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Predictive factors of malignancy in patients with cytologically suspicious for Hurthle cell neoplasm of thyroid nodules

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ABSTRACT

Background: Our aim was to evaluate predictive factors of malignancy in patients with cytologically suspicious for Hurthle cell neoplasm (HCN) of thyroid nodules.
Materials and methods: We searched cases with cytologically suspicious for HCN from 11,569 ultrasound-guided fine-needle aspirations (US-FNA) performed at our institution. Nodules that were confirmed surgically or followed-up for at least 2 years were compared with respect to age, gender, tumor size, US diagnosis, and US findings to predict malignancy.
Results: The incidence of cases with cytologically suspicious for HCN was 1.2% (143 of 11,569). Of 75 nodules that underwent sufficient follow-up or surgery, malignancies were found in 11 (14.7%). Malignant histological examination revealed oncocytic variants of papillary thyroid carcinoma (PTC) in 3 cases, classic PTC in 1, Hurthle cell carcinoma in 3, follicular carcinoma in 3 and an unclassified carcinoma in 1. In univariate analysis, tumor size was significantly larger in malignant nodules compared to benign nodules ($p = 0.026$). The best cut-off value of tumor size in predicting malignancy was 2.5 cm. ($p = 0.006$, sensitivity: 63.6%, specificity: 79.7%). The incidences of hypoechogenicity and malignant US diagnoses were higher in malignant nodules than in benign nodules ($p < 0.001$). In multivariate analysis, tumor size was an independent factor in predicting malignancies. ($p = 0.037$, odd ratio: 2.09, confidence interval: 1.046–4.161).
Conclusion: Preoperative US provides predictive factors of malignancy in thyroid nodules with cytologically suspicious for HCN. Predictive factors include tumor size of 2.5 cm or greater, hypoechoic nodule and malignant US diagnosis.

1. Introduction

Hurthle cell neoplasm (HCN) of the thyroid gland is a relatively rare tumor of follicular cell origin that is composed either predominantly or entirely of large and polygonal cells with oxyphilic features.[1] The incidence of HCN varies from 3% to 10% of all thyroid nodules.[2] Hurthle cell carcinoma (HCC) of the thyroid gland represents approximately 3% of all differentiated thyroid cancers. HCC is deemed to behave more aggressively compared to other well-differentiated thyroid cancers, resulting in the higher incidence of metastasis, lower survival rate and less responsiveness to iodine therapy.[2,3] Preoperative estimation of cytologically suspicious for HCN may affect surgeons' decisions in terms of the extent of the operation and may reduce the rate of re-operation due to a malignancy.

Ultrasound (US)-guided fine needle aspiration (FNA) is widely considered a standard method for diagnosing thyroid nodules with indeterminate or suspicious malignant findings detected on US. However, the cytological analysis in terms of HCN restricts distinguishing benign from malignant lesions.[4,5] Based on institutional experiences, frozen section examination of HCN has variable diagnostic value in determining malignancy during surgery.[5] The final diagnosis of HCN is obtained only on definite histology in which HCC and follicular carcinoma reveal capsular

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and/or vascular invasion.[2,5] Approximately 5%–35% of HCN diagnosed by cytology may be found to harbor malignancy by final histological assessment.[6] Therefore, the inability to preoperatively diagnose accurately the small subset of patients harboring malignancies can result in majority of patients undergoing potentially unnecessary operations with associated complications and morbidity.[7]

It was investigated to be associated with malignant HCN that patients had clinical and cytological predictive factors, such as male gender, old age, large size in the nodules and some cytological features of nuclear clouding, small cell dysplasia and large cell dysplasia.[4,8,9] Previous reports have produced inconsistent results with utilizing these factors.[10,11] Preoperative radiological impression facilitates increasing the accuracy of cytology and frozen section examination. With the advanced technology of US and widely accepted US criteria, we evaluated predictive factors of malignancy in patients with cytologically suspicious for Hurthle cell neoplasm (HCN) of thyroid nodules.

2. Materials and methods

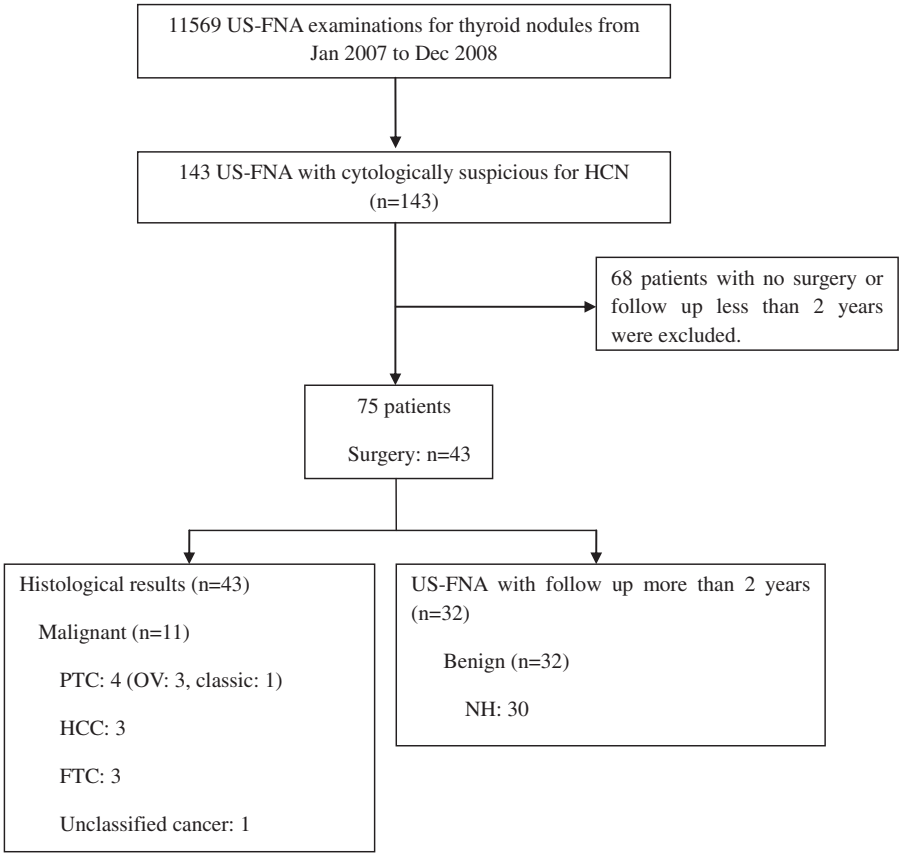
2.1. Patients

This retrospective study was approved by our International Review Board, with a waiver of informed consent. Between Jan 2007 and Dec 2008, 11,569 US-guided FNA of thyroid nodules were performed at our institution. We retrospectively reviewed cases with cytologically suspicious for HCN on cytology. Ultimately, 75 patients who underwent surgical resection or clinical and radiological follow up for more than 2 years were enrolled for statistical analysis. We evaluated age and gender of the patients and tumor size as clinical predictive factors for malignant nodules.

2.2. US and US-FNA

US was performed using high-resolution US equipment (IU22; Philips Medical Systems, Bothell, WA or HDI 5000; Advanced Technology Laboratories, Bothell, WA) with 5–12 MHz linear array transducers. US examination included the evaluation of the entire thyroid gland and lateral neck compartments. US examination was performed by one of seven radiologists. We evaluated morphologic findings and diagnosis of thyroid nodules on US as follows: size (the maximum diameter as measured); shape – oval to round or not oval to round; margin – smooth, spiculated or ill-defined; orientation – wider than tall or taller than wide; echogenicity – hyper-echoic, iso-echoic or hypo-echoic; cystic change – none or present and calcification – none or present. The diagnoses of all thyroid nodules were prospectively categorized as suspicious for malignancy or probably benign by two radiologists with an experience of 9 years and 4 years, respectively. The inclusion criteria of suspicious for malignant finding in a thyroid nodule were as follows: not oval to round shape, spiculated margin, taller than wide orientation, hypoechogenicity, and the presence of macrocalcification or microcalcification.[12] Probable benign diagnoses were attributed to thyroid nodules that were negative for malignant features.

US-FNA was followed by diagnostic US. Using freehand technique and direct US visualization, a 23-gauge needle tip was placed in the targeted lesion, below the center of the transducer and was advanced to the lesion along the image plane. The aspirated materials were placed on appropriately labeled glass slides and, smeared



HCN: Hurthle cell neoplasm, PTC: papillary thyroid cancer, OV PTC: oncocytic variant of papillary thyroid cancer, HCC: Hurthle cell carcinoma, FTC: follicular thyroid cancer, NH: nodular hyperplasia, FA: follicular adenoma, HCA: Hurthle cell adenoma

Fig. 1. Flow chart of population.

and fixed in 95% ethyl alcohol. The remainder of the material within the syringe was rinsed with ethyl alcohol for processing as a cell block. The slides were sent to the pathology department for analysis.

2.3. Cytopathologic evaluation

Cytological diagnosis of HCN was performed by one of six cytopathologists. The FNA specimen was considered adequate when at least 6 groups of well-preserved follicular cells on different slides were collected with each group including at least 10 follicular cells. The cytological criteria used for the diagnosis of HCN included cellular specimen, monotonous population of Hurthle cells or oncocytic cells (more than 75% of FNA specimen) with scant or no colloid materials and absence of nuclear features of papillary thyroid cancers.[13,14] The Bethesda system for reporting thyroid cytopathology had not been introduced in our institution at the time of the study.

2.4. Statistical analysis

The statistical analysis was performed using the SAS 9.3 (SAS institute Inc., Cary, NC, USA). The two-sample t test and Mann–Whitney test was applied to compare clinical factors between benign and malignant lesions. The tumor size receiver operating characteristic curve was developed using R 2.15.1(a language and environment for statistical computing. 2012 The R Foundation for Statistical Computing, Vienna, Austria). The best cut-off value of tumor size to predict malignancy was chosen using Youden's Index, which maximizes the sum of the sensitivity plus specificity. Fisher exact test in univariate and multivariate logistic regression analysis was applied to clinical and radiologic factors between the benign and malignant nodules with cytologically suspicious for HCN. P values < 0.05 were considered statistically significant. Numeric data were expressed as mean $\pm$ standard deviation (SD).

3. Results

The incidence of cytologically suspicious features for HCN in thyroid nodules was 1.2% (143 of 11,569 US-FNA examinations). (Fig. 1) Of the 143 patients, 68 patients who did not undergo either surgery or the follow up period of more than 2 years were excluded. Finally, 75 patients with 75 thyroid nodules were enrolled for the statistical analysis in this study. Of 75 patients, 43 (57.3%) patients underwent surgery. The remaining 32 patients had a follow up of more than 2 years (mean: 41.1 months, range: 24–54 months) and a repeat FNA following the initial FNA. All 32 thyroid nodules in 32 patients revealed no interval change at US follow-up. Of the 75 nodules with cytologically suspicious for HCN, 11 cases (14.7%) were malignant; 3 cases (3.9%) were oncocytic variants of papillary thyroid carcinoma (PTC), 1 case (1.3%) was classic PTC, 3 cases 3 (3.9%) were HCC, 3 (3.9%) were follicular thyroid carcinoma, 1 case (1.3%) was an unclassified cancer, 64 cases (85.3%) were benign thyroid nodules, 57 cases (76%) were nodular hyperplasia, 3 cases (4%) were Hurthle cell adenoma, 2 (2.7%) were follicular adenoma, 1 case (1.3%) was lymphocytic thyroiditis and one case (1.3%) was a parathyroid adenoma.

In the univariate analysis shown in Table 1, tumor sizes of malignant nodules (2.63 cm $\pm$ 1.44, range: 0.6–5) were significantly larger than that of benign nodules (1.65 cm $\pm$ 0.982, range: 0.4–4) (p value $= 0.026$). The best cut off value of tumor size in order to differentiate malignant nodules from benign nodules was 2.5 cm (p value $= 0.006$). Using the cut off value of 2.5 cm, the diagnostic performance was as follows; sensitivity: 63.6%; specificity: 79.7%; positive predictive value: 35% and negative predictive value: 92.7%. With the US findings, malignant nodules were more frequently hypo-echoic compared to benign nodules (Figs. 2 and 3). ($p = 0.011$) US diagnosis was statistically significant in terms of diagnosing malignant lesions from benign lesions of HCN. ($p < 0.001$) Gender and age of patients were not significantly different between benign and malignant nodules. Orientation, shape, margin, presence of calcification and cystic change of thyroid nodules were not significantly different between two groups. In multivariate analysis as shown in Table 2, tumor size was an independent factor in predicting malignancies ($p = 0.037$, odd ratio: 2.09, confidence interval: 1.046–4.161).

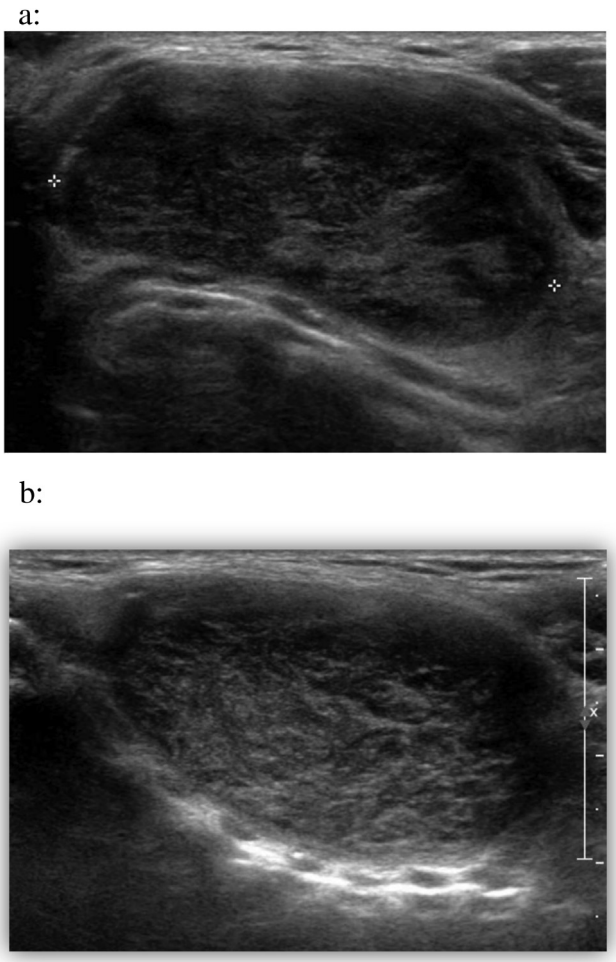


Fig. 2. A 55 year-old male suspicious for Hurthle cell neoplasm on cytology. On US, a 4.5 cm circumscribed hypo-echoic mass is seen in right thyroid lobe. US diagnosis was suspicious for malignancy. Histology revealed follicular thyroid carcinoma. (a: transverse image, b: longitudinal image).

4. Discussion

The majority of recent surgical studies have revealed that the incidence of malignant HCN ranges from 5% to 35%.[6,15] Some authors have suggested that 80% or more of HCNs in the thyroid gland are benign especially when studies include Hurthle cell adenomatous nodules found in the context of goiter and chronic lymphocytic thyroiditis.[16–18] The present study revealed concordant results. The incidence of malignancy was 25.6% (11/43 patients) among the patients who underwent surgery.

The inability to differentiate a malignant lesion of HCN on the basis of cytology has resulted in a general recommendation that patients with cytologically suspicious for HCN undergo surgical resection.[7,19] Moreover, intra-operative frozen section is not helpful in the diagnosis of follicular carcinoma and HCC since they depended on the presence of vascular and/or capsular invasion which is occasionally not identified on the frozen section.[20] Therefore, if preoperative US findings can serve as a clinical predictive factor, it may help guide surgeons in order to determining accurate results in decisions regarding the extent of the surgery. The inability of preoperative accurate diagnosis for HCN facilitates the need for a variety of diagnostic methods and the summation of these methods in order to enhance confidence with respect to the extent of surgical involvement.

Many authors have suggested variable clinical predictive factors for malignancies in thyroid lesions diagnosed as cytologically

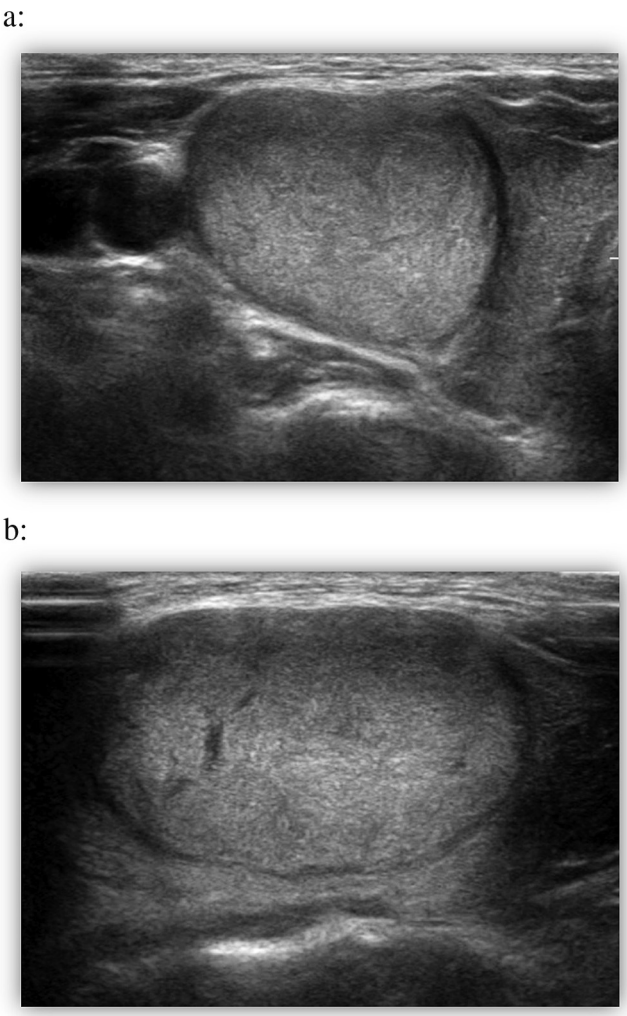


Fig. 3. A 44 year-old male suspicious for Hurthle cell neoplasm on cytology. On US, a 4 cm circumscribed iso-echoic mass without presence of calcification and cystic change is seen in the right thyroid lobe. US diagnosis was probably benign. Histology revealed follicular adenoma. (a: transverse image, b: longitudinal image).

suspicious for HCN; male gender, older age and larger tumor size. Thyroid function test was generally not estimated as a predictive factor.[6,21–23] Few studies have focused on US findings for HCN in the literature.[8,24] Kim et al. reported that suspicious malignant US findings such as hypo-echogenicity, irregular margin and calcification were not predictive factors.[8] A type of follicular thyroid carcinoma was differentiated from papillary thyroid carcinoma in terms of its US features.[10] Therefore, preoperative diagnosis using the previously reported US findings of malignant thyroid nodules may reveal a significant limitation in predicting follicular carcinomas preoperatively. In the present study, hypo-echogenicity of US findings was the only parameter that had a significant difference between benign and malignant nodules, although the significance was not consistent in the multivariate analysis. Furthermore, US diagnosis integrated from each US finding aided in predicting malignant lesions. A major strength of this study is to achieve US differentiation of nodules with cytologically suspicious for HCN in the larger population.

Larger tumor size of HCN is widely known as the most powerful predictive factor. The cut off value of the tumor size is variable ranging from 1.5 cm to 4 cm.[1,2,5,8] However, other studies have reported that the tumor size of HCN is not significantly different between benign and malignant lesions.[13,25] In the present study, the tumor size of malignant nodules was significantly larger than that of benign nodules in both univariate and multivariate analyses. Furthermore, a tumor size of 2.5 cm or greater was a unique independent factor in differentiating malignancies. Of the 11 malignant nodules, seven (63.6%) were larger than 2.5 cm. We suggest that surgeons initially consider a lobectomy for nodules with cytologically suspicious for HCN and a size less than 2.5 cm, owing to the high sensitivity and specificity of size in predicting malignancies.

Some investigators have suggested that patients with cytologically suspicious for HCN should initially undergo lobectomy followed by complete thyroidectomy, if a diagnosis of cancer is rendered on histologic confirmation.[1] Other groups have claimed that all HCNs should be regarded as malignancies and treated aggressively with total thyroidectomy since HCC has a worse prognosis than other follicular carcinomas.[1,26] US diagnosis of HCN was benign with a 75.4% concordant rate in the present study. We suggest that lobectomy is recommended as an initial surgery for nodules with benign US features.

Table 1
Comparison of clinical factors, US findings and US diagnosis in thyroid nodules with cytologically suspicious for HCN by univariate analyses.

Final results	Benign ($n = 64$)	Malignant ($n = 11$)	p Value
Gender (M:F)	17:47	3:8	1.000
Age	51.76 ± 10.87 (range: 32–77)	52.27 ± 15.33 (range: 26–76)	0.894
Size (cm)	1.65 ± 0.982 (range: 0.4–4)	2.63 ± 1.44 (range: 0.6–5)	
<2.5 cm	51(80%)	4(36.4%)	**0.026**
≥ 2.5 cm	13(20%)	7(63.6%)	
US findings			
Shape			
Oval to round	63 (98.5%)	11 (100%)	1.000
Not oval to round	1 (1.5%)	0	
Margin			
Smooth	58 (90.1%)	11 (100%)	1.000
Spiculated	2 (3.7%)	0	
Ill defined	4 (6.2%)	0	
Orientation			
Wider than tall	62 (96.9%)	11 (100%)	1.000
Taller than wide	2 (3.1%)	0	
Echogenicity			
Iso-echoic	38 (59.3%)	2 (18.2%)	**0.011**
Hypo-echoic	26 (40.7%)	9 (81.8%)	
Calcification			
None	48 (75%)	9 (81.8%)	1.000
Present	16 (25%)	2 (18.2%)	
Cystic change			
None	48 (75%)	9 (81.8%)	1.000
Present	16 (25%)	2 (18.2%)	
US diagnosis			**<0.001**
Benign	49 (75.4%)	2 (18.2%)	
Malignant	15 (24.6%)	9 (81.8%)	

The bold values indicate statistically significant p-values.

Table 2
Multivariate analyses of thyroid nodules with cytologically suspicious for HCN in predicting malignancies.

Factors	Odd ratio	p Value	Confidence interval
Gender	1.070	0.941	0.181–6.323
Age	0.970	0.373	0.907–1.037
Tumor size	**2.087**	**0.037**	**1.046–4.161**
US findings			
Echogenicity	1.533	0.775	0.082–28.554
Calcification	0.357	0.334	0.044–2.886
Cystic change	1.223	0.854	0.143–10.494
US diagnosis	13.001	0.073	0.785–215.428

The bold values indicate statistically significant p-values.

Gender and age of patients were not predictive factors in the present study. The proportion of females was much higher than males in both benign and malignant lesions. There was no statistical difference in gender as a predictive factor for malignant thyroid lesions as compared with other studies.[20,22,27] The patients with malignant lesions of HCN were statistically older in comparison to those with benign lesions; similar to findings reported in several previous studies.[5,21,28] Lopez-Penabad et al. stated that the average age of patients with malignant HCN was 8.7 years older than those with benign lesions[28] although other investigators have not found the same association.[22,29]

There were several limitations in the current study. First, the study was a retrospective analysis with a smaller population compared to other cohort studies.[1,5,8] However, the present study was focused on detailed US findings and US diagnosis. Only cases of cytologically suspicious features for HCN were included in the population and patients in the study had more sufficient clinical and radiologic follow up periods in comparison to previous studies.[8,13] Since all patients with HCN did not undergo surgery, histological confirmation was not available for all patients. However, this problem was unavoidable due to the rarity of the disease and was compensated with a sufficient follow-up period.

In conclusion, preoperative US provides predictive factors of malignancy in thyroid nodules with cytologically suspicious features for HCN. Predictive factors include a tumor size of 2.5 cm or greater, a hypoechoic nodule and malignant US diagnosis. Preoperative estimation of these nodules may affect surgeons' decisions in terms of the extent of surgery and may help to reduce the rate of potentially unnecessary surgeries.

Ethical approval

This study, approved by International Review Board of Samsung Medical Center.

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None.

Author contribution

Kwang Hwi Lee; data collection, data analysis, writing.
Jung Hee Shin; study design, data analysis.
Eun Sook Ko; data collection.
Soo Yeon Hahn; data collection.
Jee Soo Kim; data collection.
Jung-Han Kim; data collection.
Young Lyun Oh; data collection.

Conflict of interest statement

All authors have no financial and personal relationships with other people or organizations.

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