

ORIGINAL

## Reappraisal of “cyst fluid only” on thyroid fine-needle aspiration cytology

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**Abstract.** According to the Bethesda System for Reporting Thyroid Cytopathology (BSRTC), cyst fluid only (CFO) cases are classified in the non-diagnostic category. To date, no large study focusing on CFO has been conducted. To reassess the diagnostic significance of CFO, we compared CFO nodules with non-diagnostic nodules excluding CFO (ND-other). We reviewed the conventional thyroid smears of 715 CFO and 766 ND-other nodules. We compared the timing of and findings at re-aspiration, the histology of resected specimens, and the proportion of malignant nodules between the two groups. Re-aspiration was performed in 9.0% of CFO and 23.8% of ND-other cases. In 12.5% of CFO and 49.4% of ND-other cases, the interval between the first and second aspirations was <3 months. Despite this, there were no cases in which cytological interpretation was complicated by the first aspiration. Overall, 77 CFO nodules (10.8%) were surgically resected; 14 were malignant. In all cases in which re-aspiration cytology revealed malignancy, the initial ultrasound interpretation was a high or intermediate suspicion pattern. The proportion of malignancies subsequently diagnosed in nodules initially classified as CFO and ND-other was 2.0% and 5.6%, respectively ( $p < 0.01$ ). As CFO and ND-other thyroid nodules have different clinical management and malignancy rates, we would like to assert that CFO and ND-other nodules should be separated, and that the former should be considered diagnostic. In terms of clinical management, we recommend that only CFO cases with concerning features on ultrasound undergo re-aspiration.

**Key words:** Bethesda System, Non-diagnostic, Unsatisfactory, Cyst fluid only, Thyroid

**THE BETHESDA SYSTEM** for Reporting Thyroid Cytopathology (BSRTC) was developed to address terminology and other issues related to thyroid fine-needle aspiration cytology (FNAC) [1, 2]. According to the system, recommended diagnostic categories are classified into six groups: “Nondiagnostic or Unsatisfactory (ND/UNS)”, “Benign”, “Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance (AUS/FLUS)”, “Follicular Neoplasm or Suspicious for a Follicular Neoplasm (FN/SFN)”, “Suspicious for Malignancy (SFM)”, and “Malignant”. ND/UNS applies to specimens that are unsatisfactory owing to the following: 1. Fewer than six groups of well-preserved, well-stained follicular cell groups with ten cells each; 2. Poorly prepared, poorly stained, or obscured follicular cells; or 3. Cyst fluid, with or

without histiocytes, and fewer than six groups of ten benign follicular cells. Cystic papillary thyroid carcinoma (PTC) cannot be excluded in the last “cyst fluid only (CFO)” scenario, resulting in these cases being classified as non-diagnostic [1]. In Japan [3], however, CFO cases have been included in the “Benign” category, as described in the guidelines of the Papanicolaou Society of Cytopathology for the Examination of Fine-Needle Aspiration Specimens from Thyroid Nodules [4]. Whether CFO should be classified as non-diagnostic remains controversial. To date, no large study has focused on CFO cases. Our objective, therefore, was to reassess the diagnostic significance of CFO, by comparing CFO nodules with non-diagnostic nodules excluding CFO (ND-other), hypothesizing that CFO should be a diagnostic category separate from “non-diagnostic”.

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### Materials and Methods

This study involved a retrospective examination of FNAC results from thyroid gland nodule

specimens at Kuma Hospital from January to December 2007. During this period, specimens from 10,036 thyroid nodules were sent for FNAC. Each aspirate was performed using a 22-gauge needle under ultrasound-guided real-time visualisation of needle placement in the target nodule. All nodules were analysed by ultrasound examination, and the indication for FNAC was based on the 2015 American Thyroid Association (ATA) guidelines [5]. We reviewed the conventional smears stained using the Papanicolaou method. Of these, 1,481 (14.8%) were “ND/UNS”, based on the criteria of the BSRTC, stated above. The ND/UNS samples were divided into two groups: the third scenario (CFO) and the others (ND/UNS excluding CFO, referred to as “ND-other”). Of the 1,481 nodules classified as non-diagnostic, 715 (48.3%) were CFO and 766 (51.7%) were ND-other. When ultrasonographic interpretation was of a high or intermediate suspicion pattern (ATA guidelines) [5], re-aspiration was performed, regardless of the cytology reports. The remaining nodules were followed by sonographic examination. Resection and histological examination of 76 (10.6%) nodules classified as CFO and 103 (13.4%) as ND-other took place during the 8-year follow-up period. We compared the rates of re-aspiration, the histology results of resected specimens, and the risk of malignancy between the two groups. Statistical significance of the data was determined using Fisher’s probability test;  $p < 0.05$  was considered statistically significant.

## Results

### Re-aspiration

The rates of repeated aspiration of CFO and ND-other nodules were 9.0% (64 nodules) and 23.8% (182 nodules), respectively (Table 1). The interval between the first and second aspirates was less than 3 months in 8 (12.5%) CFO nodules and 90 (49.4%) ND-other nodules. Review of the FNAC results of these specimens showed a large number of fibroblasts that might have originated from granulation tissue secondary to the first aspiration in 1 (12.5%) of the CFO and 6 (6.7%) of the ND-other nodules. Cytological interpretation of the repeat specimen was not complicated by the first aspiration in any of the cases. The cytology results of the re-aspirated non-diagnostic nodules are shown in Table 2. More than half of the re-aspirated nodules (56.3% of CFO

**Table 1** Details of Nondiagnostic or Unsatisfactory nodules undergoing re-aspiration

	ND/UNS n=1,481	CFO n=715	ND-other n=766
Re-aspiration performed	246 (16.6%)	64 (9.0%)	182 (23.8%) *
Interval			
Less than 2 weeks	78 (31.7%)	7 (10.9%)	71 (39.0%)
2 weeks to 3 months	20 (8.1%)	1 (1.6%)	19 (10.4%)
3 months to 1 year	50 (20.3%)	16 (25.0%)	34 (18.7%)
1 year to 3 years	46 (18.7%)	20 (31.3%)	26 (14.3%)
More than 3 years	52 (21.1%)	20 (31.3%)	32 (17.6%)

ND/UNS, Nondiagnostic or Unsatisfactory; CFO, cyst fluid only; ND-other, Nondiagnostic or Unsatisfactory excluding CFO. \*  $p < 0.01$ .

**Table 2** Comparison of cytological results of Nondiagnostic or Unsatisfactory nodules at initial- and re-aspiration

Re-aspiration	Initial aspiration		
	ND/UNS	CFO	ND-other
ND/UNS	53 (21.5%)	17 (26.6%)	36 (19.8%) *
CFO	25 (10.2%)	17 (26.6%)	8 (4.4%) *
ND-other	28 (11.4%)	0 (0%)	28 (15.4%)
Benign	163 (66.3%)	36 (56.3%)	127 (69.8%)
AUS/FLUS	10 (4.1%)	4 (6.3%)	6 (3.3%)
FN/SFN	5 (2.0%)	2 (3.1%)	3 (1.6%)
SFM	1 (0.4%)	1 (1.6%)	0 (0%)
Malignant	14 (5.7%)	4 (6.3%)	10 (5.5%)
Total	246 (100%)	64 (100%)	182 (100%)

ND/UNS, Nondiagnostic or Unsatisfactory; CFO, cyst-fluid only; ND-other, Nondiagnostic or Unsatisfactory excluding CFO; AUS/FLUS, Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance; FN/SFN, Follicular Neoplasm or Suspicious for a Follicular Neoplasm; SFM, Suspicious for Malignancy. \*  $p < 0.01$ .

and 69.8% of ND-other) were classified as “Benign”. Seventeen (26.6%) re-aspirated CFO and 28 (15.4%) ND-other nodules did not change their original classification category, while the malignancy rates of CFO and ND-other nodules in re-aspirated specimens were 6.3% and 5.5%, respectively. There were no statistical differences between CFO and ND-other nodules in terms of the rates of benign and malignant findings on repeated FNAC. Of the 15 ND/UNS nodules that were reported as “Malignant” or “SFM” on re-aspiration, 11 were “high suspicion” on ultrasound examination (Table 3 and Fig. 1). The ultrasound interpretation of the remaining cases was “intermediate suspicion”.

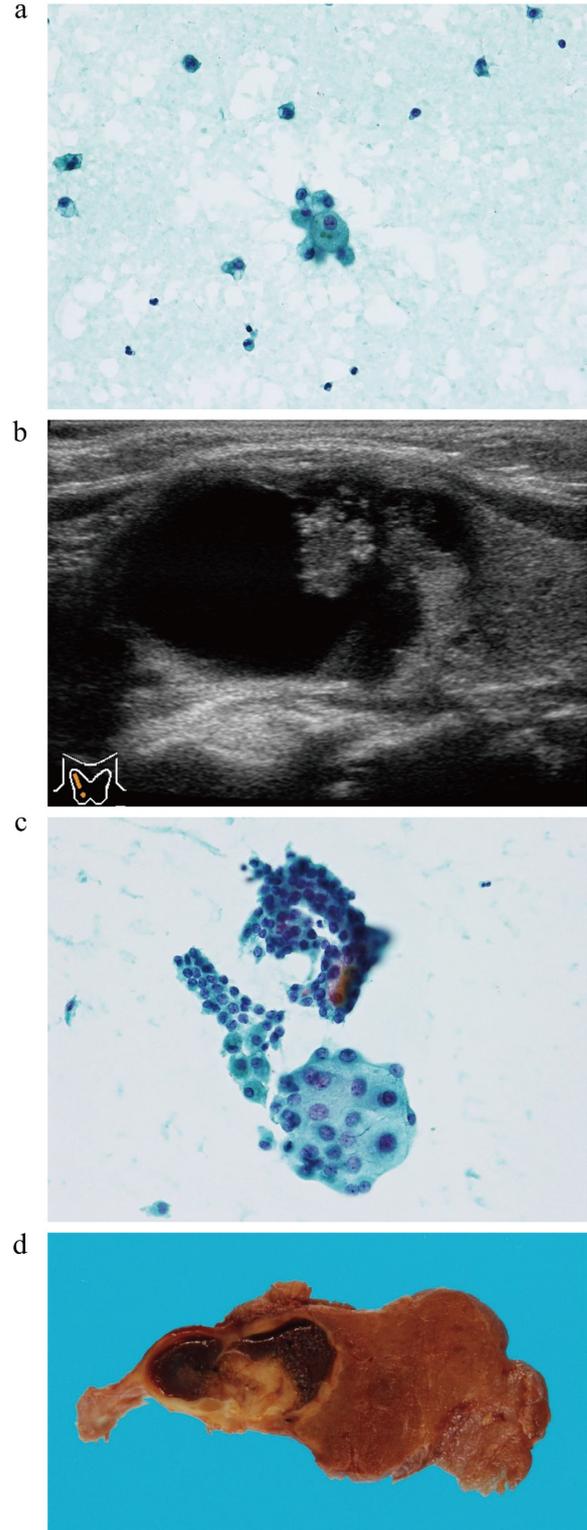
**Histology of resected specimens**

Seventy-seven (10.8%) of 715 CFO and 103 (13.4%) of 766 ND nodules excluding CFO nodules underwent thyroidectomy. The definitive indications for surgery in the CFO and ND-other nodules were “AUS/FLUS”, “SFM”, or “Malignancy” in re-aspiration cytology. Fifteen cases that were interpreted as high or intermediate suspicion patterns on ultrasound examination were included in the cases. The remaining reasons for thyroidectomy were an association with another thyroid carcinoma, Plummer’s disease, displacement of the trachea, surgery for parathyroid adenoma, ineffective drainage, or the patient’s wishes. Most of the CFO nodules (76.6%) and ND-other nodules (52.4%) were adenomatous goitre (Table 4). Fourteen (18.2%) surgically treated CFO nodules and 40 (38.8%) surgically treated ND-other nodules were malignant. Fifty of 54 malignant tumours (92.6%) were PTC. Three of them were cystic PTC, and were diagnosed as PTC in the re-aspiration (Fig. 1c). In 9 of 38 ND-other nodules that were histologically PTC, the tumours were predominantly calcified (Fig. 2).

**Table 3** Ultrasound interpretation of Nondiagnostic or Unsatisfactory nodules reported as Malignant or Suspicious for Malignancy at re-aspiration

	CFO n=5	ND-other n=10
Low suspicion, very low suspicion, or benign	0	0
Intermediate suspicion	0	4
High suspicion	5	6

CFO, cyst fluid only; ND-other, Nondiagnostic or Unsatisfactory excluding CFO.



**Fig. 1** Cystic papillary thyroid carcinoma  
**a.** First aspiration was classified as “cyst fluid only”.  
**b.** Ultrasound interpretation was cystic papillary thyroid carcinoma.  
**c.** Re-aspiration showed papillary thyroid carcinoma.  
**d.** Solid nodule was seen in cystic lesion.

**Table 4** Histology of resected Nondiagnostic or Unsatisfactory nodules

	CFO (n=77)	ND-other (n=103)
Chronic thyroiditis	0 (0 %)	2 (1.9 %)
Dyshormonogenetic goitre	0 (0 %)	1 (1.0 %)
Burn out tumour	0 (0 %)	2 (1.9 %)
Adenomatous goitre	59 (76.6 %)	54 (52.4%)
Follicular adenoma	2 (2.6 %)	1 (1.0 %)
Follicular tumour-UMP	0 (0 %)	2 (1.9 %)
Papillary carcinoma	12 (15.6 %)	38 (36.9 %)
Conventional	12	35
With massive calcification	0	9
Cystic	3	0
Follicular variant	0	3
Follicular carcinoma	2 (2.6 %)	1 (1.0 %)
Mixed medullary and follicular carcinoma	0 (0 %)	1 (1.0 %)
Parathyroid adenoma	0 (0 %)	1 (1.0 %)
Not detected	2 (2.6 %)	0 (0 %)

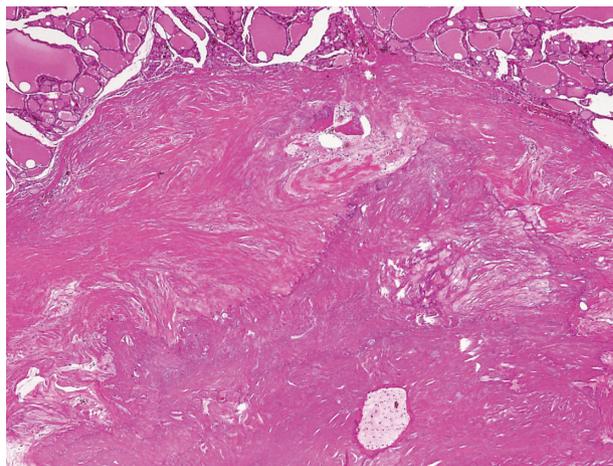
CFO, cyst-fluid only; ND-other, Nondiagnostic or Unsatisfactory excluding CFO; UMP, uncertain malignant potential.

### ***Incidence of malignancy***

Of the 715 CFO nodules, 14 (2.0%) were histologically confirmed to be malignant. In total, 43 (5.6%) of the 766 ND-other nodules ( $p < 0.01$ ) were identified as malignant, but, in three of them, diagnoses of malignancy were made on FNAC examination, and not on histologic examination. In two of the ND-other nodules diagnosed as malignant in the second FNAC, active surveillance was conducted because of low-risk papillary thyroid microcarcinoma. Therefore, histological confirmation of the diagnosis was not performed. The remaining one case was referred to another hospital without resection.

## **Discussion**

Cytological interpretation of thyroid FNAC specimens that consisted of cystic contents only, including only macrophages, remains controversial. CFO specimens are traditionally reported as benign [6]. At the National Cancer Institute Thyroid FNA State of the Science Conference in 2007 [7], because the possibility of cystic PTC cannot be excluded in CFO cases, it was decided that such cases should be classified as a subset of "ND/UNS". After the BSRTC was proposed, based on the conference proceedings, many laboratories adopted that reporting system. However, CFO cases accounted for more than half of those classified as non-diagnostic [8, 9], which is significant



**Fig. 2** Papillary thyroid carcinoma associated with massive calcification

The first aspiration for the nodule was Nondiagnostic or Unsatisfactory.

since an estimated 18–42% of aspiration cases are non-diagnostic [8–11]. It is generally recommended that the incidence of non-diagnostic specimens should ideally be  $< 10\%$  of thyroid FNAs, excluding CFO [2]. Therefore, we need to calculate the incidence of both CFO and ND-other, but doing this is complicated, given that CFO and ND-other exist in the same category.

The BSRTC recommends that nodules with an initial ND/UNS result be re-aspirated. However, follow-up strategies for CFO specimens from cystic nodules are different to those for solid nodules. When a nodule is determined to be a simple unilocular cyst on ultrasound imaging, the specimen may be considered clinically adequate, even if reported as non-diagnostic. Hence, the re-aspiration rate of CFO nodules should be lower than that of ND-other. It has been reported that the re-aspiration rates of CFO and ND-other nodules are 54.7% and 56.8%, respectively [12, 13]. In our series, re-aspiration rates of CFO and ND-other nodules were 9.0% and 23.8%, respectively ( $p < 0.01$ ). We recommend that these two different cytological findings, that have different clinical management, should be classified into separate categories.

A  $\geq 3$ -month interval between initial and repeated aspiration is generally recommended to prevent false positive interpretation due to reactive/reparative changes [1]. If carcinoma is suspected based on clinical or ultrasound findings, a shorter waiting period may be

appropriate [7]. In our series, the interval between aspirations was <3 months in 12.5% of nodules classified as CFO and 49.4% of those as ND-other. Nevertheless, there were no cases in which cytological interpretation was complicated by the first aspiration. This is consistent with findings by Lubitz *et al.*, who reported that 63% of the cases in their study classified as non-diagnostic had a repeated aspiration before 3 months, and that the timing of the second aspiration did not significantly affect the diagnostic yield [14]. According to a report by Orija [13], the median interval between aspirations being performed was 4 weeks. We think that the interval between repeated aspirations in cases with initial non-diagnostic reports should be guided by the ultrasound findings. In addition, it is noteworthy that the interval between aspirations differed between those reported as CFO and ND-other.

In our study, 6.2% and 5.5% of CFO and ND-other nodules re-aspirated were “Malignant”, respectively, while 56.8% and 69.8%, respectively, were “Benign”. In short, no significant difference was found. The results do not conclude that CFO and ND-other nodules should be classified into same category. In all cases that were identified as being “Malignant” by repeated FNAC, the initial ultrasound interpretation was high or intermediate suspicion pattern. This may have introduced sampling bias. In addition, the management of CFO should be considered in conjunction with the ultrasound findings, as recommended by ATA guidelines [5]. The following factors are important in the clinical management of CFO: detection of minute nodules within the thyroid cystic lesions, aspiration of the nodules under ultrasound guidance, and not overlooking a small number of carcinoma cells present in the fluid smears [15-17].

As non-diagnostic cases are mostly benign and rarely undergo surgical resection, it is difficult to estimate the malignancy rates accurately. However, it has been reported that they range from 0% to 35% [18]. The BSRTC does not make reference to these rates [1]. According to a report by MacDonald and Yazdi, the malignancy rates of CFO and ND-other nodules were 0% and 4.2%, respectively [8]. In contrast, Renshaw reported no difference in the rates (3.9% in each group) [10]. Garcia-Pascual *et al.* reported that the malignancy rate of CFO nodules was higher (14.3%) than that of ND-other nodules (6.7%), but that this difference was not statistically significant [19]. In our study, malignant rates in cases

classified as CFO and ND-other nodules were 2.0% and 5.6%, respectively, which were significantly different ( $p<0.01$ ). The malignant rate of CFO corresponds to that of the “Benign” category (0–3%) of the BSRTC [1]. Therefore, we propose that the clinical management of CFO and ND-other nodules should be different. According to the BSRTC, ND nodules should be re-aspirated, but CFO nodules should be considered in conjunction with the ultrasound findings [5]. We agree with this recommendation. Clinical management of CFO could conform to the “Benign” category of the BSRTC.

In Japan, the reporting system proposed by the Papanicolaou Society of Cytopathology for the examination of fine-needle aspiration specimens from thyroid nodules [7] has been adopted. In the reporting system, CFO is included in the “Benign” classification. Currently, almost all Japanese clinicians are averse to accepting CFO as non-diagnostic [20]. Our study demonstrated that CFO and ND-other nodules differ in clinical management, in the interval before re-aspiration, and in malignancy rates. Therefore, we would like to assert that CFO and ND-other nodules should be separated, and the former should be considered diagnostic. Thus, the Japanese Society of Thyroid Surgery established a novel reporting system [21], which is commonly applied in Japan and is compared with those of the BSRTC [1], Royal College of Pathologists [22], and Italian Society for Anatomic Pathology and Cytology-Italian Association of Thyroid [23] in Table 5. According to the 2015 ATA guidelines [5], as purely cystic nodules are very unlikely to be malignant, FNAC is not indicated. Therefore, CFO samples in Western countries are mostly obtained from cystic nodules with suspicious solid components. On the other hand, FNAC is considered in Japan for purely cystic nodules with a maximum dimension >2 cm [24]. This difference in the indication for FNAC may influence the categorization. The Japanese reporting system handles CFO as an independent diagnostic category, and our results support the validity of this. On clinical management, we favour a proposal from the BSRTC that CFO cases with concerning ultrasound findings should be re-aspirated [1].

## Disclosure

None of the authors have any potential conflicts of interest associated with this research.

**Table 5** Reporting system for thyroid fine needle aspiration

JSTS [21] (Japan, 2015)	BSRTC [1] (USA & Canada, 2009)	RCPATH [22] (UK, 2016)	SIAPEC-AIT [23] (Italy, 2014)
Unsatisfactory	ND/UNS	Thy1: Non-diagnostic for cytological diagnosis Thy1c: Non-diagnostic for cytological diagnosis-cystic lesion	TIR1: Nondiagnostic TIR1C: Nondiagnostic/cystic
Cyst fluid			
Benign	Benign	Thy2: Non-neoplastic Thy2c: Non-neoplastic cystic lesion	TIR2: Nonmalignant/benign
Undetermined significance	AUS/FLUS	Thy3a: Neoplastic possible, atypia/ nondiagnostic	TIR3A: Low-risk indeterminate lesion
Follicular neoplasm	FN/SFN	Thy3f: Neoplastic possible, suggesting follicular neoplasm	TIR3B: High-risk indeterminate lesion
Suspicious for malignancy	SFM	Thy4: Suspicious for malignancy	TIR4: Suspicious for malignancy
Malignant	Malignant	Thy5: Malignant	TIR5: Malignant

JSTS, Japanese Society of Thyroid Surgery; BSRTC, the Bethesda System for Reporting Thyroid Cytopathology; UK RCPATH, UK Royal College of Pathologists; SIAPEC-AIT, Italian Society of Anatomic Pathology and Diagnostic Cytology; ND/UNS, Nondiagnostic or Unsatisfactory; AUS/FLUS, atypia of undetermined significance/follicular neoplasm of undetermined significance; FN/SFN, Follicular Neoplasm/Suspicious for a Follicular Neoplasm; SFM, Suspicious for malignancy.

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