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ORIGINAL

Second opinion in thyroid fine-needle aspiration biopsy by the Bethesda System

Jae Hyun Park[1)], Hyun Ki Kim[2)], Sang-Wook Kang[3)], Jong Ju Jeong[3)], Kee-Hyun Nam[3)], Woong-Youn Chung[3)] and Cheong Soo Park[3)]

[1)]*Department of Surgery, Eulji University College of Medicine, South Korea*
[2)]*Department of Pathology, Yonsei University College of Medicine, South Korea*
[3)]*Department of Surgery, Yonsei University College of Medicine, South Korea*

Abstract. The present study was designed to determine the impact of secondary review of thyroid fine-needle aspiration (FNA) biopsy on surgical management. A retrospective review of patients referred to our institution with a thyroid FNA biopsy was conducted. Cytologic diagnoses from the report at our center and the referring institution were re-categorized by the Bethesda System for Reporting Thyroid Cytopathology. The rate of diagnostic disagreement was evaluated between Primary Diagnosis (PD) and Second Opinion Diagnosis (SOD), and the clinicopathologic correlations and the number of cases that prompted changes in treatment as a result of diagnostic disagreement were analyzed. 1499 patients meeting our study criteria were enrolled in this study. Diagnostic disagreement comprised 394 cases (26.3%). In the case of diagnostic disagreement, SOD was supported on clinicopathologic follow-up in 271 cases (68.8%), of which a change in management was made in 54 (13.7%) cases, and PD was supported in 93 (23.6%) cases, of which a change in management was made in 13 (3.3%) cases. By the second opinion, 65 (4.5%) patients received proper management, and 14 (1.0%) patients received superfluous management. Wide use of secondary cytopathologic review of thyroid FNA specimens from referring institutions was recommended.

Key words: Second opinion, Thyroid fine-needle aspiration biopsy, Bethesda System

FINE-NEEDLE ASPIRATION (FNA) of the thyroid, which is a rapid and cost-effective test, has been recommended as the initial diagnostic test in evaluation of thyroid nodules and is widely accepted as a valuable method for distinguishing neoplastic from nonneoplastic nodules and identification of patients requiring thyroid surgery [1-8]. Sensitivity of thyroid FNAs has been reported in the literature as ranging from 65-99%, and its specificity from 72-100% [2, 9-11]. Sensitivity and specificity of this screening test are dependent on the experience of both the radiologist and the cytopathologist, as the aspirator and the interpreter. According to the result of thyroid FNAs, the patient may be sent for a major procedure at the referral hospital or the patient may seek a second opinion from a physician at another clinic/hospital before or even after initiating a treatment program. Many institutions practice routine review of cytopathologic slides before surgical decision making if the patient initially underwent evaluation at another medical center. However, there is little information available regarding the usefulness of such a practice, which not only incurs additional time and costs, but can also delay curative surgery when it is needed. Although there are few data on the result of a second opinion of cytopathology materials, Abt *et al*. reported that cytology may have error rates as high as 21% [12] and Tan *et al*. reported that the discordant rate of thyroid FNAs was 18%, and, among these cases, surgical management was changed for 30% of patients [13].

The purpose of this study was to ascertain the result of the second opinion in thyroid FNA biopsy by assessing the frequency of discordant diagnoses between the referring institutions and our center, and determining the clinical impact of second opinions, and whether or not they result in change of management.

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Correspondence to: Woong Youn Chung, Department of Surgery, Yonsei University College of Medicine, C.P.O. Box 8044, 250 Seongsanno, Seodaemun-gu, Seoul 120-752, South Korea
E-mail: woungyounc@yuhs.ac
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Patients and Methods

This retrospective analysis of medical records was approved by the institutional review board of Yonsei University College of Medicine, Seoul, Korea and required neither patient approval nor informed consent. Between January 1, 2009, and December 31, 2009, cytology slides from1674 patients referred with an outside cytopathologic diagnosis were reviewed by our cytopathologists. Cytologic diagnoses from the report at our center and the referring institution were re-categorized as Nondiagnostic or Unsatisfactory (Category I), Benign (Category Ⅱ), Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance (Category Ⅲ), Follicular Neoplasm or Suspicious for a Follicular Neoplasm (Category IV), Suspicious for Malignancy (Category V), and Malignant (Category Ⅵ) by the Bethesda System for Reporting Thyroid Cytopathology [14].

Exclusion criteria included outside cases with missing paperwork, undetermined initial diagnosis, ambiguous diagnosis, as the original diagnosis was blank, in which the outside diagnosis stated ''case sent for outside opinion or pending consultation,'' in which only a differential diagnosis was given, in which a diagnosis posed a question, and in which the diagnosis was incomplete, and, thus, was not possible to classify into I of VI main categories, and less than 6-month follow up.

The final pathologic diagnosis of the thyroid was classified into benign, follicular neoplasm, as would be interpreted on FNA biopsy, and malignant categories. The final clinical diagnosis of cases who were not performed surgical management was obtained by the result of re-FNA biopsy and ultrasonography within a minimum of 6-month follow-up. The rate of diagnostic disagreement between the Primary Diagnosis (PD) and Second Opinion Diagnosis (SOD) and the clinicopathologic correlations were evaluated.

As the rational clinical management guideline that the Bethesda System recommends, patients in each of the categories were managed, such as “repeat FNA” in Categories I, Ⅲ, “clinical follow-up” in Category Ⅱ, “surgical lobectomy” in Category IV, and “near-total thyroidectomy or surgical lobectomy” in Categories V, Ⅵ [14]. The number of cases that prompted changes in treatment as a result of diagnostic disagreement was analyzed by a review of the electronic medical records in order to determine the clinical impact of the second opinion.

Results

A total of 1499 patients meeting our study criteria were enrolled in this study. The median age of the patients was 43 years (range 17 to 79 years). The study included 1253 (83.6%) women and 246 (16.4%) men. A surgical management was performed in 1383 patients. Pathologic results after surgical management are summarized in Table 1.

A total of 1105 (73.7%) cases showed diagnostic agreement between PD and SOD according to categorization by the Bethesda System. Diagnostic disagreement comprised 394 cases (26.3%). Table 2 shows the rate of diagnostic disagreement between PD and SOD. Rates of diagnostic disagreement were the lowest in Category Ⅵ (Malignant), at 7.4%, and the rates of diagnostic disagreement were the highest in Category Ⅲ (Atypia), at 89.7%.

Table 3 shows the clincopathologic correlation of FNA biopsy and the frequency of change in patient management in cases of diagnostic disagreement. In cases of diagnostic disagreement (n=394), SOD was supported on clinicopathologic follow-up in 271 (68.8%) cases, of which a change in management was made in 54 (13.7%) cases and PD in 93 (23.6%) cases, of which a change in management was made in13 (3.3%) cases. In 31 (7.9%) cases of diagnostic disagreement, neither the PD nor the SOD was supported; however, a change in management was made in 12 (3.0%) cases. One example was that the PD was “Category Ⅲ (Atypia)”

Table 1 Final pathologic diagnosis after surgical management

	N	%
Benign	22	1.6%
Adenomatous hyperplasia (AH)	15	
AH with Hurthle cell change	5	
Lymphocytic thyroiditis	1	
Hyalinizing trabecular adenoma	1	
Follicular Neoplasm	12	0.9%
Follicular adenoma	4	
Hürthle cell adenoma	2	
Follicular thyroid carcinoma	5	
Hürthle cell carcinoma	1	
Malignant	1349	97.5%
Papillary thyroid carcinoma	1344	
Medullary thyroid carcinoma	5	
Total	1383	100

Table 2 Diagnostic disagreement rate between primary diagnosis (PD) and second opinion diagnosis (SOD)

		Primary diagnosis (PD)	Second opinion diagnosis (SOD)	Diagnostic disagreement rate
Category I	(Nondiagnositc)	28 (1.9%)	65 (4.3%)	6/28 (21.4%)
Category II	(Benign)	51 (3.3%)	81 (5.4%)	12/51 (23.5%)
Category III	(Atypia)	46 (3.1%)	14 (0.9%)	40/46 (87.0%)
Category IV	(Follicular Neoplasm)	47 (3.1%)	16 (1.1%)	33/47 (70.2%)
Category V	(Suspicious, malignant)	300 (20.0%)	155 (10.3%)	227/300 (75.7%)
Category VI	(Malignant)	1027 (68.5%)	1168 (77.9%)	76/1027 (7.4%)
total		1499	1499	394/1499 (26.3%)

Table 3 Clincopathologic correlation of the FNA biopsy and frequency of management change by second opinion in cases of diagnostic disagreement

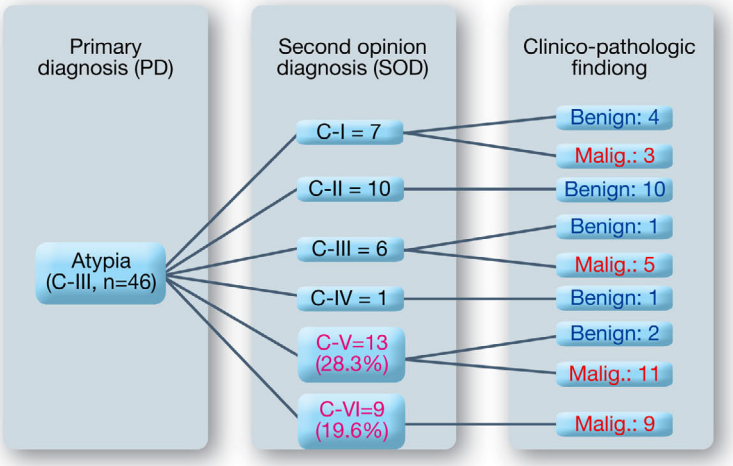
	total
PD and SOD with disagreement, but pathology or clinical follow-up supports SOD	271 (68.8%)
Change in patient management	54 (13.7%)
PD and SOD with disagreement, but pathology or clinical follow-up supports PD	93 (23.6%)
Change in patient management	13 (3.3%)
PD and SOD with disagreement, but pathology or clinical follow-up supports neither	31 (7.9%)
Change in patient management	12 (3.0%)
Total	394 (100%)
Change in patient management or therapy	79 (20.0%)

and the SOD was “Category I (Nondiagnostic)”; however, the result of the clinicopathologic follow-up was Category II (Benign). Management was not changed in this case, and re-FNA biopsy was performed. In another case, the PD was “Category III (Atypia)” and the SOD was “Category V (Suspicious, malignant)”; however, the result of the clinicopathologic follow-up was Category II (Benign). This case was changed in management from re-FNA biopsy to surgery by SOD. In 79 of 1499 (5.3%) cases, the SOD prompted a change in clinical management that was expected by PD.

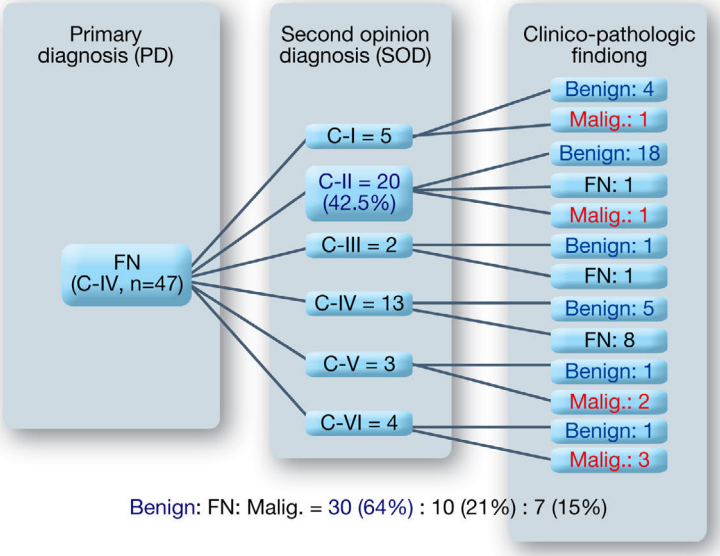
Cases prompting a change in management are summarized in Table 4. Frequencies of management change in Category VI (Malignant) and Category V (Suspicious, malignant) were low, at 6.7% and 0.5%, respectively; however, the frequencies of the management change in Category III (Atypia) and Category IV (Follicular Neoplasm) were higher than 30%.

Fig. 1 shows the flow diagram of the results of clinico-pathological correlation of Categories III (A), IV (B), and V (C) by the Bethesda System, which were relatively high in the diagnostic disagreement rate between PD and SOD, or the frequency of change in patient management. In 46 cases diagnosed as Category III in PD, the diagnoses were changed to Category V in 13 cases (28.3%) and Category VI in 9 cases (19.6%) on SOD. Follow-up clinico-pathological findings revealed malignancy in 28 cases (61%) in cases diagnosed as Category III in PD. In 47 cases diagnosed as Category IV in PD, the diagnosis was changed to Category II in 20 cases (42.5%) on SOD. Follow-up clinico-pathological findings revealed follicular neoplasm in 10 cases (21%) and benign in 30 cases (64%) in cases diagnosed as Category IV in PD. In 300 cases diagnosed as Category IV in PD, there were 227 (75.7%) cases of diagnostic disagreement between PD and SOD (Table 2); however, there were 20 cases (6.7%) of change in patient management (Table 4). This result was due to change in PD to Category VI in 198 cases (66%) on SOD. Follow-up clinico-pathological findings revealed malignancy in 284 cases (95%) in cases diagnosed as Category IV in PD.

A Category Ⅲ (Atypia)



B Category Ⅳ (Follicular neoplasm)



C Category V (Suspicious for malignancy)

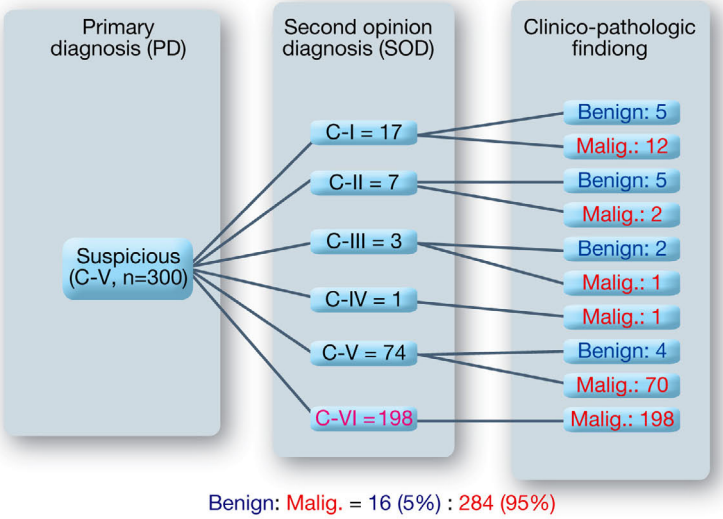


Fig. 1 Results of clinico-pathological correlation of categories Ⅲ (A), Ⅳ (B), and V (C) by the Bethesda System
FN: follicular neoplasm, C-: category, Malig.: malignancy

Table 4 Case prompting a change in management

Primary diagnosis (PD)	Second opinion diagnosis (SOD)	Pathologic diagnosis	Clinical diagnosis	Management chanage	N	Category total
Nondiagnositc	V	VI		FNAB → surgery	1	3/28 (10.7%)
(Category I)	VI	VI		FNAB → surgery	2	
Benign	I	II		F/U → FNAB (superfluous)	1	9/51 (17.6%)
(Category II)	I		II	F/U → FNAB (superfluous)	3	
	V	VI		F/U → surgery	2	
	VI	VI		F/U → surgery	3	
Atypia	II		II	FNAB → F/U	4	16/46(34.8%)
(Category III)	V	II		FNAB → surgery (superfluous)	1	
	V	VI		FNAB → surgery	5	
	VI	VI		FNAB → surgery	6	
Follicular	I		II	Surgery → FNAB → F/U	3	26/47 (55.3%)
Neoplasm	II		II	Surgery → F/U	16	
(Category IV)	III		II	Surgery → FNAB → F/U	1	
	III	IV		Superfluous FNAB	1	
	V	VI		Lobectomy → total thyroidectomy	2	
	VI	VI		Lobectomy → total thyroidectomy	3	
Suspicious,	I		II	Surgery → FNAB → F/U	4	20/300 (6.7%)
Malignant	I	VI		Superfluous FNAB	6	
(Category V)	II		II	Surgery → F/U	5	
	II	VI		Superfluous FNAB	1	
	III		II	Surgery → FNAB → F/U	2	
	III	VI		Superfluous FNAB	1	
(Category V: MTC)	V:PTC	VI:PTC		Total thyroidectomy → lobectomy	1	
Malignant	II		II	Surgery → F/U	3	5/1027 (0.5%)
(Category VI)	III		II	Surgery → FNAB → F/U	1	
	IV	IV		Total thyroidectomy → lobectomy	1	
				total	79	79/1499 (5.3%)

Discussion

FNA is one of the most widely used investigative tools in medicine. It is particularly important preoperatively for confirmation of the diagnosis to allow for planning and decision making in surgery. In the thyroid gland, FNA biopsy is the most accurate and cost-effective diagnostic test for evaluation of a patient with a thyroid nodule [15-21]. However, FNA is a procedure that is highly dependent on the skill of the individual performing the procedure and the ability of that individual to craft readable, well preserved smears that contain sufficient amounts of diagnostic cellular material lacking obscuring debris, excessive blood, air-drying artifacts, and other technical artifacts. In addition, interpretation of the nature of cell clusters can be difficult and is dependent on cytopathology expertise.

Further, until recently, there were no uniform criteria established for the various diagnostic categories and specimen adequacy [22, 23]. As a result, diagnostic inconsistencies exist among different laboratories as well as pathologists within the same laboratories. This problem causes difficulty in communicating the clinical implications of thyroid FNA results both to direct caregivers (endocrinologists and surgeons) and indirect caregivers (pathologists and radiologists) [24]. For this reason, in 2008, the National Cancer Institute (NCI) organized a conference of expert cytopathologists for the purpose of standardizing the diagnosis and reporting of thyroid FNAs. The committee proposed a six-category scheme for diagnosis and reporting of thyroid FNAs, which is often referred to as ‘‘the Bethesda System for Reporting Thyroid Cytopathology” [14]. Some have demonstrated that the Bethesda System for Reporting

Thyroid Cytopathology is excellent for reporting thyroid FNA [25] and can improve interlaboratory agreement in diagnosis of thyroid lesions and may lead to more consistent management approaches [26].

The current study attempted to assess the frequency of discordant diagnoses between PD and SOD and to determine the clinical impact of a second opinion by the Bethesda System for Reporting Thyroid Cytopathology, and reports of cytologic diagnosis from our center and the referring institution were re-categorized following published interpretation guidelines [14]. To the best of our knowledge, this is the first report to ascertain the result of the second opinion in thyroid FNA biopsy by the Bethesda System.

Twenty-eight cases (1.9%) were diagnosed as Category I in PD; however, 65 cases (4.3%) were diagnosed as Category I in SOD. This difference was due to inadequate numbers of follicular cells and poor preservation and fixation, leading to loss of chromatin details. In Category I, there were 6 cases (21.4%) of diagnostic disagreement upon SOD, and management changes were made in 3 cases (10.7%) diagnosed as Category V (1case) and Category VI (2 cases) in SOD, and, in surgical pathology, 3 cases were malignant.

Fifty-one cases (3.3%) were diagnosed as Category Ⅱ in PD; however, 81 cases (5.4%) were diagnosed as Category II in SOD. This difference was due to diagnostic disagreement between PD and SOD, as 10 cases (21.7%) of Category Ⅲ and 20 cases (42.5%) of Category Ⅳ in PD were diagnosed as Category II in SOD. In Category Ⅱ, there were 12 cases (23.5%) of diagnostic disagreement upon SOD, and management changes were made in 9 cases (17.6%) diagnosed as Category I (4case), Category V (2 cases), and Category VI (3 cases) in SOD, and, in the follow-up clinico-pathological finding, 4 cases were benign and 5 cases were malignant.

Forty-six cases (3.1%) were diagnosed as Category Ⅲ in PD; however, 14 cases (0.9%) were diagnosed as Category Ⅲ in SOD. This difference was due to a definite diagnosis upon SOD, as 10 cases (21.7%) of Category Ⅲ in PD were diagnosed as Category Ⅱ in SOD and 22 cases (47.8%) of Category Ⅲ in PD were diagnosed as Category V or VI in SOD. In Category Ⅲ, which showed the highest diagnostic disagreement and second highest management change, there were 40 cases (87.0%) of diagnostic disagreement upon SOD, and management changes were made in 16 cases (34.8%) diagnosed as Category Ⅱ (4case), Category V (6 cases), and Category VI (6 cases) in SOD, and, in the follow-up clinico-pathological finding, 5 cases were benign and 11 cases were malignant.

Forty-seven cases (3.1%) were diagnosed as Category Ⅳ in PD; however, 16 cases (1.1%) were diagnosed as Category Ⅳ in SOD. This difference was due to over-diagnosis in 20 cases (42.6%), predominantly due to overlapping cytologic criteria among hyperplastic adenomatous nodules in goiter, follicular adenomas, well-differentiated follicular carcinomas, and the follicular variant of papillary carcinomas [9, 10, 27-31]. Limitations in the ability to further characterize follicular lesions on thyroid FNA have led to debates on management approaches. There is also an overlap of cytomorphologic features among reactive follicular cells, Hürthle cell lesions, and malignancies because the presence of nuclear grooves and even pseudoinclusions is not pathognomonic of papillary carcinomas. The diagnosis of follicular or Hürthle cell carcinoma requires the presence of capsular or vascular invasion on final histologic examination, findings that cannot be assessed by FNA. The diagnosis of FN serves to recognize patients who need at least surgical lobectomy because definitive diagnosis relies on histologic examination of nodule architecture. In Category Ⅳ, which showed the highest management change, there were 33 cases (70.2%) of diagnostic disagreement upon SOD, and management changes were made in 26 cases (34.8%) diagnosed as Category Ⅱ (16 cases), Category V or VI (5 cases), and Category I or Ⅲ (5 cases) in SOD, and, in the follow-up clinico-pathological finding, 20 cases were benign, 1 case was FN, and 5 cases were malignant.

Frequencies of management change in Category V (Suspicious, malignant) and Category VI (Malignant) were low, as compared with other Categories, at 6.7% and 0.5%, respectively; however, in Category V, the diagnostic disagreement upon SOD was second highest and 227 of 300 patients (75.7%). This result was due to change of PD to Category VI in 198 cases (66%) on SOD; therefore, the frequency of management change was low, although the diagnostic disagreement was high.

A selection bias exists as a limitation of this study. Because our institution is a high-volume referral center, most referred patients represented and considered thyroidectomy in management. One would expect that almost all patients with malignancy by FNA would undergo a surgical procedure, and most patients with

atypia FNA results would also undergo surgical resection for definitive diagnosis. Conversely, one would expect that the majority of patients with benign FNA results would not undergo a surgical procedure. However, patients with benign thyroid nodules were referred to our institution for thyroidectomy due to clinical, cosmetic, and/or other concerns, regardless of the FNA results. Another limitation of our analysis was that we did not obtain long-term follow-up of patients who did not undergo a surgical procedure, so that we could ultimately exclude false-negative results in our cohort.

The clinical management of thyroid lesion is determined based on preoperative patient, tumor, and ultrasound characteristics as well as cytologic report. Molecular marker testing may also provide useful information in the decision of the clinical management. A limitation of our retrospective study could not consider these various factors to determine the clinical management, except for cytologic report. However, FNA has been widely accepted as the most accurate, cost-effective, and safe screening test for rapid diagnosis of thyroid nodules [15-21]. The routine use of FNA has reduced the number of unnecessary surgical procedures for thyroid nodules and has doubled the percentage of thyroid cancers found in pathologic specimens [5, 32]. Because accurate FNA testing is essential in the decision making process of patients with thyroid nodules, FNA results becomes ever more important. Consequently, second opinion for accurate FNA diagnosis could become an important part of determining the clinical management of thyroid lesion.

In our review, although 14 (0.9%) patients received superfluous management, 65 (4.3%) patients received the proper management by SOD in thyroid FNA biopsy. (Table 4) This figure may not appear to be particularly large; however, this number is significant when one considers the reversal of benign to malignant diagnosis and detection of cancer on repeat FNA, or vice versa. We did not address the cost-benefit ratio of cases involving management change by SOD. However, how can one calculate the money value of reversal of diagnosis of benign to malignant or vice versa? According to our experience, wide use of secondary cytopathologic review of thyroid FNA specimens from referring institutions is recommended, especially for Categories Ⅲ, IV by the Bethesda classification.

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