P-ISSN 0215-7284
e-ISSN 25279106
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Diagnostic Concordance of Fine Needle Aspiration Biopsy Versus Post Operative Histopathology in Papillary Thyroid Carcinoma in Dr. Soetomo General Academic Hospital 2019-2022.

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Received : 27-10-2022
Accepted : 07-06-2023
Published : 31-01-2025

ABSTRACT

Introduction
Thyroid carcinoma is the most common malignancy of the endocrine organ, with papillary thyroid carcinoma (PTC) being the most common variant. Fine needle aspiration biopsy (FNAB) is still one of cost-effective and less invasive preliminary tests for thyroid lesion. The Bethesda System for Reporting Thyroid Cytopathology uses six categories for thyroid reporting. The aim of this study is to observe the morphological finding of fine needle aspiration biopsy result in patients with histopathology diagnosis of PTC.

Methods
This was an observational descriptive study with retrospective approach. Data of patients with postoperative histopathology diagnosis papillary thyroid carcinoma was obtained. We then retrieved and reviewed all the previous FNAB slides. All was classified based on Bethesda system for reporting thyroid cytopathology. We considered only patients with histopathology proven diagnosis who underwent FNAB in the same institution during 2019-2022.

Results
56 cases of FNAB with post-operative histopathology diagnosis papillary thyroid carcinoma were obtained, 34 (62%) of them were diagnosed as papillary thyroid carcinoma, 9 (14.8%) cases were non diagnostic, 10 (17.8%) cases were diagnosed as benign, and 3 (5.3%) cases fell into atypia category. After being reviewed, total of 12 cases were recategorized.

Conclusion
The majority of FNAB diagnoses are in line with the histopathological result, consistent with Bethesda category VI, which showed cell atypia. architectural atypia, and overlapping nuclei. Most cases of misdiagnosis fell into the benign category, with abundant colloid and cyst macrophage being the most common feature.

Keywords: papillary thyroid carcinoma, FNAB, histopathology, diagnostic concordance, Bethesda classification

Maj Patol Indones 2025; 34(1): 842-847
DOI: 10.55816/mpi.v34i1.624

P-ISSN 0215-7284
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INTRODUCTION

Thyroid carcinoma is the most common malignancy of the endocrine organ, with papillary thyroid carcinoma being the most common varian.[1] The incident has been increasing globally.[2] Surveillance, Epidemiology, and End Result (SEER) Database showed increase on its incidence from 1975 to 2018.[3] The most common age group is middle age, although some literature state that the incident also rises in the 5th decades of life.[4,5] Risk factor for papillary thyroid carcinoma include radiation exposure and genetic factor.[4]

Most of patient with papillary thyroid carcinoma have no symptoms. The most common symptom that brings the patient to seek medical care is mass in the neck area.[5] Different variant of thyroid malignancy has different survival rate. Accurate diagnosis is important so that it can be cured on time.[6] The gold standard examination to know the exact diagnosis is histopathology from biopsy specimen. It's less effective but most accurate. Fine needle aspiration biopsy is still one of cost-effective and less invasive preliminary tests for thyroid lesion.[1] It plays a central role in the initial evaluation of thyroid nodule and helping to guide clinician choose the suitable management for the patient by triaging patient into diagnostic category with defined risk of malignancy.[7]

The purpose of this study was to compare the concordance of postoperative histopathology diagnosis with the previous FNAB examination performed at Dr. Soetomo General Hospital Surabaya from 2019-2022 and define the probable cause of misdiagnosis.

METHODS

This research was an observational descriptive study with a retrospective approach. Data of patients with postoperative histopathology diagnosis papillary thyroid carcinoma was obtained from medical record during 2019-2022 period. We then retraced the previous FNAB examination, retrieved and reviewed all the FNAB slides that was being stained using diff quick staining. All were classified based on Bethesda system for reporting thyroid cytopathology. We considered only patients with histopathology proven diagnosis who underwent FNAB in the same institution. All cases that fulfil the inclusion criteria are being included in this study (total sampling).

RESULTS

The total number of patients with histopathology diagnosis papillary thyroid carcinoma during 2019-2022 period was 170, and 56 of them underwent thyroid FNAB examination in the same institution. Sex distribution in this study revealed 14 patients were male and 42 were female (1:3). The youngest patient was 23 years old, while the oldest was 73 years old. 41-50 years was the most common age group, with mean 52.7 years old (Table 1).

Table 1. Patient characteristics.

Variable	N
Sex	
Male	14 (25%)
Female	42 (75%)
Total	56
Mean	52.7
Median	52
Age	
<30 years old	2 (3.5%)
31-40 years old	5 (8.9%)
41-50 years old	22 (39.2%)
51-60 years old	13
61-70 years old	11
>70 years old	3
Total	56

According to the initial thyroid FNAB result, 1 case was interpreted as unsatisfactory (I), 20 cases were interpreted as benign (II), 1 case was interpreted as atypia (III), no case interpreted as follicular lesions of undetermined significance (IV), 3 cases were interpreted as suspicious for malignancy (V), and 31 cases as malignant (VI). After being reviewed, turned out 7 benign cases were recategorized as non-diagnostic (I), 2 benign (II) cases were recategorized as atypia (III), and all 3 suspicious for malignancy cases were moved to malignant criteria (VI) (Table 2).

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DOI: 10.55816/mpi.v34i1.624

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Table 2. FNAB results of 56 patients with post-operative diagnosis papillary thyroid carcinoma

FNAB result	Initial examination	Reviewed examination
Non diagnostic (I)	1 (1.7%)	9 (14.9%)
Benign (II)	20 (35.7%)	10 (17.8%)
Atypia (III)	1 (1.7%)	3(5.3%)
Follicular lesion of undetermined significance (IV)	0	0
Suspicious for malignancy (V)	3 (5.3%)	0
Malignant (VI)	31 (55.3%)	34 (62%)
Total	56	100

The smallest tumor size that we observed in non-diagnostic category was 0.3 cm, with 8.5 cm being its biggest tumor diameter. Most of sample that fell into benign category has <1 cm size (50% cases), with 0.4 cm being the smallest diameter. Most malignat category has >6 cm tumor size (35.3% cases), with 10.8 cm being the biggest diameter (Table 3).

Table 3. Biggest tumor diameter observed in post-operative thyroid specimens.

Biggest tumor diameter (cm)	ND (9)	Benign (10)	Atypia (3)	FLUS (0)	Suspicious (0)	Malignant (34)	Total
	I	II	III	IV	V	VI	n
<1	3	5	1			0	9
1	2	1	0			1	4
2	3	1	1			0	5
3	0	1	0			3	4
4	0	1	0			6	7
5	0	0	0			5	5
6	0	1	0			7	8
>6	1	0	1			12	14
	9	10	3			34	34

We then describe features in the non-malignant result of the FNAB, each looking into adequacy of follicular epithelia, presence of obscuring blood, abundant colloid matter, cyst macrophage, hipercellularity, atypic cells, architectural atypia (papillary fronds, vascular stalk, anatomical edge), overlapping nuclei, intranuclear inclusion, nuclear groove, inflammatory cells, and other feature squamous metaplasia & psamomma bodies) (Table 4).

Table 4. Cytopathology feature of all FNAB specimens.

	ND (9)	Benign (10)	Atypia (3)	FLUS (0)	Suspicious (0)	Malignant (34)	Total
	I	II	III	IV	V	VI	n
Obscuring blood	9	0	0			0	8
Inadequate follicle cells	9	7	0			0	8
Abundant colloid	0	10	3			0	13
Cyst macrophage	0	10	2			5	17
Normal follicle cells	8	10	2			0	20
Inflammatory cells	2	0	1			0	3
Cell atypia	0	0	3			34	37
Hipercellularity	0	0	0			34	34
Microfollicle feature	0	0	0			2	2
Architectural atypia	0	0	2			34	36
Overlapping nuclei	0	0	2			34	36
Nuclear groove	0	0	0			34	34
Intranuclear inclusion	0	0	0			34	34

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The most common feature of PTC features in our sample were cell atypia. architectural atypia, and overlapping nuclei. All of the feature from non-diagnostic criteria (I) was obscuring blood and inadequate number of follicle cells. All of cases from benign category (II) showed abundant spread of colloid matter and abundant cyst macrophages with few normal follicle epithelial cells. No cytological atypia was observed. 2 cases from atypia category (III) showed mild architectural atypia (papillary structure) and overlapping nuclei, with very few atypical cells (enlarged nuclei with irregular border), but lacking nuclear characteristic of PTC. 3 cases from suspicious of malignancy (V) were re-classified as malignant. These cases showed architectural atypia, including papillary frond, hyper cellularity, and presence of atypia cells with overlapping nuclei but very few nuclear inclusions. All of malignant category (VI) showed typical PTC feature (Figure 1).

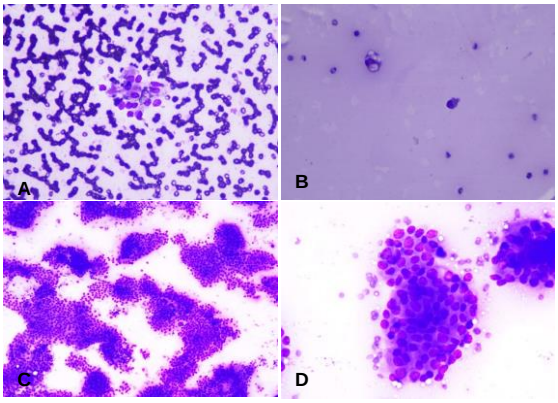

Figure 1. A. Non diagnostic smear (I), with obscuring blood and inadequate cluster of follicle epithelial cell (400 times). B. Benign, colloid nodule (II) showed hypo cellular smear with abundant colloid matter and cyst macrophages (400 times). C. Malignant smear consistent with PTC showed hyper cellular smear, papillary architecture with anatomical edge (200 times), and D) atypical cell with overlapping nuclei, intranuclear inclusion and nuclear groove (400 times).

DISCUSSION

Thyroid nodules can be caused by different benign and malign disorders. Initial assessment of the patients with a thyroid nodule includes a detailed history and physical examination. Thyroid ultrasound is performed to confirm the presence of nodules, the size, and characteristic of the nodule. The next step is a FNA biopsy. It may be performed by palpation or with ultrasound guidance. In this study, all FNABs were done by palpation. FNAB is recommended for the thyroid nodules larger than 1 cm; it is not usually performed on nodules smaller than that.[8]

In this study we have 9 cases of non-diagnostic criteria (14.9%), 3 of them have <1 cm tumor size. Based on Bethesda category suggestion, repeat FNAB with USG guidance should be done, because non diagnostic result has 5-10% risk of malignancy.[9] Some nodules remain persistently non diagnostic even after USG guidance. Excision is considered for persistently non diagnostic nodules. For bigger nodule, possible factors that might influence non diagnostic include absence of USG report/ imaging and presence of cystic area or other lesion such as adenomatous goitre that lead to the inaccurate sampling.[9,10] In our initial result, only 1 case was categorized as non-diagnostic (I). Upon review, we then found 7 benign (II) specimens lacking adequate follicle cells with obscuring blood, so we ended up recategorized them as non-diagnostic (I). This categorization is very important because it carries different next plan of care for these patients.

The AUS (III) or FLUS (IV) subgroup is a heterogeneous category that includes cases in which the cytological findings are not convincingly benign, yet the degree of cellular or architectural atypia is not sufficient enough for an interpretation of follicular neoplasm.[12] The Bethesda consensus publication estimates that such a nodule would be associated with a low risk of malignancy (5–15%) and, in the absence of other suspicious features, could be managed with a repeat FNAB.[13] In contrast to the Bethesda recommendations, the guidelines released by the American Association of Clinical Endocrinologists/Associazione Medici Endocrinology/European Thyroid Association (AACE/AME/ETA) Task Force combine Bethesda Categories III and IV (both defined as indeterminate). This group recommends surgery in most instances, with observation only in cases with favourable clinical, cytologic, and sonographic features.

In this study, we initially had 1 case of atypia (III), upon review, we then moved 2 cases of benign category into atypia. 2 of them had abundant colloid matter, cyst macrophages, and few atypical cells with overlapping nuclei (Figure 2). It is important to acknowledge that this study was based on retrospective review of primary pathology reports. As such, the varying reporting practices of individual cytopathologists may have adversely affected the power of the study to detect the importance of various qualifiers in AUS or FLUS.

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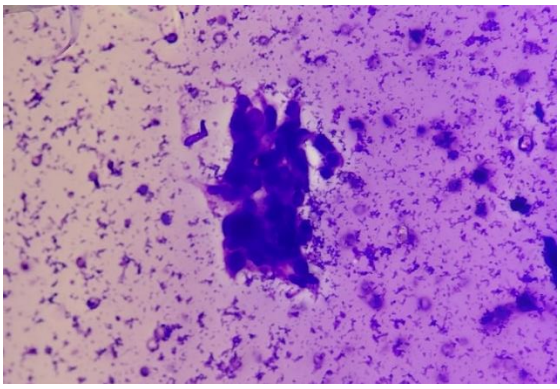

Figure 2. Cluster of cells with enlarged and overlapping nuclei with abundant colloid background and cyst macrophages (400 times) that was initially diagnosed as colloid nodule.

Study by Ho et al revealed that the risk of malignancy in AUS/FLUS thyroid nodule is higher than estimated by Bethesda category (26.6-37.8%). The appropriate level of risk to assign to Bethesda Category III (AUS/FLUS) nodules remains ambiguous. Shi et al found that eliminating the use of AUS/FLUS as a diagnosis considerably decreased FNA sensitivity, increasing false positive and false negative rates. Nevertheless, the exact risk of malignancy has been unclear, as many AUS/FLUS nodules are observed with no pathologic confirmation available.[14]

In this study we have 10 cases of misdiagnosis (17.8%) result that were being classified as benign (II). Lesion that fell under this category include nodular goitre, colloid nodule, Grave's disease, Hashimoto thyroiditis, and sub-acute thyroiditis. Most of the tumor size in benign category was <1 cm, thus it may affect the accuracy of the FNAB. A study comparing USG imaging with FNAB result stated that sub-centimetre nodules are significantly associated with the risk of malignancy.[10] A study conducted by Iliopoulos et al showed 1.53% rate of malignancy, with PTC being the most common subtype. According to literature, 70% thyroid FNAB were categorized as benign (II), with 8-14% false negative rate based on surgical series report. Specimen related problems such as inadequate sampling is responsible for the majority of false negative diagnosis. Other probable factors include low quality slide preparation and lack experience of cytopathologists.[15]

Another factor is the size of the nodule. Studies point out that nodules greater than 4 cm are more prone to false positive FNAB, with false positive rate reaching 17-19%. Kim, et al stated that the false negative rate is higher in larger nodule, especially >4 cm size.[16] In this study, 34 cases of histologically proven PTC diagnosis has >4 cm size, and 2 of them had benign FNAB result. The Bethesda system recommendation on benign category is to do the clinical and USG follow up.[11] Repeated FNAB of initially benign result has been proven to decrease the false negative rate from 17% to 11%. In cases in which malignant cells constitute a portion of a mass, repeat FNAB can be a viable alternative. However, when a thyroid nodule is benign on both initial and repeat FNAB, the likelihood that it is a truly benign nodule is nearly 100%. Surgical treatment may be considered if the nodule had suspicious ultrasonography feature, despite benign cytology report.[15, 16]

Three cases of suspicious of malignancy (V) were reclassified as malignant (Figure 3). These cases showed architectural atypia, including papillary frond, hyper cellularity, and presence of atypia cells with overlapping nuclei but very few nuclear inclusions. A study by Punthakee, et al revealed that nuclear pseudo inclusion only found in 33 from 57 FNAB result of PTC (sensitivity 57%, specificity 33%).

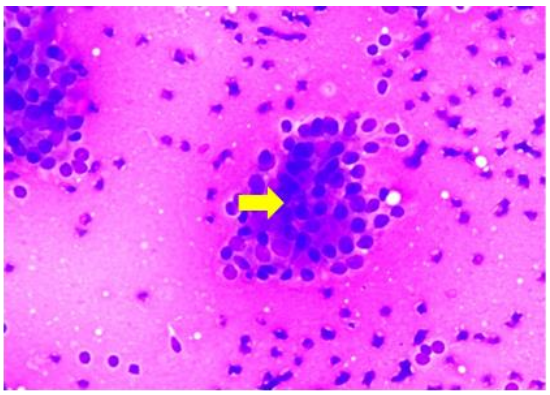

Figure 3. Specimen initially diagnosed as suspicious of malignancy (V) was recategorized as malignant (VI). It had feature of papillary frond, hyper cellularity, overlapping nuclei, and nuclear groove but nuclear inclusion is hard to find (arrow) (400 times).

In conclusion, the majority of FNAB diagnoses are in line with the histopathological result (62%), consistent with Bethesda category VI, which showed cell atypia. architectural atypia, and overlapping nuclei. Most cases of misdiagnosis fell into the benign category (17.8%), with abundant colloid and cyst macrophage being the most common feature.

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ACKNOWLEGDEMENT

The authors are grateful for support from the director and research and development unit Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests.

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