The Bethesda System for Reporting Thyroid Cytopathology: Current Status and Future Directions

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Abstract

This article summarizes the diagnostic criteria for each of the six categories of The Bethesda System for Thyroid Cytopathology (TBSRTC) and reviews the impact of using TBSRTC in diagnosing and clinical management of thyroid nodules in USA. In summary, there is evidence that TBSRTC facilitates more consistent and uniform reporting of thyroid FNA and leads to more consistent management approaches. Without affecting overall rate of cytohistologic concordance, the overall rate of histologically proven malignancy and/or diagnostic accuracy, implementing TBSRTC may result in lower nondiagnostic rate, less descriptive or implicit interpretation, decreased rate of surgical follow-up for benign and AUS/FLUS categories as well as a reduction of histology-confirmed malignancy in benign category. However, optimal diagnosis and management of indeterminate thyroid nodules is still a major challenge. It is important for practitioners from all relevant specialties to have a clear understanding of their own institution’s practice patterns throughout the process of diagnosis and management of the patients. The authors believe that FNA cytopathology combined with molecular testing will improve the diagnostic accuracy and lead to a better clinical management of patients with thyroid nodules.

Keywords: Thyroid, fine needle aspiration, Bethesda System

Introduction

Fine needle aspiration (FNA) as a simple and cost-effective triage procedure, has been widely used in the management of thyroid nodules. It aims to distinguish thyroid nodules that require surgical interventions from those that may be managed conservatively with clinical and imaging follow-up (1-4). Various criteria for assessment of specimen adequacy, as well as different diagnostic categories and terminology had been used for the cytologic evaluation of thyroid aspiration specimens not only among institutions but also among pathologists in the same institution (5-9). The lack of uniform criteria for adequacy assessment and standardized diagnostic terminology had resulted in diagnostic inconsistency between pathologists and difficult communications with clinicians. This prompted some laboratories to develop institutional standard criteria for assessment of specimen adequacy and diagnostic terminology. In this regard, we implemented an institutional diagnostic system which was established according to Guidelines of the Papanicolaou Society of Cytopathology for the Examination of Fine-Needle Aspiration Specimens from Thyroid Nodules with minor modification (10). We found that use of the institutional standard on FNA diagnosis of thyroid nodules has provided significant benefits, including a reduction in non-diagnostic rate and rate of descriptive diagnosis, improvement of diagnostic consistency among the pathologists as well as better and more uniform communication between the pathologists and the clinicians (11).

To address the relevant issues associated with FNA diagnosis of thyroid nodules, the National Cancer Institute (NCI) hosted the NCI Thyroid FNA State of the Science Conference. The conclusions regarding terminology and morphologic criteria from the NCI meeting led to the publication of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) in 2010. It is expected that the approach to standardization will facilitate the following aspects: 1) communication among cytopathologists, endocrinologists, surgeons, radiologists, and other health care providers; 2) cytologic-histologic correlation for thyroid diseases; 3) research into the epidemiology, molecular biology, pathology, and diagnosis of thyroid diseases; and 4) easy and reliable sharing of data from different laboratories for national and international collaborative studies (12).

TBSRTC is a uniform, six-tiered reporting system consisting of the following categories: nondiagnostic/unsatisfactory, benign, atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS), follicular neoplasm or suspicious for follicular neoplasm (FN/SFN), suspicious for malignancy (SFM), and malignant. TBSRTC provides standardized nomenclature and definitions for each of the six diagnostic categories. Furthermore, TBSRTC predicts the risk of malignancy and outlines the recommendations for clinical management of each category. The individual categories are briefly reviewed below.

Nondiagnostic/Unsatisfactory

A diagnostic/satisfactory specimen must contain at least six groups/clusters of well persevered, well-visualized follicular cells and each group/cluster consists of a minimum of ten cells. Accordingly, a specimen is considered nondiagnostic/unsatisfactory if it contains suboptimal number of follicular cells and/or cyst fluid consisting of predominantly macrophages (Figure 1). A specimen with only bronchial ciliated bronchial cells is also nondiagnostic (Figure 2). However, there are exceptions to the requirement of follicular cells. The minimum number of follicular...
Fig. 1. Non-diagnostic (cyst fluid only). The specimen shows numerous histiocytes without follicular cells (smear, Papanicolaou stain).

Fig. 2. Non-diagnostic. The specimen contains a group of ciliated bronchial cells only (smear, Diff-Quik stain).

Fig. 3. Colloid nodule. The smear shows abundant thick/dense and thin/watery colloid without follicular cells (smear, Diff-Quik stain).

Fig. 4. Benign follicular nodule. Follicular cells are arranged mainly as large, honeycomb sheets (A) and/or intact follicles (B) (smears, Diff-Quik stain).

cells is not required if the specimen contains any of the following: 1) atypical follicular cells or atypical cells of other origins; 2) moderate to abundant amount of inflammatory cells, i.e., polymorphous lymphocytes, neutrophils and aggregates of histiocytes (granuloma); and 3) abundant colloid materials (Figure 3). When examination of follicular cells is compromised due to extensive obscuring materials such as blood, ultrasound gel, etc., or the presence of severe air-drying artifact in alcohol-fixed smear, nondiagnostic/unsatisfactory category is appropriate to use. A repeat FNA with ultrasound guidance and rapid on-site evaluation (ROSE) are preferred if a solid nodule is initially interpreted as nondiagnostic/unsatisfactory. Cystic nodules with an initial result of nondiagnostic/unsatisfactory should be re-aspirated if the ultrasound features are worrisome. An interval of three months between the aspirations is recommended to avoid over-interpretation of reactive or reparative changes.
Fig. 5. Benign follicular nodule. Nuclei contained in the honeycomb sheets (A) and spheres (B) are evenly distributed without nuclear crowding/overlapping. The nuclei are round or oval with smooth nuclear membrane, granular chromatin and inconspicuous nucleoli (smears, Diff-Quik stain).

Benign

This category includes mainly a group of benign follicular nodules and thyroiditis. Benign follicular nodules share similar cytologic features and their histology counterparts include nodular goiter, hyperplastic (adenomatoid) nodules, colloid nodules, nodules in Grave’s disease, and a subset of follicular adenomas (macrofollicular type). In general, specimens contain various amounts of colloid material, benign appearing follicular cells, Hurthle cells, and macrophages. Benign follicular cells are arranged as monolayered, honeycomb-like sheets and/or three-dimensional spheres (Figure 4). The follicular cells contained within the sheets/spheres are evenly distributed and nuclear polarity is maintained. The follicular cells have scant to moderate amount of delicate cytoplasm, round to oval nuclei, granular chromatin and inconspicuous nucleoli (Figure 5). Hurthle cells may appear as single cells and/or flat sheets. Hemosiderin-laden macrophages may be accompanied by cyst-lining cells. It is not uncommon that benign follicular nodules may contain a minor portion of microfollicles.

In an appropriate clinical context, “consistent with lymphocytic (Hashimoto’s) thyroiditis” is applied to the specimens that contain polymorphous lymphocytes with or without follicular cells or Hurthle cells. If present, Hurthle cells are arranged as single cells and/or sheets and contain abundant granular cytoplasm, large nuclei and prominent nucleoli. Mild anisonucleosis may be present (Figure 6).

Granulomatous thyroiditis (subacute thyroiditis) is seldom aspirated unless a co-existing neoplasm or malignancy is suspected. Depending on the stage of disease, the aspirates show variable cellularities with follicular cells and mixed inflammatory cells (neutrophils, lymphocytes, eosinophils, macrophages). Without aggregates of histiocytes (granulomas), the cytologic features are not specific.

Acute thyroiditis may be seen in patients with immunosuppression. The specimens contain abundant neutrophils admixed with follicular cells, fibrin, and necrotic debris. Pathogens may be appreciated on specimens with or without the help of special stains.

Riedel’s thyroiditis is rare. The aspirates are often acellular or pauci-cellular with collagen strands, spindle cells and chromatic inflammatory cells.

Thyroid nodules categorized as benign may carry 0-3% risk of malignancy. TBSRTC recommends clinical follow-up at 6-18 months intervals for at least 3-5 years after the initial diagnosis. Repeat FNA is performed for nodules with marked growth or suspicious ultrasound features. Surgical intervention is recommended under the circumstances of large and symptomatic nodules, nodules showing worrisome clinical and ultrasound features, or the nodules being associated with malignancy.

AUS/FLUS

There have been concerns associated with the lack of consensus on interpretation of the atypical category among cytopathologists and institutions (13, 14). The diagnostic inconsistency may affect the clinician’s understanding of this category, resulting in much variations on subsequent patient management and clinical outcomes (15). To minimize the problems, TBSRTC has made great efforts to provide specific criteria while defining the category of AUS/FLUS. While advising judicious use of this category, TBSRTC sets a provisional goal that proportion of AUS/FLUS interpretation falls into the range of approximately 7% of all thyroid FNA interpretations in most clinical setting. TBSRTC estimates the risk of malignancy for the AUS/FLUS category is between 5 and 15% based on the previous studies (16, 17, 19, 21).

AUS/FLUS represents a heterogeneous diagnostic category and by TBSRTC definition, it is reserved for specimens that contain cells with architectural and/or nuclear atypia that is not qualitatively and/or quantitatively sufficient for classification as
Fig. 6. Hashimoto’s thyroiditis. The specimen shows a polymorphous population of lymphocytes (A), and some are interspersed with Hurthle cells (B) (smears, Papanicolaou stain).

Fig. 7. Follicular lesion of undetermined significance. Hypocellular specimen with follicular cells which are trapped within fibrin and appear crowded (smear, Papanicolaou stain).

Fig. 8. Follicular lesion of undetermined significance. Intranuclear pseudoinclusions are present. No other features of papillary carcinoma are identified (smear, Papanicolaou stain).

“suspicious for follicular neoplasm”, “suspicious for malignancy”, or “malignant”. Conversely, the atypia is significantly enough that it cannot be convincingly attributed to benign changes. Briefly, TBSRTC recommends using AUS/FLUS when specimens reveal any of the following features: 1) various cellularities with some cells arranged in a microfollicular pattern, insufficient for the category of “FN/SFN” (Figure 7); 2) hypocellularity with predominantly Hurthle cells and scant amount of colloid; 3) suboptimal preparation with air-drying or clotting artifacts; 4) moderate cellularity to hypercellularity with exclusively Hurthle cells while the clinical setting suggestive of lymphocytic (Hashimoto’s) thyroiditis or multinodular goiter; 5) focal features of papillary thyroid carcinoma, especially in the clinical setting of Hashimoto’s thyroiditis or benign nodules (Figure 8); 6) benign background with cyst-lining cells showing some features of papillary thyroid carcinoma (Figure 9); 7) minor population of atypical follicular cells in patients with a history of radioactive iodine or pharmaceutical treatment; 8) atypical lymphocytes, insufficient for the category of “SFM”; and 9) not otherwise categorized.

FN/SFN (including Hurthle cell type)

TBSRTC combines FN and SFN into one category and points out that both terms are equally acceptable, and further, TBSRTC acknowledges that some laboratories may prefer SFN over FN since some literatures demonstrate that up to 1/3 of such cases had been proved to be nodular goiter rather than neoplasms (16, 18-20).
Fig. 9. Follicular lesion of undetermined significance. Cyst-lining cells with elongated nuclei, distinct nucleoli and intranuclear grooves (smear, Papanicolaou stain).

Fig. 10. Follicular neoplasm/Suspicious for follicular neoplasm. Follicular cells are arranged as microfollicles with nuclear crowding/overlapping (A). The follicular cells appear uniform with round or oval nuclei, fine chromatin. Nucleoli are occasionally seen (B) (smears, Diff-Quik stain).

Fig. 11. Follicular neoplasm/Suspicious for follicular neoplasm, Hurthle cell type. Smears show almost exclusively Hurthle cells which are arranged as single cells, loose clusters or syncytial fragments. Some cells have uniform nuclei with high nuclear/cytoplasmic ratio (A) and others show at least two times variation in nuclear size (B and C). Transgressing vessel may present in the fragment (C) (smears, Papanicolaou stain).
The specimens are cellular with scant or without colloid. The follicular cells are arranged as microfollicles or trabeculae with nuclear crowding or overlapping. Single cells may be present in the background. Follicular cells have a uniform appearance with or without enlargement. Nuclei are usually round and mildly hyperchromatic and nucleoli are occasionally seen (Figure 10). Occasionally, specimens may contain various-sized atypical nuclei with nuclear enlargement and prominent nucleoli. Cases with features of papillary thyroid carcinoma are excluded from this category.

FN/SFN, Hurthle cell type is used for the specimens containing almost exclusively Hurthle cells with architectural alteration manifested by syncytial fragments, loose clusters or single cells. Transgressing vessel may be present in the fragments. Some Hurthle cells may have high nuclear/cytoplasmic ratio (small cell dysplasia), while others may show at least two times variation in nuclear size (large cell dysplasia) (Figure 11).

The studies referred by TBSRTC reported that 65-85% of cases in this category proved to be neoplasms and the rate of malignancy was between 15-30% (16, 17, 19). A hemithyroidectomy or lobectomy is often recommended.

### SFM

This category is used when specimens show some features that are strongly suspicious, but not definitive for malignancy. Subclassifications include 1) suspicious for papillary carcinoma (Figure 12); 2) suspicious for medullary carcinoma (Figure 13); 3) suspicious for lymphoma; and 4) suspicious for malignancy, not otherwise specified. SFN (including Hurthle cell type) is excluded from this category.

Since “suspicious for papillary carcinoma” represents majority of the SFM cases. TBSRTC further outlines four patterns associated with suspicious for papillary carcinoma, including A) patchy nuclear changes; B) incomplete nuclear changes; C) sparsely cellular specimen; and D) cystic degeneration.

Ancillary tests play an important role for establishing a definitive diagnosis in patients with an initial diagnosis of SFM. In this regard, an elevated serum calcitonin level, positive special stain for Congo Red, and/or immunocytochemical study showing positive expression of calcitonin, chromogranin, synaptophysin, CD56, and CEA supports the diagnosis of medullary carcinoma. Flow cytometry demonstrating monoclonal population of lymphocytes may provide a definitive diagnosis and subclassification of lymphomas.
The risk of malignancy is estimated between 60-75% for SFM category and the patients are managed with lobectomy or near-total thyroidectomy.

Malignant

Malignant thyroid FNA diagnosis accounts for 4-8% of all thyroid FNAs and majority of the malignant cases are papillary carcinoma(16,17,21). TBSRTC defines and discusses the cytologic criteria of the following: 1) papillary carcinoma and variants; 2) medullary carcinoma; 3) poorly differentiated thyroid carcinoma; and 4) undifferentiated (anaplastic) carcinoma and squamous cell carcinoma of the thyroid; and metastatic tumors and lymphomas

Papillary carcinoma

For conventional and variants of papillary carcinoma, TBSRTC illustrates the following cytomorphological features: hypercellularity, papillae and/or syncytial tissue fragments, follicular cells with characteristic nuclear features including nuclear enlargement, oval or irregular shaped nuclei with crowding/overlapping/molding, intranuclear longitudinal grooves and cytoplasmic pseudoinclusions, powdery chromatin, marginally located micronucleoli, Psammoma bodies, and multinucleated giant cells (Figure 14).

TBSRTC indicates that variants of papillary carcinoma show the essential nuclear features of papillary carcinoma, while exhibiting different architectural pattern, unusual cytoplasmic features or different background. Among all variants of papillary carcinoma, follicular variant is most commonly encountered. The others include but are not limited to macrofollicular variant, cystic variant, oncocytic variant, Warthin-like variant, tall cell variant, columnar cell variant and hyalinizing trabecular tumor. It is noteworthy mentioning that precise subtyping may not always be possible at the time of FNA, however, making the distinction is not necessary as the initial management with total thyroidectomy is the same for all papillary carcinomas.

Medullary carcinoma

Medullary carcinoma has a great variety of cytomorphic features. Commonly, specimens show moderate cellularity to hypercellularity with or without dense, amorphous amyloid material in the background. The cells are arranged as dyshesive, single cells or syncytial groups. The cells may show various shapes with plasmacytoid, polygonal, round and/or spindled appearances and contain variable amounts of granular cytoplasm. Some cells may have long cytoplasmic processes. Moderate pleomorphism is often appreciated though rare large, bizarre cells may be present. Bi- or multi-nucleations, intranuclear pseudoinclusions, salt and pepper chromatin may be seen. Nucleoli are usually inconspicuous though it can be prominent (Figure 15a and 15b). TBSRTC advises to correlate the cytomorphic findings with the results of ancillary tests, such as serum calcitonin level, special stain for Congo Red (Figure 15c), and/or immunocytochemical studies. With regard to the latter, a panel of immunostains consisting of calcitonin, CEA, chromogranin A, and synaptophysin (Figure 16), as well as thyroglobulin is preferred over a single antibody stain.

Primary medullary carcinoma is usually managed with total extracapsular thyroidectomy with lymph node dissection.

Poorly differentiated thyroid carcinoma

By TBSRTC definition, poorly differentiated thyroid carcinoma is a thyroid carcinoma of follicular cell origin. It is a rare malignancy and accounts for 4-7% of all thyroid carcinomas. Clinically, it is more aggressive compared to well-differentiated thyroid carcinomas (papillary carcinoma, follicular/Hurthle cell carcinoma) and less aggressive than undifferentiated (anaplastic) thyroid carcinoma, respectively. The most classic poorly differentiated thyroid carcinoma shows insular growth pattern while solid and trabecular patterns may also be seen. FNA specimens are cellular with single or clusters of monotonous follicular cells. The cells often show scant amount of cytoplasm, high nuclear/cytoplasmic ratio, and variable nuclear atypia. Apoptosis, mitosis, and necrosis are present (Figure 17). As described, the morphological features of poorly differentiated thyroid carcinoma are not very specific. Thus, using immunocytochemical studies may be necessary to distinguish it
Clinical prognosis of poorly differentiated thyroid carcinoma is poor and thus, it is usually managed more aggressively than the well-differentiated thyroid carcinoma.

**Undifferentiated (anaplastic) thyroid carcinoma**

Less than 5% of thyroid malignancy is anaplastic thyroid carcinoma which is extremely aggressive and carries the poorest prognosis among all thyroid malignant neoplasms. As a high grade malignancy, specimens show various cellularities with isolated or groups of neoplastic cells. The cells show round, polygonal, plasmacytoid, spindled, and/or rhabdoid appearance with marked size variation. Nuclear enlargement, pleomorphism in nuclear size and shape, coarse chromatin, prominent nucleoli, intranuclear
inclusions and multinucleation are present (Figure 18). To distinguish anaplastic thyroid carcinoma from other primary thyroid carcinomas and metastatic malignant neoplasms, TBSRTC advises clinical/imaging correlation and use of immunocytochemical studies. Anaplastic thyroid carcinoma may be positive for pancytokeratin and vimentin, but negative for TTF-1 and thyroglobulin.

Squamous cell carcinoma

The specimens contain almost exclusively malignant cells with features of squamous differentiation. It is impossible to make a distinction between primary and metastatic squamous carcinoma base on morphological features and immunoprofile. Clinical and imaging correlation may be helpful.

Metastatic neoplasms

Metastatic malignancy involving the thyroid is commonly from lung, breast, skin, colon and kidney (Figure 19), and malignancy arising from the nearby structures may also extend to thyroid, such as those from pharynx, larynx, esophagus, mediastinum, and lymph nodes. The metastatic neoplasms show the morphological characteristics of the corresponding primary malignant neoplasms. Clinical/imaging correlation as well as immunocytochemical studies plays a vital role in making a definitive diagnosis.

Lymphoma involving thyroid gland

Majority of the lymphoma arising within thyroid gland are non-Hodgkin lymphoma. Among which, diffuse large B-cell lymphoma (DLBL) (Figure 20) and extranodal marginal zone B cell lymphoma of mucosa-associated lymphoid tissue (MALT) are most commonly encountered. The aspirates are hypercellular with lymphoglandular bodies in the background. Lymphoid cells may show a mixture of small and large lymphocytes, monotonous population of large lymphocytes, or monomorphous small lymphocytes. Flow cytometry and/or immunocytochemical studies plays an important role in making a definitive, specific diagnosis.

Impact of using TBSRTC in USA

There are a number of published English literatures reporting experiences of using all categories of TBSRTC in USA alone. A total of 11 publications are obtained when using key words including Bethesda system, thyroid, and FNA to search the National Library of Medicine PubMed database (Table 1 and Table 2). Among those studies, five used a solely retrospective approach to reclassify the previously-assessed specimens using TBSRTC (19, 22-26), while remaining six employed a prospective approach and compared the data generated from post-TBSRTC period with that of pre-TBSRTC period (27-32). Three studies focused on the cases which were subsequently treated with surgery (23, 27, 30) and the remaining eight studies included the cases with and without surgical follow-up; among the latter, five studies investigated a relatively large cohort and each consisted of 1382 to 3885 specimens which were evaluated using the criteria of TBSRTC (22, 24, 25, 29, 32). All the studies assessed the distribution across all six diagnostic categories of TBSRTC and the proportion of histology-proven malignant cases for each category. The commonly, incidental microcarcinoma on subsequent excision was not considered as malignant.
As can be seen in Table 1, these studies showed marked variation in the distribution across the diagnostic categories as follows: 3.0 – 38.0% for nondiagnostic, 34.0 – 75.0% for benign, 3.0 - 29.0% for AUS/FLUS, 22 - 25.0% for FN/SFN, 0 - 10.0% for malignant, and 1.0 - 18.0% for malignant. Furthermore, these studies also revealed differences in the proportion of histology-proven malignancy for almost all categories except malignant categories (Table 2). Accordingly, the rate of histology-proven malignancy among the surgically-treated case for the individual categories was as follows: 0 - 50.0% for nondiagnostic, 0 - 15.0% for benign, 6.0 - 67.0% for AUS/FLUS, 12.5 - 67% for FN/SFN, 0 - 88% for SFM, and 76.9% - 100% for malignant. Four individual studies demonstrated the rate of histology-proven malignancy for individual categories that either fell into or was closed to the TBSRTC-recommended range for risk of malignancy (22, 24, 30, 32), while the majority of the studies demonstrated the malignant rate that were deviated from that of TBSRTC. Marchevsky et al. noted that TBSRTC proposed the “risks of malignancy” based on the data from retrospective studies in which non-uniformed diagnostic terminology were used and the predictive value for malignancy was obtained using various metrics. They then conducted a retrospective study to compare four sets of malignant risk that were calculated for each of the six diagnostic categories by using the results of all initial FNAs and four different denominators (the number of FNAs, of thyroidectomies, of FNAs plus thyroidectomies, and of all patients) and calculating four proportions of malignancy (or risks of malignancy). They explained that a higher histology-proven malignant risk may be related to patient selection bias as patients managed by surgery usually have clinical and imaging findings, along with FNA features suspicious for malignancy (33).

It is noteworthy to mention that the majority of malignant thyroid tumors is papillary thyroid carcinoma and among which, non-invasive follicular variant has caught special interest of practitioners who have recognized its indolent clinical course and molecular profile that is different from that of classic papillary thyroid carcinoma and other high-risk variants. These facts have prompted pathologists to investigate the potential change of malignant risk for each of TBSRTC categories while non-invasive follicular variant is not considered as carcinoma. One institutional study has demonstrated a reduced rate of malignancy across all diagnostic categories and nearly 50% of reduction was observed.

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# Prospective studies, Non-dx: nondiagnostic

# Table 2: Histology-confirmed malignancy for each diagnostic category of TBSRTC

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# Prospective studies; ^the proportion of malignancy in total benign (surgical + non-surgical); Non-dx: nondiagnostic
for SFM category (34). Overall, it is very important that practitioners have a clear understanding of their institution’s practice patterns in order to be able to appropriately counsel patients with regard to treatment options and recommendations for continued surveillance versus surgery.

Benefits/advantages of using TBSRTC have been documented in different institutions. In this regard, the application of TBSRTC may provide more consistent and uniform reporting of thyroid FNA, improve interlaboratory agreement, and lead to more consistent management approaches (22, 29). Compared to the diagnostic parameters from the pre-TBSRTC period, the implementation of TBSRTC resulted in lower nondiagnostic rate (29, 32), less descriptive or ambiguous and implicit cytologic interpretation (28, 29), decreased rate of surgical follow-up for benign and AUS/FLUS categories (32), reduced overall rate of surgical intervention (28, 32), as well as a reduction of histology-confirmed malignancy in benign category (28). It is noteworthy to mention that implementation of TBSRTC did not affect overall rate of cytohistologic concordance, the overall rate of histologically proven malignancy and/or diagnostic accuracy (28, 32).

Additionally, Olson et al. conducted a retrospective review of the largest series (n = 3885) based on TBSRTC criteria and changed diagnostic classification in 32% of the cases. The finding may potentially lead to significant changes in clinical and surgical management (25). The study conducted by McElroy et al. showed an elevated non-diagnostic rate and improved prediction of malignancy for post-TBSRTC period (26). Kiernan et al. reviewed 777 cases with surgical follow-up and concluded that the adoption of the TBSRTC increased the proportion of indeterminate category; however, the diagnostic accuracy improved for SFM category (30).

Performance of TBSRTC diagnoses has been evaluated in a couple of studies. Krane et al. recommended use of AUS/FLUS to malignant ratio of 1.0 to 3.0 as a reference. Accordingly, the ratios > 3.0 are likely the result of overdiagnosis of AUS/FLUS or underdiagnosis of malignant; on the contrary, the ratios < 1.0 are mostly due to a low rate of AUS/FLUS, at the likely expense of sensitivity (35). However, Fazeli et al. expressed a different opinion claiming that the ratios of diagnostic frequencies are not reproducible, thus are unlikely to prove sufficient for benchmarking laboratory precision (36). Walts et al. noted a considerable overlap in the malignancy risk estimates for the AUS/FLUS and FN/SFN categories and for the SFM and “malignant” categories. They proposed a simplified four-category scheme (unsatisfactory, benign, FLUS/FN, and SFM/malignant) and indicated that use of the simplified four-category scheme significantly improved intra- and interobserver diagnostic agreement, significantly increased the sensitivity of FNA for a diagnosis of carcinoma in the subsequently resected thyroid glands, and provided non-overlapping risk of malignancy estimates for each diagnostic category (37).

Some studies focused on AUS/FLUS category only. Increased diagnosis of AUS/FLUS with the implementation of the TBSRTC was documented (38). There were various results in terms of the relationship between the reporting frequency and the level of reviewer’s experiences (24, 34, 39). Our own experience suggested that the group consensus review minimized AUS/FLUS, offered an optimal level of interobserver agreement, and most importantly, promoted a better cytohistologic concordance (40).

Due to the reported wide range of risk of malignancy for AUS/FLUS category, some efforts have been attempted to identify cytologic features that may predict higher or lower malignant risk among this heterogeneous group. The features that may indicate higher risk for malignancy included presence of atrophic microfollicle (39) and nuclear atypia (41-43). A retrospective review of 512 AUS/FLUS cases demonstrated that most malignancies associated with this category were papillary carcinoma and follicular variant was the most common type; architectural atypia alone was less likely to be papillary carcinoma and more likely to be follicular adenoma (44). The data obtained from the same study cohort did not show statistically significant difference in malignancy rate among patients having a single versus 2 successive AUS/FLUS diagnoses, and patients with a benign interpretation after AUS/FLUS diagnosis. The authors suggested reevaluation of TBSRTC guidelines for repeated FNA for most cases (45). However, one study reported the malignant rate of 25.6% in patients without a repeat FNA versus 38.8% in patients with repeat FNA (46).

One study investigated whether malignancies that were categorized as SFM or malignant have more aggressive features than malignancies that were categorized as AUS/FLUS or FN/SFN. Similar to the aforementioned study, follicular variants of papillary thyroid carcinoma was the most common type for AUS/FLUS or FN/SFN categories, whereas classic papillary thyroid carcinoma was found in cases categorized as SFM and malignant. They concluded that Bethesda category may help to predict the most likely histologic subtype of thyroid cancer, but it does not have any prognostic significance once the histologic diagnosis is known (47).

Vivero et al. assessed the impact of descriptive diagnosis on management of AUS/FLUS and indicated that in practice settings that follow TBSRTC management guidelines, descriptive report terminology does not modify patient treatment. In less standardized settings, terminology associated with differing risk of malignancy on subsequent excision, pathologist recommendations, and phrases indicative of limited sampling significantly alter patient management (48).

In summary, the impact of TBSRTC implementation may vary among different institutions. It is important for practitioners from all relevant specialities to have a clear understanding of their own institution’s practice patterns throughout the process of diagnosis and management of the patients. There is evidence that TBSRTC facilitates more consistent and uniform reporting of thyroid FNA and lead to more consistent management approaches. Without affecting the overall rate of cytohistologic concordance, the overall rate of histologically proven malignancy and/or diagnostic accuracy, implementing TBSRTC may result in lower nondiagnostic rate, less descriptive or implicit interpretation, decreased rate of surgical follow-up for benign and AUS/FLUS categories as well as a reduction of histology-confirmed malignancy in benign category. However, optimal diagnosis and management of indeterminate thyroid nodules is still a major challenge. The role of molecular analysis as an adjunct to FNA cytology in stratification of thyroid nodules is being extensively studied. Although the details are beyond the scope of this review, we believe that FNA cytopathology combined with molecular testing will improve the diagnostic accuracy and lead to a better clinical management of patients with thyroid nodules.

**Conflicts of Interest:** None

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