Thyroid Fine Needle Aspiration Cytology: Current and Future
Proposal of A New Diagnostic System for Reporting Thyroid Cytology

Kennichi Kakudo1*, Kaori Kameyama2, Toru Takano3

1Department of Pathology, Nara Hospital, Kindai University Faculty of Medicine; 2Division of Diagnostic Pathology, Keio University School of Medicine; 3Department of Metabolic Medicine, Osaka University Graduate School of Medicine, Japan.


Abstract

One of the most significant issues in thyroid cytology is the marked differences in diagnostic category proportion, resection rate, and malignant risk in literature. In addition to this issue, the present study observed that there were significant observer discrepancies in the morphologic criteria of papillary thyroid carcinoma between Western and Eastern cytopathologists, which should be standardized. Furthermore, the borderline tumor category in thyroid tumor classification, which has recently been proposed by our group and by others, has not yet been established in the 2004 edition WHO tumor classification. Introduction of the borderline thyroid tumors into the thyroid tumor classification system requires establishment of cytological categories. A new reporting system for thyroid FNA cytology was proposed in this opinion paper, which adopted the classification of borderline lesions and addressed the recent progress made in molecular testing. This diagnostic system included new thyroid cytology terminologies and sub-classifications of the papillary carcinoma and follicular adenoma/follicular carcinoma lineages. Thus, these diagnostic categories will no longer be the grey zone or indeterminate, providing clear-cut instructions for clinical management of the patents with the aid of molecular tests.

Keywords: Fine-needle aspiration cytology, indeterminate, thyroid carcinoma, diagnosis, borderline malignancy, precursor lesions.

Introduction

One of the most striking findings identified among the papers of this special issue and those in the literature, when examining the rate of surgery and risk of malignancy for the indeterminate thyroid nodules, is the fact that these values vary significantly. Despite the efforts to standardize the diagnostic terminologies and diagnostic criteria by the National Cancer Institute at the National Institute of Health, USA, and other organizations, there remain significant differences in the morphological criteria of cytological diagnosis as well as histological diagnosis. It is clear that the non-invasive follicular thyroid neoplasm with papillary like nuclei (NIFT) is classified as a malignant tumor in Europe and USA, while majority of the NIFT are benign tumors in China and Japan, due to the different diagnostic criteria for papillary thyroid carcinoma (PTC) type nuclear features (PTC-N) (1-7). In the articles by Sugino et al. and Zhu et al. in this special issue, it was clearly stated that diagnosis of the non-invasive encapsulated follicular variant (high nuclear score NIFT) or well-differentiated tumor of uncertain malignant potential (WD-T-UMP or low nuclear score NIFT) was rare in their patients’ series, and thus these lesions were not classified as carcinoma (5, 6). In 2015, the world experts of thyroid pathology gathered in Boston, MA, and proposed NIFT to be a biologically benign precursor lesion that does not require total thyroidectomy and radioactive iodine (RAI) treatment (7). However, this epoch-making change not only has a significant impact on the histopathologic diagnosis of PTC, but also on the cytological diagnosis. Strickland et al. from an esteemed academic center in the USA showed that NIFT comprised approximately 25% of the thyroid carcinomas, and the rate of malignancy in the suspicious category dropped from 87.2% to 45.7% when NIFT was no longer termed a carcinoma (8). However, the proportion of carcinomas in the cytological category of suspicious for malignancy remains high (more than 90%) in Chinese and Japanese patients’ series, where majority of the NIFT cases have already been removed from the malignant tumor (5, 6, 9). Thus, it is clear that the cytological criteria for PTC in thyroid fine-needle aspiration (FNA) cytology between Western and Eastern cytopathologists must have significant differences even with the tremendous efforts made for standardization of terminology and cytological criteria as provided by the Bethesda system (10). The differences may be due to the possibility that the cytological and histological correlation in daily practice for quality control strongly adjusts and tunes the cytological and histological criteria to one another. This feedback function may create significant and wide discrepancy in the cyto-morphological criteria between Western and Eastern cytopathologists, because more NIFTs are diagnosed as malignant by Western pathologists, and the vast majority of NIFTs are diagnosed as benign by Eastern pathologists. To address this issue in the current practice of thyroid cytology, further studies are needed to identify the discrepancy in the diagnostic criteria, and to establish standardized morphological criteria in thyroid cytology. Herein, we propose a new reporting system for thyroid FNA cytology that includes new diagnostic terminologies and sub-classification of indeterminate category of thyroid cytolgy (Table 1), borderline lesions, and application of the recent progress in molecular testing.

Received: August 25, 2015; Accepted: September 2, 2015
*Correspondence author: Kennichi Kakudo, MD, PhD, Department of Pathology, Nara Hospital, Kindai University Faculty of Medicine, Otoda-cho, 1248-1, Ikoma-city, Nara, 630-0293, Japan
E-mail: kakudo@thyroid.jp
**Table 1: Proposed diagnostic categories for reporting thyroid FNA cytology and subcategories when molecular tests are fully accessible**

<table>
<thead>
<tr>
<th>Category</th>
<th>Subcategory with molecular test</th>
<th>Risk of malignancy/clinical management</th>
</tr>
</thead>
<tbody>
<tr>
<td>ND (non-diagnostic)</td>
<td>ND: negative:</td>
<td>&lt;10% clinical follow up</td>
</tr>
<tr>
<td></td>
<td>ND: positive:</td>
<td>diagnostic surgery</td>
</tr>
<tr>
<td>Benign</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borderline categories</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTC lineage</td>
<td>LRA (low-risk atypia)</td>
<td>10-50% clinical follow up</td>
</tr>
<tr>
<td></td>
<td>LRA: negative:</td>
<td>diagnostic surgery</td>
</tr>
<tr>
<td></td>
<td>LRA: positive:</td>
<td>60-97% (diagnostic surgery)</td>
</tr>
<tr>
<td></td>
<td>HRA or SM (high-risk atypia or suspicious for malignancy)</td>
<td></td>
</tr>
<tr>
<td>FA/FTC lineage</td>
<td>LGFN (low grade follicular neoplasm)</td>
<td>10-30% clinical follow up</td>
</tr>
<tr>
<td></td>
<td>LGFN: negative:</td>
<td>diagnostic surgery</td>
</tr>
<tr>
<td></td>
<td>LGFN: positive:</td>
<td>40-80% clinical follow up</td>
</tr>
<tr>
<td></td>
<td>HGFN (high grade follicular neoplasm)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HGFN: negative:</td>
<td>diagnostic follow up</td>
</tr>
<tr>
<td></td>
<td>HGFN: positive:</td>
<td>diagnostic surgery</td>
</tr>
<tr>
<td>Malignant</td>
<td></td>
<td>&gt;98% (surgical treatment)</td>
</tr>
</tbody>
</table>

**Precursor lesions and borderline lesions**

In 2009, we proposed a new histologic classification of thyroid tumors, which was further modified in 2012 and 2015 (Table 2) (4, 11-14). We have observed that this new histological classification is useful to stratify the patients' prognosis more precisely in the cases treated with a curative surgery (13). In this classification system, a new diagnostic category of borderline tumors was created between benign and malignant tumors, which was not established in the 2004 version of the WHO classification system of thyroid tumors (15). We suggested that there should be a borderline thyroid tumor category between benign and malignant, which is theoretical precursor lesions of thyroid carcinomas, despite it has not yet been clarified in any textbooks (4, 11-15). This category in our classification system included some tumors formerly termed as carcinomas: 1) non-invasive encapsulated papillary carcinoma (both conventional and follicular variant); 2) WDT-UMP; 3) capsular invasion-only follicular carcinoma; 4) follicular tumour of uncertain malignant potential (FT-UMP); and 5) papillary microcarcinoma (Table 2). Some of these, such as the non-invasive encapsulated papillary carcinoma (only the follicular variant) and the WDT-UMP, were proposed to be renamed as NIFT by Nikiforov et al. (7), and the papillary microcarcinoma had already been renamed as a papillary microtumor in 2003 (16). We expect further discussion on the other low-risk and indolent thyroid tumors, and their placement in the borderline malignancy or precursor lesion category in the future. These tumors are generally curable with simple removal, and do not require more aggressive treatment, such as total thyroidectomy plus RAI treatment. However, please bear in mind that we are not suggesting that all benign tumors in the current WHO classification, such as follicular adenomas and hyperplastic adenomatous nodules, are truly benign and will not undergo oncogenic alterations leading to malignancy. We suspect that a significant proportion of diagnosed benign tumors may already have some oncogenic changes or may be in the process of progression, simply because pathologists are unable to identify any evidence of malignancy defined by the WHO classification, such as capsular invasion and/or vascular invasion (15). It is possible that some of the currently classified benign tumors may be removed from the benign category in the future, and may be placed in the non-invasive carcinoma (carcinoma in situ) category or true malignant category when a certain genetic change or high probability of recurrence is documented in these tumors. We are soon leaving a historical period of thyroid pathology, when pathologists have had only two diagnostic choices for thyroid tumors (benign and malignant), and are entering a new era with three choices (benign, borderline, and malignant), similar to the classification systems utilized in other organ systems.

**Proposal of diagnostic categories for reporting thyroid FNA cytology and their sub-categories when molecular tests become more reliable and fully accessible (Table 1)**

Once the borderline thyroid tumor category is established in the thyroid tumor classification system, it is then required to establish new cytological categories to accept those borderline tumors in the thyroid cytology. Our proposed diagnostic system is designed to have two separate lineages, the PTC and FA/FTC (follicular adenoma/follicular thyroid carcinoma) lineages, similar to the current diagnostic systems (9, 10, 17-21). Those in the PTC...
Kakudo K et al. Thyroid FNA cytology, JBCM 2015; 4(2):110-114

Table 2: Classification of follicular cell tumors and Ki-67 labeling index (modified from reference 13 by Kakudo et al.)

1) Benign Tumors (Ki-67 labeling index: <3%)
   A: Follicular Adenoma
2) Borderline Tumors ([T1, N0, EX0, and M0] and Ki-67 labeling index: <3%)
   A: Encapsulated Tumors
      i) Noninvasive and Encapsulated Papillary Carcinoma
      ii) Conventional type with papillary growth
   b: Well-Differentiated Tumor of Uncertain Malignant Potential (= NIFT)
   c: Capsular Invasion Only Follicular Carcinoma
   d: Follicular Tumor of Uncertain Malignant Potential
   B: Non-encapsulated Tumors (formerly called papillary microcarcinoma)
      a: Papillary Microtumor (<1 cm)
3) Malignant Tumors (Invasive carcinoma and >1 cm)
   A: Low Risk (Ki-67 labeling index: <5%)
   B: Moderate Risk (Ki-67 labeling index: 5-10%)
   C: High Risk (Ki-67 labeling index: 10-30%)
   D: Undifferentiated Carcinoma (Ki-67 labeling index: >30%)

Thyroid specialists have proposed the follicular variant of noninvasive and encapsulated papillary carcinoma and the well-differentiated tumors of uncertain malignant potential in this table to be biologically benign precursor (borderline) tumors, rather than true malignant tumors (7). Papillary microcarcinomas had already renamed as papillary microtumors in 2003 (16). NIFT: non-invasive follicular thyroid neoplasm with papillary like nuclei.

lineage are risk-stratified into two categories: low-risk atypia (LRA) for tumors with mild PTC-N, and high-risk atypia (HRA) or SM (suspicious for malignancy) for those with PTC-N but not conclusive for malignancy. In the FA/FTC lineage, follicular pattern lesions with no PTC-N are classified into two categories: low grade follicular neoplasm (LGFN) and high grade follicular neoplasm (HGFN). The LGFN includes those showing mild cytological features of loss of cellular polarity (LCP) and loss of cellular cohesiveness (LCC), and the HGFN includes those showing prominent LCP/LCC, adapted from the Japanese system (6, 9, 20, 21). A significant proportion of thyroid carcinomas in the indeterminate category was found to be NIFT, 48% of malignancy in SM and 45% of malignancy in AUS as reported by Strickland et al. from USA (8), while thyroid carcinomas in the indeterminate categories have been shown to be biologically indolent (low stage and low risk) by other researchers (22-25). These findings may provide an additional new insight into the so-called indeterminate thyroid cytology category. We hypothesize that the thyroid tumors at an early stage of thyroid carcinogenesis (borderline and precursor lesions) have a higher probability being classified into the indeterminate category because they have less well-developed morphological characteristics of malignant tumors (Figure 1) (26), which is also discussed in detail by Ohori in this special issue (27).

Subclassification of FVPTC was proposed by Rivera et al. and Ganly et al. from the Memorial Sloan Kettering Cancer Center, USA, because these subgroups of FVPTC were reported to have different prognoses and different oncogene alterations (28, 29). The subgroups of FVPTC are A) non-invasive encapsulated/well-circumscribed FVPTCs (equal to NIFT encompass WDT-UMP); B) invasive encapsulated/well-circumscribed FVPTCs (equal to invasive encapsulated follicular variant PTC (EnFVPTC) encompass well differentiated carcinoma not otherwise specified); and C) infiltrative FVPTC (non-encapsulated and not well-circumscribed FVPTC with invasion into thyroid parenchyma). The relationship among these three subtypes of FVPTC and their corresponding cytological categories are schematically explained in the Figure 1. Nikiforov et al. studied more than 100 cases of non-invasive encapsulated/well-circumscribed FVPTCs and found them to be biologically benign after simple excision, and postulated a progression from NIFT to invasive EnFVPTC based on the multistep carcinogenesis theory (7). However, such a viewpoint may be controversial; some researchers believe that each of these tumors develop from different origins, and thus a benign tumor cell can never progress into a malignant one (30-33). Nonetheless, we would like to emphasize that cyto-morphological examination alone can reliably stratify the thyroid tumors into benign, borderline, low-risk, and high-risk groups (9, 20, 21, 26, 34).

One of the unique features of our new diagnostic system is that it is prepared in anticipation for an era when molecular diagnosis will become more reliable and fully accessible. As a result, it will no longer be necessary to identify these categories as indeterminate or grey zone, because clinical management and patient care can be decided with a more confident diagnosis. This is the key to solve the problems of the so-called indeterminate categories, and with the aid of molecular tests, the cytological diagnosis will provide clear information as to whether to perform surgical treatment or to follow-up. In this process, the morphological diagnosis remains necessary, and will decide which molecular tests need to be performed, when to do, and the reasons for doing so.

As shown in this special issue, there are significant differences among different reporting systems for thyroid FNA cytology (35). We persistently need a universally accepted thyroid FNA cytology reporting system strengthened by standardized morphological criteria and reliable molecular tests, and such a system will allow the thyroid nodules diagnosed in the same way anywhere in the world. In a recent commentary on thyroid FNA symposium in the 38th European Congress of Cytopathology by Rossi et al., they confessed that “Is it realistic to envision such a system?” and further stated, “Can we build and cross a common bridge?” (36). We hope the new diagnostic system in this paper...
shall be included in this discussion to cross the bridge and built the universal diagnostic system for thyroid cytology to which Japanese cytopathologists wish to join and contribute significantly.

Acknowledgements

The authors wish to express a deep appreciation to all members of the Committee for the Clinical Guidelines of the Japan Thyroid Association for their invaluable support.

Conflicts of Interest: None

References

8. Strickland KC, Howitt BE, Marqusee E, Alexander EK, Cibas ES, Krane JF, Barletta JA. The impact of non-invasive follicular variant of papillary thyroid carcinoma on rates of malignancy for fine-needle aspiration diagnostic categories. Thyroid 2015; [Epub ahead of print].
15. DeLellis RA, Lloyd RV, Heitz PU, Eng C. Tumours of Endocrine Organs, World Health Organization Classification

Fig. 1. NIFT (non-invasive encapsulated/well-circumscribed FVPTC encompass WDT-UMP), Invasive EnFVPTC (invasive encapsulated/well-circumscribed FVPTC encompass well differentiated carcinoma not otherwise specified), Infiltrative FVPTC (non-encapsulated and not well-circumscribed FVPTC with invasion into thyroid parenchyma) and their corresponding cytological categories are illustrated. All three types of thyroid tumors are classified as malignant, which were formerly categorized as carcinoma. However, the non-invasive type encapsulated/well-circumscribed FVPTC was recently renamed NIFT, and recategorized as a benign precursor lesion (7). PTC: papillary thyroid carcinoma; PTC-N: papillary thyroid carcinoma type nuclear features; FVPTC: follicular variant PTC; EnFVPTC: encapsulated follicular variant PTC.