent.

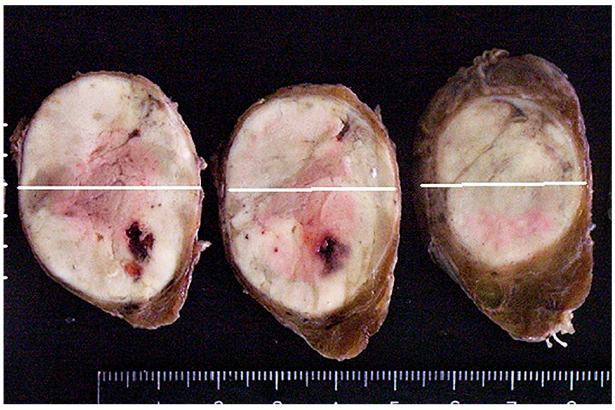

Fig. 2 Cutting and gross examination
Slice an oval tumor and make many specimens to well inspect the border.

2) When a follicular carcinoma is suspected macroscopically, it is desirable to cut out many areas, especially of the tumor capsule, because vascular invasion is observed in and beneath the capsule.

3) For apparent malignant tumors, it is necessary to prepare specimens including attached organs such as the muscles.

4) It is necessary to prepare specimens of all the parathyroid glands and lymph nodes that are attached to the sample.

Histological Classification

Thyroid tumors are mainly classified as 1. benign tumors, 2. malignant tumors, 3. other tumors, 4. unclassified tumors, and 5. tumor-like lesions (Table 1). A benign tumor is only a follicular adenoma. Malignant tumors are classified as papillary, follicular, poorly differentiated, anaplastic, medullary carcinomas, or lymphoma respectively.

Table 1 Histological classification of thyroid tumors

1. Benign tumors	
a. Follicular adenoma	8,330/0
Variants	
1) Follicular adenoma, oxyphilic cell (oncocytic) variant	8,290/0
2) Follicular adenoma, clear cell variant	8,330/0
2. Malignant tumors	
a. Papillary carcinoma	8,260/3
Variants	
1) Papillary carcinoma, follicular variant	8,340/3
2) Papillary carcinoma, macrofollicular variant	8,340/3
3) Papillary carcinoma, oxyphilic cell (oncocytic) variant	8,342/3
4) Papillary carcinoma, diffuse sclerosing variant	8,350/3
5) Papillary carcinoma, tall cell variant	8,344/3
6) Papillary carcinoma, solid variant	8,260/3
7) Papillary carcinoma, cribriform variant	8,260/3
8) Papillary carcinoma, hobnail variant	8,260/3
9) Other variants	8,260/3
b. Follicular carcinoma	8,330/3
Subtypes according to invasive pattern	
1) Follicular carcinoma, minimally invasive	8,335/3
2) Follicular carcinoma, encapsulated angioinvasive	8,339/3
3) Follicular carcinoma, widely invasive	8,330/3
Variants	
1) Follicular carcinoma, oxyphilic cell (oncocytic) variant	8,290/3
2) Follicular carcinoma, clear cell variant	8,330/3
c. Poorly differentiated carcinoma	8,337/3
d. Anaplastic carcinoma	8,020/3
e. Medullary carcinoma	8,345/3
f. Mixed medullary and follicular cell carcinoma	8,346/3
g. Lymphoma	9,590/3
3. Other tumors	
a. Hyalinizing trabecular tumor	8,336/1
b. Columnar cell carcinoma	8,344/3
c. Mucinous carcinoma	8,480/3
d. Mucoepidermoid carcinoma	8,430/3
e. Intrathyroid thymic carcinoma (ITTC)	8,589/3
f. Spindle cell tumor with thymus–like differentiation (SETTLE)	8,588/3
g. Squamous cell carcinoma	8,070/3
h. Sarcomas	8,800/3
i. Others	
j. Secondary (metastatic) tumors	
4. Unclassified tumors	
5. Tumor–like lesions	
a. Adenomatous goiter	
b. Amyloid goiter	
c. Cyst	

Description of Histological Types

Benign tumors

Follicular adenoma

Follicular adenoma (FTA) is a benign tumor derived from the follicular epithelium and it is encapsulated by a fibrous capsule. The neoplastic cells are almost uniform in size and form, and mainly proliferate in a follicular pattern. It does not demonstrate capsular invasion, vascular invasion, or distant metastasis.

FTAs are usually solitary, proliferate to compress the neighborhood thyroid tissue, and are encapsulated by a fibrous capsule. The capsule of the FTA covers the entire circumference, although the thickness varies for each case. The capsule is occasionally calcified and ossified. Capsular connective tissue does not usually extend or separate into tumors.

The tumor cells are relatively monotonous in size and shape within one tumor, although they may have cubic, columnar, and polyhedral shapes. There is a rare case of outstanding signet-ring cells.

Although the large and small follicles are mixed, the predominant growth pattern is a small follicular structure. FTA may show a papillary structure in some cases, although it does not show the characteristic nuclear features of papillary carcinoma. When FTAs are accompanied by hyperthyroidism (toxic adenoma or hyperfunctioning adenoma), the neoplastic cells are highly columnar, and papillary structures and absorption vacuoles are partly seen.

FTAs usually have a narrow stroma and rich capillary vessels among follicles. FTAs are sometimes locally accompanied by secondary changes such as edema, fibrosis, hyalinization, hemorrhage, calcification, cartilaginous and bone metaplasia, and cyst formation. There are rare cases of stromal adipose tissue (lipoadenoma) and mucin deposition (FTA, mucinous type).

Lesions previously diagnosed as papillary adenoma are now considered either FTAs showing papillary structure, adenomatous goiter with marked papillary structure, and encapsulated papillary carcinoma. Therefore, the diagnosis of papillary adenomas is currently obsolete.

Variants

1) Follicular adenoma, oxyphilic cell (oncocytic) variant

An oxyphilic FTA is a tumor consisting mainly of acidophilic cells (more than 75%) and is called a Hürthle cell adenoma. Macroscopically, it is brownish and occasionally has a scar at the center. Neoplastic cells have abundant acidophilic granular cytoplasm and often hyperchromatic nuclei. The nuclei are occasionally large, pleomorphic, and have clear nucleoli. An oxyphilic FTA is distinguished from an oxyphilic-type papillary carcinoma, in which the nucleus shows characteristics of papillary carcinoma. The cytoplasmic characteristic of this tumor originates from the abundant mitochondria.

2) Follicular adenoma, clear cell variant

A clear cell FTA is an FTA in which all or most of the cells have a clear cytoplasm. Cytoplasmic clearing depends on mitochondrial ballooning, accumulation of fat or glycogen, and retention of thyroglobulin. This tumor should be differentiated from the metastasis of clear cell type follicular carcinoma, adenoma of the parathyroid gland, and renal cell carcinoma.

Appendix

*** Follicular adenoma with bizarre nuclei**

FTA with bizarre nuclei shows severe structural and cellular/nuclear atypia. This tumor reveals neither capsular nor vascular invasion, although it often shows more severe atypia than ordinary follicular carcinoma.

Malignant tumors

Papillary carcinoma

Papillary carcinoma (PTC) is a malignant follicular cell-derived tumor with a set of distinctive nuclear features. Although the basic structure of PTC is papillary, it is interspersed to various degrees with neoplastic follicles. An exclusively follicular growth pattern is occasionally observed. Therefore, the cardinal morphological features of PTC are not dependent on histological structure, such as papillary or follicular, but on cytological findings, especially nuclear features.

The nuclei of PTC cells are large and show irregular contours, and there are few mitotic figures. Typical nuclear features include overlapping nuclei, ground glass-like nuclei, nuclear grooves, and intranuclear cytoplasmic (pseudo-)inclusions. Overlapping nuclei, which lie one upon another, are mainly found in the papillary structures. Ground glass-like nuclei indicate a pale appearance due to finely textured, evenly distributed chromatin. The nuclear grooves are found parallel to the long axis. Because intranuclear cytoplasmic inclusions constitute deep cytoplasmic invaginations into the nucleus, they are the same as cytoplasmic coloring. Intranuclear cytoplasmic inclusions are observed in other tumors such as medullary carcinoma. The cytoplasm of PTC is slightly or moderately eosinophilic, and squamous metaplasia is occasionally observed.

Papillary structures seen in PTC are irregularly arranged with a fibrovascular core, which is edematous in some cases. On the other hand, papillary structures observed in adenomatous goiter, follicular adenoma, *etc.*, do not contain fibrovascular cores. Psammoma bodies (laminated micro-calcified foci) are frequently found in lymphatic channels or within the stroma. Hyalinization or calcium deposition is occasionally detected within the

abundant stroma. Cystic change is occasionally observed and accompanied by only a few PTC cells.

PTC may be accompanied by poorly differentiated carcinoma components, such as solid/trabecular/insular growth patterns. In addition, PTC may include an anaplastic carcinoma component with highly pleomorphic and isolated cells. If a PTC case consists predominantly of a poorly differentiated carcinoma component (>50%), it should be diagnosed as poorly differentiated carcinoma. On the other hand, a PTC case including an anaplastic carcinoma component should be classified as anaplastic carcinoma regardless of its predominancy.

Variants

1) Papillary carcinoma, follicular variant

Although the nuclear features are analogous to those of PTC, this variant shows an exclusively follicular growth pattern without a papillary structure. The encapsulated follicular variant of PTC has a fibrous capsule and mild cellular atypia. Therefore, the main differential diagnosis of encapsulated follicular variant of PTC is a follicular tumor with a fibrous capsule.

2) Papillary carcinoma, macrofollicular variant

This variant consists of large follicles containing colloids with nuclear features of PTC. The differential diagnosis of this variant includes follicular adenoma or adenomatous goiter.

3) Papillary carcinoma, oxyphilic cell (oncocytic) variant

This variant is characterized by the presence of acidophilic and granular cytoplasm with nuclear features of PTC (nuclear grooves, intranuclear cytoplasmic inclusions, *etc.*) and distinct nucleoli.

4) Papillary carcinoma, diffuse sclerosing variant

This variant is characterized by diffuse involvement of one or both thyroid lobes without a dominant nodule. It occurs mainly in young patients. Tumor cells have a propensity to invade numerous intrathyroidal dilated lymphatic spaces with dense stromal fibrosis and extensive lymphocytic infiltration. Squamous metaplasia of tumor cells and psammoma bodies is frequently observed.

5) Papillary carcinoma, tall cell variant

This variant tends to occur in elderly patients with extrathyroidal extension and vascular invasion. It consists of elongated tall cells that are more than three times taller than their width. Because tall cell areas are frequently present in conventional PTCs, tall cells account for more than 50% of all tumor cells for the diagnosis of this variant.

6) Papillary carcinoma, solid variant

This variant predominantly consists of solid and/or trabecular growth patterns with nuclear features of PTC (>50%). In cases of marked nuclear pleomorphism, high mitotic count, or tumor cell necrosis, it is regarded as a poorly differentiated carcinoma.

7) Papillary carcinoma, cribriform variant

This variant can occur in both familial and sporadic forms. The familial form is characterized by multifocal thyroid nodules in patients with familial polyposis coli. Young women are affected more frequently. Histologically, it consists of an intimate admixture of follicular and cribriform growth patterns without intraluminal colloid. Papillary and trabecular growth patterns are usually observed. The tumor cells are columnar to cuboidal in shape. Their nuclei are slightly large with grooves and frequently show a clear chromatin pattern (nuclear clearing). They occasionally appear spindle shaped. Squamous metaplasia with a morula is detected. Immunohistochemistry reveals aberrant expression of β-catenin in tumor cell nuclei.

8) Papillary carcinoma, hobnail variant

This variant consists of papillary structures with apically placed nuclei and bulging of the apical surface (hobnail features). It is defined by the presence of more than 30% of the tumor cells with hobnail features. Recurrence and metastasis are frequent, and the prognosis is poorer than that of conventional PTC.

9) Other variants

PTC, clear cell variant, Warthin tumor-like PTC, PTC with fibromatosis-like stroma, and PTC with squamous cell or mucoepidermoid carcinoma are described as other variants of PTC.

Appendix

***1 Microcarcinoma**

It is defined as a carcinoma measuring 1 cm or less in diameter. Most microcarcinoma cases are PTC, but other histological types also occur as microcarcinomas.

***2 Encapsulated papillary carcinoma**

This variant is surrounded by a fibrous capsule. Regional lymph nodes and distant metastases are rare.

Follicular carcinoma

Follicular carcinoma (FTC) is a malignant tumor with follicular growth patterns derived from the thyroid follicular epithelium. FTC lacks the nuclear features characteristic of papillary carcinoma. The diagnosis of malignancy requires a demonstration of invasion to the capsules, vessels, and/or extrathyroidal tissues. The cytological atypia of neoplastic cells cannot distinguish FTC from benign follicular neoplasms.

FTC shows a predominant follicular architecture with scant interstitial components. FTC is well differentiated, and the cytoarchitectural features of FTCs are sometimes indistinguishable from those of normal thyroid tissue.

Capsular invasion refers to the complete penetration of tumor cells through the capsule, and the tumor cells should be bulging out from the capsular margins, invading thyroid and/or extrathyroidal tissues. Capsular

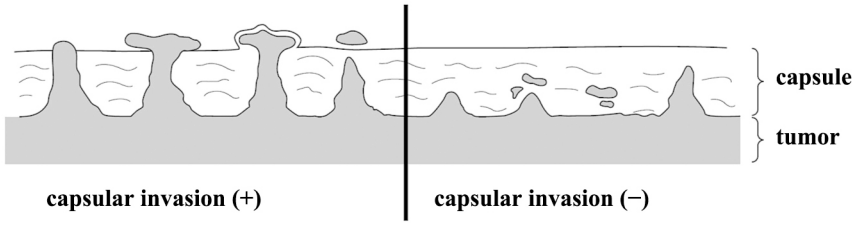

Fig. 3 Schematic diagram of the capsular invasion
Capsular invasion is defined as complete penetration of tumor cells through the entire thickness of the capsule. When the tumor cells stay within the capsule, they are evaluated as negative for invasion regardless of the irregular tumor margins.

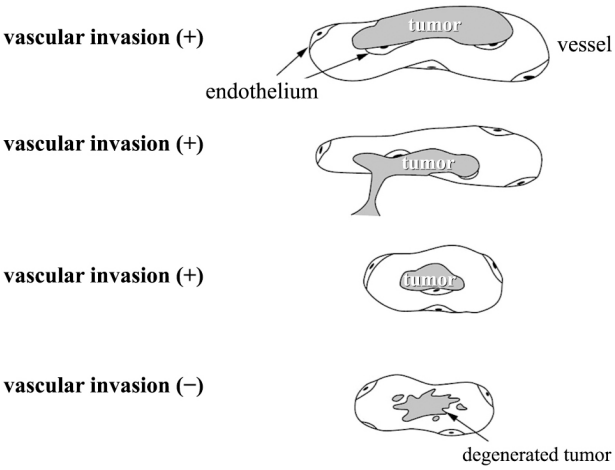

Fig. 4 Schematic diagram of the vascular invasion
Vascular invasion is defined as presence of tumor cells in the lumens of vessels located within or near the capsules. Endothelial cells can be found on the surface of the tumors in the vascular lumens. Degenerated inviable tumor cells floating in the vascular lumens are not defined as vascular invasion.

invasion is defined as shown in Fig. 3. Pseudoinvasion can be observed around the scar of the fine needle aspiration.

Vascular invasion should be carefully evaluated by observing the vessels within or near the capsule (Fig. 4). The vascular cavity is defined as a true cavity lined with endothelial cells. Vascular invasion requires intravascular tumor cells that are covered by the endothelium or thrombus. Degenerated inviable tumor cells floating in the vascular lumen or aggregation of tumor cells, capillaries, and lymphocytes within the capsules are not defined as vascular invasion.

The diagnosis of primary thyroid FTC can also be achieved by existence of the metastatic lesion, even though the intrathyroidal lesion does not meet the above-mentioned malignancy criteria, which was formerly referred to as metastasizing goiter or malignant adenoma.

Atypical adenomas often show more severe cytological atypia than conventional FTC. The differential diagnosis of FTC and atypical adenoma should be made based on capsular/vascular invasion and metastasis, but not on cytological atypia. Consequently, the diagnosis of FTC requires careful examination of the tumor margins containing both tumor capsules and adjacent normal thyroid tissues by making a sufficient number of tissue blocks.

FTC is subclassified into three groups based on the patterns of invasion

1) Follicular carcinoma, minimally invasive

FTC, minimally invasive, is macroscopically well-demarcated with a thick fibrous capsule characteristic of follicular neoplasms. Minimally-invasive FTC can be distinguished from follicular adenoma by the identification of microscopic capsular invasion.

2) Follicular carcinoma, encapsulated angioinvasive

FTC, encapsulated angioinvasive, is defined as an encapsulated follicular neoplasm with vascular invasion, regardless of capsular invasion. FTC with extensive vascular invasion (≥4 vessels) has a poorer prognosis than those with limited vascular invasion (<4 vessels). Encapsulated-angioinvasive FTC with extensive vascular invasion and with limited vascular invasion were classified as widely-invasive FTC and minimally-invasive FTC, respectively, in the previous GRDTC (7th edition).

3) Follicular carcinoma, widely invasive

FTC, widely invasive, shows extensive invasion of the thyroid and extrathyroidal tissues with ill-defined margins. Fibrous capsules are often indistinct in widely-invasive FTC.

Variants

1) Follicular carcinoma, oxyphilic cell (oncocytic) variant

FTC, an oxyphilic cell variant, consists mainly of >75% tumor cells with eosinophilic granular cytoplasm. Macroscopically, it is typically reddish brown and occasionally has hemorrhage, cyst formation, fibrosis, and infarction. Microscopically, the tumor has solid, trabecular, and papillary growth patterns without nuclear features characteristic of papillary carcinoma. In this classification, the diagnosis of FTC, an oxyphilic cell

variant, requires evidence of capsular/vascular invasion or metastasis, although some pathologists believe that all tumors with eosinophilic granular cytoplasm have malignant potential.

2) Follicular carcinoma, clear cell variant

FTC, a clear cell variant, mostly consists of tumor cells with clear cytoplasm. Cytoplasmic clearing of the tumor cells is due to the ballooning of the mitochondria and accumulation of lipids, glycogen, and/or thyroglobulin. The diagnosis of FTC requires the exclusion of metastatic clear cell renal cell carcinoma. Evidence of thyroglobulin production confirmed by immunostaining strongly supports the diagnosis of FTC, a clear cell variant.

Poorly differentiated carcinoma

Poorly differentiated carcinoma (PDTC) is defined as a malignant follicular cell-derived tumor showing intermediate morphological features and biological behavior between well-differentiated thyroid carcinoma (WDTC; PTC and FTC) and anaplastic carcinoma. It has a higher incidence of distant metastasis and poorer prognosis than WDTC.

Macroscopically, PDTC exhibits invasive growth and occasionally a fibrous capsule. Diagnosis requires histological confirmation of the presence of capsular invasion, vessel invasion, or distant metastasis, and poorly differentiated components with solid/trabecular/insular growth patterns occupying more than 50% of the tumor. Diagnostic criteria also exclude tumors with nuclear features that are characteristic of papillary carcinoma. Mitotic figures and coagulation necrosis are frequently observed. Both cellular atypia and mitosis are more significant than WDTC, but less significant than that of anaplastic carcinoma.

The PDTC may be accompanied by a component of the WDTC. If a case predominantly shows a component of WDTC, it is diagnosed as WDC with a poorly differentiated component instead of PDTC. A PDTC case with a minor component of anaplastic carcinoma is diagnosed as anaplastic carcinoma.

Anaplastic carcinoma

Anaplastic carcinoma (ATC) is a malignant epithelial tumor with high-grade structural and cellular atypia.

ATC rapidly enlarges and is frequently accompanied by necrosis and hemorrhage. Cell atypia is highly significant compared to WDTC and PDTC. ATC shows highly pleomorphic and mixed histology, consisting of spindle-shaped cells resembling high-grade pleomorphic sarcoma, squamoid cells, and giant cells.

ATC may include a component of WDTC and PDTC, suggesting anaplastic transformation of preexisting lesions. A rare subset of ATC may include heterologous components such as bone and cartilage. ATC is usually immunopositive for cytokeratins, which is useful for differentiating from non-epithelial tumors resembling ATC. Carcinosarcoma should be classified as ATC in the thyroid.

(also see the “Saracomas” section).

Medullary carcinoma

Medullary carcinoma (MTC) is a malignant epithelial tumor derived from C-cells that characteristically secrete calcitonin. Stroma has amyloid deposits that express positivity with Congo Red or direct fast scarlet (DFS) staining and are frequently accompanied by coarse calcifications.

MTC exhibits a wide variety of morphologies with both histological and cytological features. Histological features typically show solid growth. MTC cases consisting of follicular, papillary, and trabecular structures resemble follicular cell-derived tumors. MTC shows various cytological features, such as polygonal, round, and spindle-shaped, and may comprise small and giant cells.

C-cell differentiation is confirmed using immunohistochemistry for calcitonin. It is also immunopositive for CEA, synaptophysin, and chromogranin A.

Genetic background is well known in a subset of MTC, which possesses a functional gain-type point mutation in the *RET* protooncogene in germ cells. Most patients with an autosomal dominant family history are cases of multiple endocrine neoplasia (MEN) type 2A and 2B complicating neoplasia in the adrenal medulla and parathyroid, or cases of familial MTC without any complicated neoplasia. In hereditary cases, C-cell hyperplasia is frequently observed in non-neoplastic thyroid tissues.

Mixed medullary and follicular cell carcinoma

This tumor is defined as a malignant epithelial tumor that shows differentiation of both C -and follicular cells in the same lesion. The histological type of follicular cell-derived neoplasia includes both PTC and FTC. Components of FTC in this tumor should be carefully differentiated from incorporated normal follicles.

Lymphoma

Primary lymphoma accounts for 1%–5% of thyroid malignancies, frequently affects elderly women, and usually arises in a background of chronic thyroiditis. Grossly, it is a gray-whitish rubbery mass on the cut surface that involves single or both lobules.

Almost all are B-cell type lymphomas with immunoreactivity for CD20 expression, such as extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) and diffuse large B-cell lymphoma (DLBCL). Furthermore, several cases can transform to DLBCL from MALT lymphoma, which may have a phenotype distinct from that of *de novo* DLBCL and must be subclassified from a prognostic point of

view. Other rare types include follicular lymphoma, mantle cell lymphoma, Burkitt-like lymphoma, and T-cell lymphoma. Most cases formerly designated as plasmacytoma are currently considered MALT lymphomas that show extreme differentiation to plasma cells.

MALT lymphoma comprises a variety of B-cell-lineage lymphocytes, including mainly centrocyte-like cells and monocytoid B cells, as well as small lymphocytes, plasmacytes, and rarely immunoblasts, and exhibits a diffuse or unclear nodular growth pattern. Neoplastic lymphocytes mainly proliferate in the outer zone of reactive lymphoid follicles and infiltrate into the internal part, which resembles follicular lymphoma and is called follicular colonization. Lymphoma cells characteristically infiltrate into the thyroid follicles, forming lymphoepithelial lesions (LELs) or MALT balls, which are packed cells in their lumen. MALT lymphoma is a low-grade malignancy. Genetically, it has a rearrangement of the immunoglobulin heavy-chain variable region (IgH) gene, which is useful in differentiating from reactive lymphoid lesions such as Hashimoto thyroiditis.

DLBCL is a biologically high-grade malignancy that consists of diffuse proliferation of large lymphoma cells, such as centroblasts and immunoblasts, and frequently shows destructive growth with infiltration to surrounding tissue and/or strap muscles. The immunophenotype of each subtype follows the WHO classification.

Other tumors

Hyalinizing trabecular tumor

Hyalinizing trabecular tumor (HTT) is a follicular cell-derived tumor characterized by a trabecular growth pattern and hyalinized stroma containing abundant basement membrane material. HTT is a solid and well-demarcated tumor with or without a thin fibrous capsule. Tumor cells are generally polygonal or elongated spindles, and occasionally have a rich clear cytoplasm. Tumor cells frequently show nuclear grooves and intranuclear cytoplasmic inclusions and may show yellow bodies, which are pale yellowish cytoplasmic inclusions with a peripheral halo. Stromal hyalinization, which is positive for periodic acid-Schiff (PAS) reaction, is due to abnormal thickening of the basement membrane, demonstrating intercellular irregular deposits or dendrite-like structures.

Immunohistochemistry showed that cytokeratin 19 (CK19) is negative in HTT and consistently positive in papillary carcinoma. The membranous and cytoplasmic positivity of Ki-67 (MIB-1) is a unique immunoreactivity for HTT. Hyalinized stroma is immunopositive for laminin and type IV collagen. Medullary carcinoma is a differential diagnosis because amorphous hyalinization mimics amyloid material.

Columnar cell carcinoma

Columnar cell carcinoma is composed of pseudostratified high columnar cells arranged in papillary, trabecular, follicular, acinar, and solid growth patterns. Colloid materials are usually lacking in follicles or acinar lumen. The nuclei are round to oval-shaped, with dark chromatin. Tumor cells may show sub- or supra-nuclear vacuoles that mimic the endometrium during the secretory phase. Columnar cell carcinoma shows aggressive behavior than that of conventional papillary carcinoma.

Mucinous carcinoma

Mucinous carcinoma is an epithelial malignancy which produces extensive extracellular mucin and shows differentiation to thyroid follicular cells. Other thyroid tumors with intracytoplasmic mucin, including follicular adenoma, papillary carcinoma, follicular carcinoma, medullary carcinoma, and mucoepidermoid carcinoma, are excluded from the definition of mucinous carcinoma. Immunohistochemically the tumor cells are positive for cytokeratin.

Mucoepidermoid carcinoma

Mucoepidermoid carcinoma of the thyroid shows histological features similar to those of mucoepidermoid carcinoma of the salivary gland. The tumor is composed of a mixture of squamous cells, mucous cells, and intermediate cells. Cyst formation, containing mucin or keratin material, is occasionally observed in tumors. Papillary carcinoma may coexist with mucoepidermoid carcinoma.

Sclerosing mucoepidermoid carcinoma with eosinophilia showed prominent fibrosis and infiltration of eosinophils, lymphocytes, and plasmacytes in the tumor. Tumor cells with distinct nucleoli arranged in a trabecular pattern show invasive growth. In almost all patients, histological findings of Hashimoto thyroiditis (chronic lymphocytic thyroiditis) are observed in non-neoplastic thyroid tissues.

Intrathyroid thymic carcinoma

Intrathyroid thymic carcinoma (ITTC) is a malignant thyroid tumor that histologically resembles a thymic epithelial tumor. Synonyms of ITTC include carcinoma showing thymus-like differentiation (CASTLE) and intrathyroidal epithelial thymoma (ITET). ITTC mainly occurs in the lower lobes of the thyroid gland. Tumor cells are arranged in variable-sized islands with dense fibrous stroma. Lymphocyte and plasmacyte infiltration is observed in the entire tumor. Tumor cells are polygonal or spindle-shaped, with large nuclei, prominent nucleoli, and indistinct cell borders. Immunohistochemistry revealed that the tumor cells are positive for CD5.

Spindle cell tumor with thymus-like differentiation

Spindle cell tumors with thymus-like differentiation (SETTLE) commonly affect children and young adults.

The tumor is grossly lobulated. Microscopically, SETTLE shows a biphasic pattern, including a fascicular-arranged spindle cell component and a glandular component composed of cuboidal/columnar cells. Immunohistochemically, both histological components are positive for cytokeratin and negative for thyroglobulin. Squamous differentiation is a rare histological finding of SETTLE.

Squamous cell carcinoma

Primary thyroid squamous cell carcinoma is a thyroid epithelial malignancy composed of tumor cells with distinct squamous differentiation. The prognosis of SCC is poor as same as anaplastic carcinomas. The tumor commonly shows invasive growth and extension to the extrathyroidal tissues. Differential diagnoses include squamous metaplasia of papillary carcinoma, metastasis or direct invasion of non-thyroidal squamous cell carcinoma, and carcinoma with thymic differentiation. When squamous cell carcinoma and papillary carcinoma coexist in the tumor, both components should be recorded in pathology reports.

Sarcomas

Primary thyroid sarcomas include leiomyosarcoma, angiosarcoma, fibrosarcoma, and osteosarcoma. The most frequent differential diagnosis is spindle cell type anaplastic carcinoma, mimicking true sarcoma. In the thyroid, the so-called carcinosarcoma is classified as anaplastic carcinoma.

Others

Rare primary thyroid tumors include teratomas, ectopic thymomas, smooth muscle cell tumors, peripheral nerve sheath tumors, paragangliomas, solitary fibrous tumors, follicular dendritic cell tumors, and Langerhans cell histiocytosis.

Secondary (metastatic) tumors

Secondary tumors are excluded from GRDTC. However, these are critical for the differential diagnosis of primary thyroid tumors. Secondary tumors include direct invasion of non-thyroidal neck malignancies and metastatic carcinomas from other organs, such as the kidney, lung, and breast. Immunohistochemistry for thyroglobulin is useful for differentiating primary thyroid tumors from secondary tumors.

Unclassified tumors

These are rare thyroid tumors which are unclassifiable in the above categories.

Tumor-like lesions

Adenomatous goiter

Adenomatous goiter is a nodular enlargement of the thyroid due to non-neoplastic multiple nodules. Nodules are characterized by morphological and gross heterogeneity. The number, distribution, size, and histology of the nodules vary among patients. Secondary degeneration, including hemorrhage, necrosis, cystic formation, fibrosis, hyalinization, and calcification, are variably observed in each nodule.

The fibrous capsule is either incomplete or absent. The size of follicles and morphology of epithelial cells are significantly variable in each nodule. Large follicles with rich colloid and small follicles with less colloid are variably mixed in the nodules. Epithelial cells are columnar, cuboidal, or flat. Nodules are predominantly composed of oxyphilic cells. Sanderson polster, a cluster of small follicles projecting into large follicles, is a histological characteristic of adenomatous goiter. Adenomatous goiter may show papillary structure and nuclear overlapping but lacks typical nuclear features of papillary carcinoma. The stromal component is commonly rich and may show fibrosis, granulation tissue, inflammatory cells, hemosiderin deposits, and calcification. Cyst with foamy macrophages and lymph-follicle formation are common findings in adenomatous goiter.

Nodules show no compression of the surrounding thyroid tissues, which is distinct from follicular adenomas. For instance, the histological findings of nodules, follicular cells, and lymphoid follicles are similar to those of non-nodular areas. A single nodule is called an adenomatous nodule. Adenomatous nodules generally show no marked enlargement of the thyroid gland. Hyperthyroidism may be complicated by adenomatous goiter or adenomatous nodules. Congenital defects in the synthesis of thyroid hormones may cause multi-nodular enlargement of the thyroid (dyshormonogenetic goiter).

Amyloid goiter

Amyloid goiter is a hard enlargement of the thyroid due to amyloid deposits. Primary and secondary amyloidosis, including Hashimoto's thyroiditis, may cause amyloid goiter. The differential diagnosis is amyloid deposition in medullary carcinoma.

Cyst

True thyroidal cysts are relatively rare. Hypoglossal duct cysts, originating from the remnant of the thyroglossal tract, are located in the middle of the neck. Hypoglossal duct cysts are lined by columnar, ciliated columnar, and/or squamous cells.

Lymphoepithelial cysts are lined by squamous cells with a subepithelial lymphocytic infiltrate. Hashimoto thyroiditis is commonly found in the non-cystic area of the thyroid.

Secondary cysts are pseudocysts that develop due to degeneration, necrosis, and hemorrhage in various thyroid nodules. Adenomatous goiters and follicular adenomas may present as secondary cysts.

Commentary on Major Differences from WHO Classification, 4th Edition (2017)

1) Borderline lesions

In the WHO classification, a new category of borderline lesions is proposed for "encapsulated follicular-patterned follicular cell tumor" with uncertain malignant potential or extremely indolent behavior (Fig. 5). In this propose, terms of "malignant tumors" or "carcinomas" are not used when invasive growth (capsular and vascular invasion) is absent or questionable. The borderline lesions consist of 1) Follicular tumor of uncertain malignant potential (FT-UMP), 2) Well-differentiated tumors of uncertain malignant potential (WDT-UMP) and 3) Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). FT-UMP is defined as a borderline lesion between follicular carcinoma and follicular adenoma. Some follicular variant papillary carcinomas, defined in the current GRDTC, may be reclassified into NIFTP and WDT-UMP.

1) FT-UMP is an encapsulated follicular-patterned tumor with questionable invasion and without nuclear features of papillary carcinoma. FT-UMP may be classified as follicular adenoma in GRDTC.

2) WDT-UMP is an encapsulated follicular-patterned tumor with questionable invasion. The nuclear features of papillary carcinoma are present or questionable. WDT-UMP may be classified as follicular adenoma or encapsulated follicular variant papillary carcinoma in GRDTC.

3) NIFTP is an encapsulated follicular-patterned tumor without invasion. The nuclear features of papillary carcinoma are present or questionable. NIFTP may be classified as follicular adenoma or encapsulated follicular variant papillary carcinoma in GRDTC.

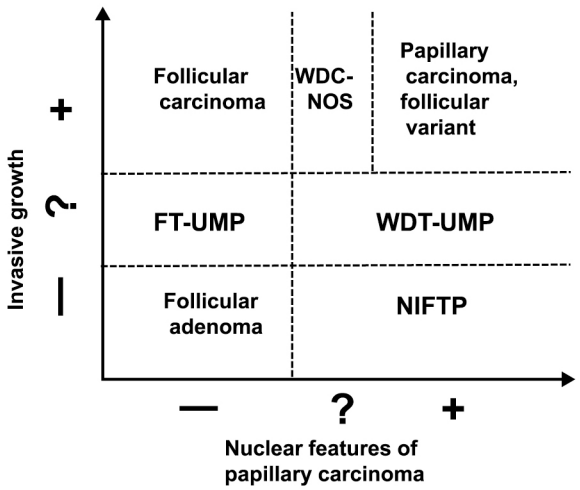

Fig. 5 Diagnosis of encapsulated follicular-patterned follicular cell tumors (WHO classification, 4th edition)

2) Poorly differentiated carcinoma

In the current GRDTC, conventional Japanese diagnostic criteria are applied to poorly differentiated carcinomas. In the 4th edition of the WHO classification, the Turin proposal (2007) was adopted for the histological diagnosis of poorly differentiated carcinoma in addition to conventional criteria. The Turin proposal includes the following: (1) the presence of a solid/trabecular/insular pattern of growth, (2) absence of the conventional nuclear features of papillary carcinoma, and (3) presence of at least one of the following features: convoluted nuclei, mitotic activity ≥3 × 10 HPF, and tumor necrosis.

Checklists for Pathological Diagnosis Report (Table 2)

Cytology

Fine needle aspiration cytology is the most used morphological method for diagnosing thyroid lesions because it is simple, less painful, repeatable, and qualitatively as accurate as needle biopsy. In addition, cytology with an imprint smear is useful in intraoperative rapid consultation because frozen sections often show intranuclear cytoplasmic inclusion-like structures as artifacts causing a misdiagnosis.

Informed consent

Prior to an aspiration, it is necessary to explain the procedure to the patient and obtain his/her consent to minimize his/her fear and obtain full cooperation during the examination.

a. Explain detected lesions of the patient.
b. Explain several methods of diagnosis and their advantages, disadvantages, and complications.
c. Explain the technique of aspiration cytology to get the patient's cooperation.
d. Explain that aspirated specimens are inspected by cytotechnologists and by cytopathologists.
e. Assure the patient that the obtained specimens are used only for diagnostic purposes. Alternatively, we obtain his/her consent to use the specimen for other purposes.

Aspiration technique

The details of the equipment required for sampling and processing are available in the literature. Following is a brief list of precautions and procedures for the puncture.

a. To safely obtain cells from the appropriate site for diagnosis, ensure that the needle tip reaches the target site under ultrasound guidance.
b. To obtain cells in a clipping motion under negative

Table 2 Checklists for pathological diagnosis report

1. Macroscopic findings Tumor site: □ right lobe □ left lobe □ isthmus and pyramidal lobe □ upper □ middle □ lower Tumor size (maximum diameter): □ _____cm Cut surface: □ Localized, solid □ Localized, cystic □ Diffuse Tumor focality: □ Multifocal □ Unifocal □ Cannot be determined
2. Histological findings Primary tumor (pT) □ pTx □ pT0 □ pT1a □ pT1b □ pT2 □ pT3a □ pT3b □ pT4b Regional lymph node (pN) □ pNX □ pN0 □ pN1a □ pN1b Vascular invasion (for follicular carcinoma) □ Not identified □ Present □ <4 vessels □ ≥4 vessels □ Cannot be determined Extrathyroidal extension □ Not identified □ Present □ Perithyroidal adipose tissue □ Strap muscles □ subcutaneous soft tissue □ Larynx □ Trachea □ Esophagus □ Recurrent laryngeal nerve □ Prevertebral fascia □ Carotid artery □ Mediastinal vessels. □ Cannot be determined
3. Pathological diagnosis Histological type □_____

pressure, move the needle tip quickly back and forth within the mass or rotate within it. It is important to understand that cells are not simply placed in the needle under negative pressure.

c. The amount of specimen within the injection needle should be sufficient for diagnosis. If puncture-aspiration materials are aspirated into the syringe, the operation is stopped immediately. An exception is made when liquid materials are aspirated.

d. Remove the needle after the release of the negative pressure. If the needle is removed under negative pressure, the specimens move into the syringe and become dry, causing cellular degeneration. It is impossible to remove the collected cells from the syringe.

e. Remove the needle once, fill the syringe with air, reattach the needle, and then blow out the specimens within the needle onto glass slides.

f. In cystic lesions with a solid area, puncture the solid area.

g. No-aspiration method: This is a sampling method in which the needle is held directly with the finger. In cases of cell-rich lesions, a sufficient number of cells can be obtained without aspiration. It is recommended for vascular-rich lesions (follicular adenoma and follicular carcinoma) and lesions prone to cellular degeneration (lymphoma). However, hypocellular lesions or fibrous lesions tend to cause poor sampling.

Specimen preparation

Smearing methods

Select the most appropriate smearing method depending on the nature and volume of the obtained specimen.

Semi-solid specimens, viscous liquid specimens, and small amount of liquid specimens

The specimen is placed between two glass slides then pressed and release by separating slides vertically (press and release method). This method is suitable for observation of both cytological characteristics and tissue architecture because it minimizes cell destruction and maintains tissue architecture.

Large amount of specimens

Place the specimen between the two glass slides and stretch the specimen by shifting the glasses horizontally (press and rubbing method). Alternatively, repeat the press and release method.

Specimen containing tissue fragments

The specimen is placed between two glass slides, and pressure is applied with the fingers to compress the specimen (compression method).

Very small amount of specimens

To prevent drying artifacts, the specimen is blown onto a glass slide and fixed immediately without any

treatment (blowing method). Subsequently, the remaining samples is prepared for liquid-based cytology (LBC) using a needle washout fluid.

Cyst fluid

Smear the sediment after centrifugation. Alternatively, perform LBC preparation.

Specimens contaminated with blood

Immediately after smearing, the slide glasses are turned diagonally or vertically, and the blood component is allowed to flow downward. If the blood does not flow, gently tap the glasses. Most of the cellular components remain as granular materials in the first smeared area. After removing the blood, the press and release method is performed.

Fixation method

Wet fixation is typically performed. There are several methods for wet fixation, including the dipping method (95% ethanol), spraying method, and dropping method. Fixation should be performed after smearing, but only for liquid specimens. It is recommended to wait 5–10 seconds after smearing to prevent cell detachment. Dry fixation should be used for Giemsa staining.

Liquid-based cytology (LBC)

In the LBC method, specimens are transferred to a special preservation solution and smeared onto glass slides. There are two methods: filter transfer and centrifugal sedimentation. The washout fluid of the needle after smearing or all aspirated materials are used for LBC preparation. LBC-specific fixative solutions with hemolytic and proteolytic effects are recommended. The advantage of LBC is that the aspirated cells can be collected efficiently, which contributes to a reduction in the unsatisfactory rate. The LBC method is useful in cases where the aspirated cells are considered to be few, peripheral blood is contaminated, and fluid sample is aspirated. The cellular morphology of the LBC specimens is similar to that of conventional smears. Therefore, knowledge and experience are required to observe the LBC specimens.

Reporting system of GRDTC

The GRDTC reporting system specifies categories and descriptions for reporting thyroid aspiration cytology. Accordingly, there are seven categories: unsatisfactory, cystic fluid, benign, undetermined significance, follicular neoplasm, suspicion for malignancy, and malignancy. Describe the presumed histological type as much as possible based on the histological classification of GRDTC (Table 1).

Categories for thyroid aspiration cytology

Unsatisfactory
Cyst Fluid
Benign
Undetermined Significance
Follicular Neoplasm
Suspicious for malignancy
Malignant

Diagnostic criteria for category (Table 3)

Unsatisfactory

This refers to specimens that cannot be cytologically diagnosed because they are poorly prepared or do not contain enough cells or components to infer a lesion (Table 4). For specimens that are considered unsatisfactory, the reason should be clearly stated (*e.g.*, small number of follicular cells, desiccation or degeneration of cells, peripheral blood contamination, poor smearing, *etc.*). Histiocytes suggestive of cysts, bloody components, muscle, and hair cells are not included in the criteria. A clinical recommendation for this category is repeated aspiration.

Cyst fluid

Specimens that are cyst fluid and do not contain colloid or follicular cells fall into this category. Most cysts in this category are benign. Since cystic papillary carcinoma may be included in rare cases, a regular follow-up is recommended. If there is a solid area within the cyst on imaging, re-aspiration from the solid area is also recommended.

Benign

This refers to specimens that do not show malignant cells. This category includes normal thyroid gland, adenomatous goiter, thyroiditis (acute, subacute, chronic, and Riedel), and Graves' disease.

Undetermined significance

This refers to specimens that are difficult to differentiate cytologically as benign or malignant. It includes specimens that do not fall into any of the other categories and specimens that are difficult to diagnose. Specimens presumed to be follicular neoplasms and their oxyphilic variants are excluded. This category includes the possibility of papillary carcinoma (a small number of cells suggestive of papillary carcinoma, difficulty differentiating adenomatous goiter from papillary carcinoma, difficulty differentiating follicular tumor from papillary carcinoma, and difficulty differentiating Hashimoto thyroiditis from papillary carcinoma), a small number of atypical cells that are difficult to identify, difficulty differentiating adenomatous goiter from follicular neoplasm, and difficulty differentiating Hashimoto thyroiditis from lymphoma. Re-aspiration is desirable for this category.

Follicular neoplasm

Specimens with presumed or suspected follicular adenomas or carcinomas are included in this category. Specimens presumptive of oxyphilic cell variants of follicular neoplasm and follicular adenoma with bizarre

Table 3 Diagnostic categories for thyroid aspiration cytology and explanation

Categories	Statement	Explanation
Unsatisfactory	Cannot be diagnosed	Poorly preserved specimen No cells or components to infer with the lesion (Table 4)
Cyst fluid	Cyst fluid without colloid or follicular cells	Almost all benign cysts, rarely cystic papillary carcinoma
Benign	No malignant cells	Normal thyroid gland, adenomatous goiter, thyroiditis (acute, subacute, chronic, and Riedel), and Graves' disease
Undetermined Significance	Difficulty in differentiating between benign and malignant, Not included in any of the other categories, Difficulty making a diagnosis	Possibility of papillary carcinoma (a small number of cells suggestive of papillary carcinoma, difficulty differentiating adenomatous goiter from papillary carcinoma, difficulty differentiating follicular tumor from papillary carcinoma, and difficulty differentiating Hashimoto thyroiditis from papillary carcinoma); a small number of atypical cells that are difficult to identify; difficulty differentiating adenomatous goiter from follicular neoplasm; and difficulty differentiating Hashimoto thyroiditis from lymphoma
Follicular Neoplasm	Presumed or suspected follicular adenoma or follicular carcinoma	Mostly follicular adenoma and follicular carcinoma, oxyphilic cell variants of follicular neoplasm, follicular adenoma with bizarre nuclei, adenomatous goiter, papillary carcinoma, and parathyroid adenoma may be included
Suspicious for malignancy	Only a few cells that appear to be malignant, insufficient findings to determine malignancy	A variety of malignant tumors and hyalinizing trabecular tumor are included, mostly papillary carcinoma, papillary carcinoma is suspected but follicular tumor cannot be ruled out, follicular adenoma with bizarre nuclei, adenomatous goiter, and Hashimoto thyroiditis may be included
Malignant	specimens with malignant tumors	Papillary carcinoma, poorly differentiated carcinoma, undifferentiated carcinoma, medullary carcinoma, lymphoma, metastatic carcinoma, etc.

Table 4 Criteria for satisfactory and unsatisfactory specimens

Satisfactory: Any of the following four scenarios shall be considered satisfactory.
1) A minimum of six groups of well-visualized follicular cells, with ≥10 cells per group
2) Abundant colloid
3) Cells with significant cytological atypia
4) Inflammatory cells, including lymphocytes, plasma cells, or histiocytes
Unsatisfactory: Any of the following two scenarios should be considered unsatisfactory.
1) Poorly preserved specimens, including degeneration due to desiccation, poor fixation, obscuring blood, clotting artifacts, and smearing failures
2) None of the above satisfactory four scenarios.

nuclei are also included. The majority of cases in this category are follicular adenomas and follicular carcinomas, but adenomatous goiter, papillary carcinoma, and parathyroid adenoma may also be present. It is unlikely that the results of re-aspiration are classified into any other category.

Suspicious for malignancy

This refers to specimens that could not be confirmed as malignant because there are only a few cells that appear to be malignant or have insufficient findings to determine malignancy. This category includes a variety of malignancies, most of which are papillary carcinomas. A diagnosis of "suspected follicular carcinoma" does not exist in this category. Specimens in which papillary carcinoma is suspected but follicular tumors that cannot be ruled out are also included. HTTs, follicular adenoma with bizarre nuclei, adenomatous goiter, and Hashimoto thyroiditis may be included in this category.

Malignant

This refers to specimens with malignant tumors. This category includes papillary carcinoma, poorly differentiated carcinoma, anaplastic carcinoma, medullary carcinoma, lymphoma, and metastatic carcinoma.

Supplementary

1) The frequency of aspirated nodules categorized as "Unsatisfactory" is recommended to be ≤10%; if it exceeds 10%, the aspiration and smearing methods should be checked.
2) The recommended frequency of nodules with "Undetermined significance" is ≤10% of adequate

samples.

3) The recommended frequency of nodules with "Follicular neoplasm" is ≤10% of adequate samples.
4) It is recommended that more than 80% of nodules with "suspicious for malignancy" should be histologically confirmed to be malignant.
5) Clear deviation from 10% for tumors of undetermined significance or follicular neoplasm, and 80% for suspected malignancy, requires cytodiagnostic studies. Cytodiagnostic considerations are warranted when the frequency of "undetermined significance" or "follicular neoplasm" clearly deviates from 10%, and when the frequency of malignancy in "suspicious for malignancy" clearly deviates from 80%.
6) The cytological report should be made in accordance with the clinical imaging findings.

Comparison of the GRDTC system and the Bethesda System

1) Terminology

The terms used in the GRDTC system are reduced compared to those in the Bethesda system. In the Bethesda system, "atypia of undetermined significance; AUS or follicular lesion of undetermined significance; FLUS," "follicular neoplasm; FN or suspicious for follicular neoplasm; SFN" are referred to as "undetermined significance" and "follicular neoplasm," respectively, in the GRDTC system. They are simple and widely accepted by Japanese cytopathologists and cytotechnologists.

2) Cyst fluid lesions

In the Bethesda system, cyst fluid with only foam cells is classified as "Nondiagnostic/Unsatisfactory; ND/UNS," because the possibility of cystic papillary carcinoma cannot be ruled out. In this rule, the risk of malignancy in such cases is lower than that of "unsatisfactory specimen" and is almost the same as that of "benign specimen," so it is judged adequate and reported as "cyst fluid" in a separate category.

3) Classification of follicular lesions with nuclear findings of papillary carcinoma

Specimens showing a follicular arrangement with mild nuclear findings suspicious of papillary carcinoma, such as enlarged nuclei, irregular-shaped nuclei, and clear chromatin pattern, are classified as "follicular neoplasm" in the Bethesda system but are classified as "undetermined significance" or "suspicious for malignancy" in the GRDTC system.

4) Risk of malignancy and recommended clinical management

The Bethesda system describes the risk of malignancy and recommends clinical management. However, because the frequency of each tumor, indications for resection, and social conditions differ between Japan and the West, it is difficult to introduce Western standards directly to Japan. Therefore, we decided not to mention the risk of malignancy and recommended clinical management in the GRDTC system.

Cytological findings

In fine needle aspiration cytology, the tissue itself, including not only the tumor cells but also the stromal cells, can be collected. Therefore, when observing specimens, it is important to pay attention to the structure of cell clusters and stromal components, in addition to individual cell findings, and to recognize the three-dimensional structure of clusters.

Adenomatous goiter

The cell findings of adenomatous goiter are also diverse, reflecting the diversity of tissue findings. Follicular cells are generally small, round to cuboidal, and appear sheet-like, follicular, and sometimes papillary. The size of the follicles varies from small to large. Cytoplasmic staining also varies, and eosinophilic cells may be the main component. In May-Giemsa staining, lipofuscin granules (paravacuolar granules) with vacuoles are often found in the cytoplasm of follicular cells. Colloid, foamy cells, hemosiderin-laden macrophages, multinuclear cells, fibroblasts, and degenerated RBCs are observed in the background, but their frequency and proportion vary depending on the case.

In the case of cystic lesions, a large amount of liquid sample is collected, and most of the cell components are foamy cells. If there are few or no follicular cells, they are placed in the "cystic fluid" category. In this case, care should be taken because cystic papillary carcinomas may show similar findings.

Subacute thyroiditis

The appearance of multinucleated giant cells and epithelioid cells is characteristic of subacute thyroiditis, accompanied by lymphocytes, neutrophils, and karyoclastic cells. Follicular cells are swollen or degenerated and difficult to recognize because of the unclear cytoplasm.

Hashimoto thyroiditis

In Hashimoto thyroiditis, eosinophilic follicular cells are found in the background of many lymphocytes. Eosinophilic cells appear in the form of sheets and follicles. If the size of the nucleus is different or the nucleolus is swollen, care must be taken not to mistake it for a malignant tumor. Small lymphocytes predominate, and medium-to-large lymphocytes coexist.

Follicular neoplasms

Diagnosis of follicular carcinoma is made when capsular invasion, vascular invasion, or metastasis is histologically confirmed. Therefore, because cytological findings are not the main criterion, it is difficult to distinguish follicular adenoma from follicular carcinoma based

on cytological findings alone, and it is currently appropriate to diagnose FN.

FNA specimens from FN are often bloody with no colloids, lymphocytes, or foamy cells in the background. The number of tumor cells collected is usually high. Tumor cells are uniform in size and morphology and appear in the form of small follicles or cords. A small follicular aggregate is a cell clump of 15 or less, and the cells are arranged in a circumferential shape. Concentrated round colloids may be observed in follicles. Cytoplasmic stainability is lighter than that of papillary carcinoma, and the cell boundaries are unclear. In some cases, capillaries are found between follicles.

In cases of the oxyphilic cell variant, the cytoplasm of tumor cells favorably stains light green, is granular, and has clear cell boundaries. The nucleolus is large and conspicuous. It should be noted that in follicular adenomas with bizarre nuclei, large atypical cells are scattered and easily confused with malignant tumors.

Hyalinizing trabecular tumor

Hyalinizing trabecular tumors are characterized by the appearance of tumor cells that surround the hyalinized material with unclear boundaries. Poor binding, no papillary, follicular, or sheet-like arrangements exist. Tumor cells are round to spindle-shaped, cell boundaries are extremely obscure, and the cytoplasm is lightly stained. A light-stained yellow body with a halo around it is observed in the cytoplasm. Intranuclear cytoplasmic inclusions and nuclear grooves are observed, however, ground glass-like nuclei and nuclear overlapping are not observed.

Papillary carcinoma

In papillary carcinoma (PTC), the amount of collected cells is abundant, and tumor cells appear as papillary, follicular, sheet-like, isolated, and scattered. The papillary cluster is a fibrovascular stromal component surrounded by tumor cells. When only tumor cells are smeared without stromal components, they appear as monolayer sheets, with bends at the edges of the sheets and linear palisade arrangements in the nucleus.

The nuclei are densely crowded and present in a round or slightly oval shape. The nuclear findings are characterized by fine granular (ground glass-like) chromatin, intranuclear cytoplasmic inclusion bodies, nuclear grooves, and lobulated nuclei. Although intranuclear cytoplasmic inclusions and nuclear grooves are observed more frequently than tissue specimens, it is dangerous to diagnose PTC based on their presence alone. The cytoplasm is light green favorable, and the cell boundaries are often clear. In cases of cyst-forming tumors, many septate intracytoplasmic vacuoles may be found in the cytoplasm of tumor cells.

The psammoma body in the background, the ropy colloid in the shape of a stretched chewing gum, and the bizarrely shaped polynuclear giant cells are also findings suggestive of PTC. Lymphocytes sometimes stand out from the background.

Poorly differentiated carcinoma

The number of collected cells is high in poorly differentiated carcinomas. It is characterized by a cell cluster and appears as a large solid (island-like), cord-like, or scattered. Vascular endothelial cells adhering to the margins of island-shaped or cord-shaped clusters are observed. Tumor cells are round, show a relatively uniform morphology, and are less atypical than anaplastic carcinomas. The cytoplasm is pale, and cell boundaries are unclear. Mitosis is often observed.

Anaplastic carcinoma

Anaplastic carcinoma (ATC) is not mistaken for a benign tumor because large tumor cells showing a high degree of atypia are collected in this case. When there are abundant connective tissue components or inflammatory cells, it is difficult to collect tumor cells, making diagnosis difficult. Tumor cells are poorly bound, exhibit various morphologies such as polygonal, spindle-shaped, and rounded, and have many findings suggestive of malignancy such as anisocytosis, hyperchromatic nuclei, large nucleoli, and mitotic figures. Inflammatory cells, mainly neutrophils, are often found in the background, and necrotic substances are common. ATC requires distinction from metastatic tumors and sarcomas. The component of papillary or follicular carcinoma may present as preceding lesions.

Medullary carcinoma

Tumor cells of medullary carcinoma are poorly bound and do not show a clear arrangement pattern. The cell shape is round, sometimes spindle-shaped, and plasma cell-like when round cells appear scattered. The nucleus is eccentric and protruded from the cytoplasm. Nuclear chromatin is in the form of coarse granules, and nuclear atypia and anisocytosis are often stronger than papillary carcinoma, double nuclear cells, hyperchromatic giant nuclei, and intranuclear cytoplasmic inclusions may be found. The cytoplasm is lightly stained and shows fine granules, and the cell boundaries are unclear. May-Giemsa staining reveals metachromatic granules in some cells. The presence of amyloid substances in the background is one of the characteristics of this tumor, but it does not appear in all cases. Congo red staining is useful for distinguishing amyloids from connective tissues and concentrated colloids. The tumor cells are positive for calcitonin and CEA by immunostaining.

Malignant lymphoma

In diffuse large B-cell lymphoma, tumor cells are round cells of the size corresponding to large lymphocytes and appear scattered. The cytoplasm is relatively

abundant and stained with light. Nuclear membrane depressions and deformed nuclei are often observed. Lymphoglandular bodies and non-neoplastic small lymphocytes are observed in the background. In MALT lymphoma, tumor cells are small to medium-sized lymphocytes, with mild atypia, and are often difficult to distinguish from Hashimoto thyroiditis. In Hashimoto thyroiditis, the types of cells appearing are diverse, whereas in MALT lymphoma, they are monotonous and the chromatin pattern is uniform regardless of the size of the nucleus. When a definitive cytological diagnosis is difficult, it is necessary to apply a surface marker using flow cytometry.

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