Classification of Thyroid Malignancies

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Pathologic Assessment and Classification of Thyroid Tumors

Many thyroid tumors arise in essentially normal thyroid tissue; however, one must be aware of the fact that definition of normal thyroid tissue in the era of ultrasound is subjective since approximately 60 % of the US population has one or more thyroid nodules. Thyroid neoplasms demonstrate a variety of morphologic patterns, which complicate their pathological interpretation [1]. All neoplasms that arise either from follicular or C cells may have some functional capacities. They may respond to TSH and may even produce excessive amounts of thyroid hormones or, if medullary carcinoma, release abnormal quantities of calcitonin and/or other hormones [2]. Localization of thyroid transcription factor (TTF-1) and thyroglobulin or calcitonin by immunohistochemistry aids in the classification of unusual thyroidal tumors and in providing definite identification of metastatic thyroid carcinomas [3]. Most thyroid cancers grow slowly and are amenable to appropriate treatment. The majority are papillary cancers, especially in those areas of the world in which adequate iodides are present in the diet and environment.

Proper pathologic assessment of the thyroid specimens is necessary for accurate diagnosis. Incomplete fixation of any thyroid tissue may produce loss of cellular details and pale nuclei in the sections (thus, a superficial resemblance to the nuclei of papillary carcinoma). The pathologic assessment of the thyroid lesions includes fine-needle aspiration and diagnosis, intraoperative evaluation, gross pathologic examination, and histopathologic reporting.

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Fine-Needle Aspiration (FNA) of Thyroid Lesions

Fine-needle aspiration (FNA) of the thyroid has now been established as reliable and safe and has become an integral part in the management of thyroid nodules. Based on the examination of few groups of cells, it can effectively triage cases requiring clinical or surgical follow-up (for further discussion on FNA technique and specimen processing, please refer to Chap. 19). Thyroid FNA specimens are usually classified by employing a tiered system. Several classification schemes have been proposed by various authors based on personal/institutional experiences. In 2007, a six-tiered classification scheme for classifying thyroid FNAs known as Bethesda classification for thyroid FNA specimen was proposed (Table 8.1). In this scheme each diagnostic category is assigned a risk of malignancy based on literature review along with recommendations for management. It is also recommended that for some of the diagnostic categories, some degree of subcategorization can be informative and is often appropriate. Additional descriptive comments (beyond such subcategorization) are optional and left to the discretion of the cytopathologist [4, 7].

The brief description of the diagnostic categories in the Bethesda classification is as follows:

I. *Nondiagnostic or unsatisfactory*:
   (a) This diagnostic category applies to specimen which are nondiagnostic due to limited cellularity, no follicular cells, and adequate specimen which are uninterpretable due to poor fixation and preservation, i.e., obliteration of cellular details.
   (b) In some cases of solid nodules, it may be prudent to process and examine the entire specimen.

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Table 8.1 The Bethesda system for reporting thyroid cytopathology: implied risk of malignancy and recommended clinical management [4–6]

Diagnostic category	Risk of malignancy (%)	Usual management
Nondiagnostic or unsatisfactory		Repeat FNA with ultrasound guidance
Benign	0–3 %	Clinical follow-up
Atypia of undetermined significance or follicular lesion of undetermined significance	~5–15 %	Repeat FNA
Follicular neoplasm or suspicious for a follicular neoplasm	15–30 %	Surgical lobectomy
Suspicious for malignancy	60–75 %	Near-total thyroidectomy or surgical lobectomy
Malignant	97–99 %	Near-total thyroidectomy

(c) It is recommended that solid nodules with repeat nondiagnostic FNA results should be excised because malignancy is eventually diagnosed in about 9 % of such cases.

II. *Benign*:
   (a) The reported rate of malignancy for this diagnostic category is 0–3 %.
   (b) The diagnostic terms in this category include but are not limited to nodular goiter, hyperplastic/adenomatoid nodule in goiter, chronic lymphocytic thyroiditis, and subacute thyroiditis.
   (c) A thyroid nodule with a benign diagnosis should be followed periodically by US examination; a repeat FNA may be considered if the nodule increases in size (as per ATA guidelines the increase should be in 20 % in two dimensions of the nodule and that of solid component in case of cystic nodules) [8].

III. *Atypia of undetermined significance/follicular lesion of undetermined significance* (*AUS/FLUS*):
   (a) The literature review of the large cases series published after Bethesda classification scheme shows that this represents a heterogeneous diagnostic category (a true gray zone). The reported malignancy risk for cases diagnosed as such in these studies ranges from 6 to 48 % [9–11].
   (b) It is recommended that the number of cases diagnosed as such should be kept to minimum, 7 % of the total diagnoses. The question arises what can serve as a guide for keeping the AUS/FLUS diagnosis in an acceptable range. One obvious answer is to use the AUS/FLUS to malignant diagnoses ratio similar to atypical squamous cell of undetermined significance to squamous intraepithelial lesion (ASCUS:SIL) ratio in cervical cytology; however, this needs to be proven by independent studies from multiple institutions.
   (c) It is optional to describe the reason(s) for AUS/FLUS diagnosis. Some authors have shown that subclassifying this diagnosis further stratifies the risk of malignancy for this diagnostic category.
   (d) It has been shown that repeat FNA is effective in arriving at definite management-based diagnosis in thyroid nodules initially diagnosed as indeterminate. Therefore, repeat FNA should be recommended in cases diagnosed as AUS/FLUS. These studies are clearly evident that RFNA has a definite role in the management of patients with thyroid nodules diagnosed as FLUS/AUS.

IV. *Follicular/follicular neoplasm with oncocytic features* (*AKA Hurthle cell*) *neoplasm or suspicious for follicular or follicular neoplasm with oncocytic features* (*AKA Hurthle cell*) *neoplasm*:
   (a) These diagnostic terms encompass both benign and malignant tumors, i.e., follicular adenoma and carcinoma and oncocytic follicular adenoma and carcinoma. The cytologic diagnosis of "neoplasm" reflects the limitations of thyroid cytology, since the diagnosis of follicular carcinoma is only based on the demonstration of capsular and/or vascular invasion. Several authors have shown that, at most, only 20–30 % of cases diagnosed as "follicular neoplasm" are diagnosed as malignant on histological examination and the rest are either follicular adenomas or cellular adenomatoid nodules, i.e., benign. Interestingly, half or more of the malignant cases diagnosed as follicular neoplasm or suspicious for follicular neoplasm (FON/SFON) are found to be follicular variant of papillary thyroid carcinoma (FVPC) on surgical excision.

V. *Suspicious for malignancy*:
   (a) This term includes suspicious for papillary carcinoma (malignancy risk 60–75 %), medullary carcinoma, other malignancies, lymphoma (flow cytometry can be recommended with repeat FNA), metastatic carcinoma/secondary tumor, and carcinoma (includes poorly differentiated and anaplastic carcinoma).

VI. *Malignant*:
   (a) The thyroid FNA cases diagnosed as such carry a 97–100 % risk of malignancy.

   The malignant tumors of the thyroid diagnosed on FNA include papillary carcinoma and variants, medullary carcinoma, poorly differentiated carcinoma, anaplastic carcinoma, metastatic carcinoma (with immunohistochemistry), and lymphoma (combined with flow cytometry).

Intraoperative Assessment/Frozen Section Examination of Thyroid Tumors

It has been shown that although frozen section diagnosis of thyroid tumors may be specific (90–97 %), it is not sensitive (60 %). In addition, deferred diagnoses at frozen section do nothing to alter the operative procedure or guide the surgeon [12]. In lieu of frozen sections, the initial approach to diagnose a thyroid nodule should be an aspiration biopsy (fine-needle aspiration (FNA)) [12–14]. For thyroid nodules which are unequivocally diagnosed as malignant, the surgeon should proceed with the appropriate surgery for that malignant diagnosis. In cases where the FNA diagnosis is suspicious for malignancy and that suspected lesion is papillary carcinoma or a variant thereof, intraoperative frozen section may be useful since the diagnosis relies on the nuclear morphology and not the finding of invasion. If the FNA diagnosis is "neoplasm/suspicious for neoplasm," frozen section will not provide a definitive diagnosis and therefore should not be requested [3, 15–17], since the limited sampling at the time of frozen section may not detect a random microscopic focus of capsular or vascular invasion required for the diagnosis of follicular carcinoma.

Gross Examination of Thyroid Specimens

As part of the macroscopic assessment of thyroid resection specimens, pertinent clinical and historical data should be provided to the pathologist. This includes age and sex of the patient, relevant clinical history (previous history of fine-needle aspiration biopsy and diagnosis, treatment, history of head and neck radiation, and family history of thyroid disease), and identification of the procedure type (lobectomy, near-total or total thyroidectomy). Radiologic, functional, and laboratory data should also be included. A detailed gross examination of a thyroid should be performed on the fresh specimen received and tumor size and appearance be documented before sections are taken for frozen section or other studies. The specimen should be oriented spatially by the surgeon. A detailed gross examination of the specimen should include weight and measurement (in three dimensions) of the specimen and *d*escription of the external surface and the cut surface (color, consistency); location, size, and physical characteristics (encapsulation, color, hemorrhage, FNA tracks, solid, cystic, calcified, necrosis) of the nodule(s) should be described. The surgical margins should be highlighted with ink, and the presence of gross extra-thyroidal extension should be noted. If the specimen contains regional lymph nodes, description of levels and characteristics of any grossly involved nodes should be given. The presence of parathyroid gland(s) should be documented. The gross examination determines the number of sections to be taken for histopathologic evaluation. Diffuse lesions of the thyroid such as thyroiditis or Graves' disease without any obvious nodules, up to three sections, should be submitted from each lobe and one from the isthmus. In the case of a solitary or dominant encapsulated nodule, it is recommended that the entire circumference of the nodule be sectioned. Each section should include tumor capsule and main tumor mass with a margin of normal surrounding parenchyma if present. For a nonencapsulated nodule, it is recommended that one section per 0.5 cm should be submitted.

Histopathologic Reporting of Thyroid Tumors

The final histopathologic report should be comprehensive and include all of the known prognostic parameters. The tumor description should include histologic type (Table 8.2) [18], number/multicentricity, size, encapsulation, the presence of tumor capsule and vascular invasion, perineural invasion, and extra-thyroidal invasion. If lymph node sampling or dissection was performed, the presence of lymph node metastases, by number and size, should be recorded. The identification of extra-nodal extension into the soft tissues should be mentioned. The number of parathyroid glands removed during

Table 8.2 Histologic classification of thyroid tumors [18]

Primary malignant tumors	1. *Malignant tumors of follicular cells*
	(a) Papillary carcinoma
	(b) Follicular carcinoma
	(c) Poorly differentiated carcinoma
	(d) Undifferentiated (anaplastic) carcinoma
	2. *Malignant tumor of C cells*
	(a) Medullary carcinoma
	3. *Malignant tumors of mixed follicular and C cells*
	4. *Miscellaneous epithelial tumors*
	(a) Squamous cell carcinoma
	(b) Mucoepidermoid carcinoma
	(c) Mucin-producing carcinoma
	(d) Spindle epithelial tumor with thymus-like differentiation (SETTLE)
	(e) Carcinoma showing thymus-like differentiation (CASTLE)
	(f) Hyalinizing trabecular neoplasms (predominantly adenomas)
	(g) Neoplasms associated with familial intestinal adenomatous
Thyroid adenoma and related tumors	1. Follicular adenoma
	2. Hyalinizing trabecular neoplasm
Malignant non-epithelial tumors	1. Lymphoma
	2. Sarcoma
Secondary tumors	Metastatic malignant tumors

surgery if any should be documented and their location given if possible. Additional pathologic findings in the thyroid such as nodular goiter, thyroiditis, and benign tumors should be described. Additional (optional) areas to include in the report are correlation with FNA findings (especially in discrepant cases) and correlation with intraoperative diagnosis and clinical information. The tumor stage should also be added according to the current AJCC staging system [19]. The results of special studies, special stains (Congo red for amyloid, elastic stain for vessels), immunostains (calcitonin, thyroglobulin, endothelial markers for vascular invasion), molecular studies, and flow cytometry, should be added as appropriate.

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