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BREAST IMAGING
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Follow-up design of unexpected enhancing lesions on preoperative MRI of breast cancer patients

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PURPOSE
We aimed to analyze the characteristics and long-term follow-up results of unexpected enhancing lesions on preoperative magnetic resonance imaging (MRI) of breast cancer patients.

METHODS
From August 2007 through February 2010, second-look ultrasound (SLUS) was recommended for 84 of 312 breast cancer patients having unexpected enhancing lesions on MRI. SLUS was performed for 85 unexpected enhancing lesions in 72 patients. We performed a retrospective review to determine the size, lesion type, enhancement kinetic curve, and location in relation to the index cancer. We obtained the pathologic outcome of the detected lesions and in case of a negative finding on SLUS, we performed follow-up examinations for at least two years.

RESULTS
Of 85 unexpected lesions, 72 (85%) were detected on SLUS. In total, 41 lesions (56.9%) were confirmed as malignant and 31 lesions (43.6%) as benign. Cancer rate was statistically higher in lesions having type III enhancement pattern, located at the same quadrant as the index cancer. However, no significant association was observed between the cancer rate and the lesion size and type. None of the 13 negative cases on SLUS developed cancer on follow-up.

CONCLUSION
In case of unexpected enhancing lesions on preoperative MRI of breast cancer patients, SLUS can be useful to find out the matched lesion. Lesions with type III enhancement pattern or those located at the same quadrant as the index cancer should be considered as a separate cancer. In the absence of any suspicious findings on SLUS, patient may be followed up with confidence.

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Dynamic contrast-enhanced magnetic resonance imaging (MRI) has been the most accurate technique for the detection and delineation of invasive and some in situ breast cancers (1–6). Despite the high sensitivity of MRI (83%–100%), the reported specificity of this modality is relatively low and ranges from 40% to 80% (7, 8). MRI identifies additional lesions much more frequently than other imaging modalities do (9). On preoperative MRI of breast cancer patients, other enhancing lesions are frequently detected in addition to the index cancer. Since the probability of malignancy is high for additionally detected lesions on MRI of breast cancer patients, MRI-guided percutaneous biopsy is a reasonable next step, but it is an expensive and time-consuming procedure, and it is not yet widely available all over the world. Alternatively, ultrasonography (US)-guided biopsy is preferable, because it is less expensive and more convenient for the patients.

Second-look ultrasound (SLUS) is a reevaluation method for MRI-detected lesions with the information provided by MRI. Sometimes, SLUS is used even when there is no antecedent US examination. This technique has become increasingly important for detecting unexpected enhancing lesions on MRI, especially for breast cancer patients.

Several reports demonstrated the usefulness of SLUS (5, 10, 11). If a lesion can be detected on SLUS, a new malignant lesion can be differentiated from a false-positive enhancing lesion on MRI to conclude the diagnostic workup. Also US guidance can be used for biopsy instead of MRI guidance. Nevertheless, few studies have reported the characterization and meaning of additionally detected lesions on preoperative MRI and SLUS of breast cancer patients (10, 11). In addition, there has not been a study examining the long-term follow-up results of additional enhancing lesions that could not be detected by US and could not be biopsied with MRI guidance due to lack of equipment, as is the case in our center.

Therefore, in this study we aimed to analyze the characteristics and long-term follow-up results of unexpected enhancing lesions on preoperative MRI of breast cancer patients and to determine the feasibility of managing these lesions without MRI-guided biopsy.

Methods

Patient selection and data collection

Our institutional review board approved this retrospective study and waived the requirement for written informed consent. From August 2007 through February 2010, 312 patients underwent breast MRI for preoperative evaluation of breast cancer. Indications for an MRI examination included preoperative evaluation before planned breast conserving

operation to exclude multicentricity and bilaterality, assessment of axillary lymph node status, and evaluation of residual tumor after excisional biopsy at other hospitals. We defined additional lesions on MRI according to the definition of Liberman et al. (12). MRI lesions were considered as a separate entity if they were located in a different breast quadrant than the index cancer, if they were in the same quadrant but separated from the index cancer by at least 1.0 cm of intervening normal-appearing tissue on MRI, or if they were in the same quadrant and contiguous with the index cancer but extended at least 4.0 cm beyond the site of the index cancer. We defined unexpected enhancing lesions as enhancing lesions that had not been detected on the initial US performed at our hospital. We excluded patients who had single cancer (n=97) and those who did not have the initial US at our hospital (n=24). We also excluded lesions that correlated properly with the initial US (n=66), and those that correlated with another enhancing lesion but had a typical benign nature (n=41). Among 312 patients, 84 patients were recommended for SLUS for suspicious, unexpected enhancing lesions. Of 84 patients, 12 patients were excluded for the following reasons: transfer to another hospital (n=5), scheduled for neoadjuvant chemotherapy (n=3), and refusal to undergo SLUS (n=4). Therefore, we performed SLUS for 85 unexpected enhancing lesions in 72 patients. The median age of 72 patients in this study was 49 years (mean age, 54 years; range, 29–73 years).

Conventional diagnostic imaging

The initial mammography examination was completed in all but seven patients. In these seven patients, the mammogram was available from different referral centers. We performed whole-breast US on all patients using 5–12 MHz transducers on an HDI-5000 or IU-22 unit (Philips Medical System, Bothell, Washington, USA). All cancers were confirmed by US-guided biopsy using 14-gauge core needle devices (Stericut, TSK Laboratory, Tochigi, Japan) or mammography-guided wire localization and excision.

MRI technique and interpretation

MRI was performed using a 1.5 T scanner (Gyroscan Intera, Philips Medical System, Best, the Netherlands) or a 3.0 T scanner (Achieva 3.0T TX-series, Philips Medical System). Dedicated four-element sensitivity encoding (SENSE)-compatible breast surface coils were used for 1.5 T MRI units and dedicated 16-element SENSE-compatible breast surface coils were used for 3.0 T MRI units. All patients underwent MRI in the prone position with the breasts immobilized. For 1.5 T MRI, dynamic contrast-enhanced bilateral axial breast imaging for high spatial and temporal resolution was used with active fat suppression. After obtaining bilateral SPAIR images (TR/TE, 4317.80/90) of the breasts, T1-weighted turbo field echo three-dimensional (3D) gradient-echo sequence with active fat suppression was performed after injection of contrast material. The imaging parameters were as follows: TR/TE, 5.4/2.1; flip angle, 15°; FOV, 33 cm; matrix, 320×320; section thickness, 2 mm interpolated to 1 mm; and acquisition time, 60 seconds. The temporal resolution was 60 seconds per dynamic acquisition. A dynamic study in the axial plane was performed before and 60, 120, and 360 seconds after the initiation of an IV injection of 0.1 mmol/kg of Gadobutrol (Gadovist, Bayer Schering Pharma, Berlin, Germany) at a rate of 2 mL/s, followed by a 20 mL saline flush at a rate of 2 mL/s. For 3.0 T MRI, four-phase dynamic contrast-enhanced bilateral axial breast imaging studies for high spatial and temporal resolution and contrast-enhanced affected and contralateral/unilateral sagittal breast imaging studies for in-plane and through-plane high spatial resolution with active fat suppression protocol were used. After obtaining bilateral fat-saturated T2-weighted images (TR/TE, 7202/71) of the breasts, a T1-weighted high-resolution isotropic volume examination 3D gradient-echo sequence with active fat suppression was performed before and 43 seconds after the injection of contrast material. The imaging parameters were as follows: TR/TE, 6.2/3.1; flip angle, 12°; FOV, 34 cm; matrix, 424×368; section thickness, 1.5 mm interpolated to 0.9 mm; and acquisition time, 82 seconds. Two radiologists with three and five years of experience in breast imaging performed the retrospective review of all lesions using the BI-RADS classification for MRI (13). Abnormal enhancement was dichotomized as mass- or non-mass-like enhancement. According to BI-RADS, the lesion type is classified as either focus, mass and non-mass-like enhancement on MRI. In this study, four lesions measured 4 mm in length and should have been defined as focus by strict definition; however, due to their low number, we included these four lesions as mass. The size of the lesions was documented at the greatest diameter. Three types of enhancement kinetic curves were obtained by assessing the signal intensity values in breast tissue over time after contrast material injection: type I, progressive enhancement pattern, where a continuous increase in signal intensity is seen over time; type II, plateau pattern, where the initial uptake is followed by a plateau phase; and type III, washout pattern, where a rapid uptake is followed by a reduction in enhancement (13). Signal intensities were obtained from the precontrast and each postcontrast series using operator-defined region-of-interest (ROI). We placed round-shaped ROIs with the smallest possible pixel size at the most enhancing area of the lesion. The location of each lesion was documented based on its relationship to the index cancer by quadrant.

MRI and US correlation and second-look ultrasound

We correlated enhancing lesions on MRI with the previously obtained US. SLUS was performed after an average of seven days following the MRI by the same radiologists who had interpreted the results of MRI. Radiologists carefully scanned breast tissue with the knowledge of enhancing lesions. We considered location, size, and shape of lesions and the relationship between the lesion and other breast landmarks, such as the nipple, subcutaneous fat, glandular tissue and subglandular fat. We also used 3D MR reconstruction images and multiplanar views for position changes between US and MRI. The location of additionally detected enhancing lesions with the index can-

cer was determined to be in the same quadrant of the ipsilateral breast, other quadrant of the ipsilateral breast, or contralateral breast.

Follow-up protocol

MRI-guided biopsy was not available at our hospital; therefore, in case of negative findings on SLUS, we performed image follow-up with mammography, US, and MRI for at least two years. The follow-up interval was one-year for mammography and six months for US. In case of MRI follow-up, MRI was performed approximately one year after the surgery, and no further follow-up was performed if a lesion was no longer visible or had typically benign features.

Statistical analysis

Information about patient demographics, imaging data, and pathology results were collected from our hospital's information and picture archiving and communication system. Pearson's chi-square test or Fisher's exact test was used to assess the relationship between the cancer rate and the enhancement pattern, type, and location of the lesions. Fisher-Freeman-Halton test was used in comparison of cancer rate and the size of lesions. For all tests used, a *P* value of less than 0.05 was considered statistically significant. The statistical analysis was performed using a statistics software (Stata release 9.0, Stata Corporation, Texas, USA).

Table. MRI findings in all lesions versus malignant lesions

MRI findings			Total number of lesions n (%)	Malignant lesions n (%)	*P*
Type	Mass		76 (89.4)	37 (48.7)	1.000
	Non-mass		9 (10.6)	4 (44.4)	
Size	0–5 mm		19 (22.4)	8 (42.1)	0.679
	6–10 mm		51 (60)	27 (52.9)	
	11–15 mm		4 (4.7)	1 (25)	
	>15 mm		11 (12.9)	5 (45.4)	
Enhancement pattern	Type I		22 (25.9)	2 (9.1)	<0.001
	Type II		17 (20)	5 (29.4)	
	Type III		46 (54.1)	34 (73.9)	
Location	Ipsilateral	Same quadrant	48 (56.5)	34 (70.8)	<0.001
		Another quadrant	15 (17.6)	2 (13.3)	
	Contralateral		22 (25.9)	5 (22.7)	

Results

After careful correlation between preoperative MRI and US in 312 patients with cancer, we performed SLUS on 85 unexpected enhancing lesions in 72 patients. In total, 72 of 85 unexpected enhancing lesions (85.0%) were detected on SLUS. Of these 72 lesions, 41 (56.9%) were confirmed to be malignant, 27 (37.5%) were benign and four (5.5%) were nontumorous. The malignant lesions included invasive ductal carcinoma (n=28), ductal carcinoma in situ (n=12), and microinvasive ductal carcinoma (n=1). The benign lesions included fibrocystic change (n=10), fibroadenoma (n=6), atypical ductal hyperplasia (n=2), sclerosing adenosis (n=2), fat necrosis (n=2), and one each of the following other benign lesions: fibroadenomatous mastopathy, intraductal papilloma, adenosis, papillary neoplasm, and usual ductal hyperplasia.

Table shows the rate of malignant lesions in relation to the lesion type, size, enhancement pattern, and location. Of 85 lesions, 76 were masses, and nine were non-mass-like enhancing lesions. Thirty-seven masses (37/76, 49%) and four non-mass-like enhancing lesions (4/9, 44%) were malignant. Nineteen lesions were ≤5 mm, 51 lesions were 6–10 mm, four lesions were 11–15 mm and 11 lesions were ≥16 mm in size. Eight ≤5 mm lesions (8/19, 42%), twenty-seven 6–10 mm lesions (27/51, 53%), one 11–15 mm lesion (1/4, 25%) and five ≥16 mm lesions (5/17, 46%) were malignant. In terms of the enhancement pattern, 22 lesions were type I, 17 were type II and 46 were type III. Two type I lesions (2/22, 9%, $P < 0.001$), five type II lesions (5/17, 29%, $P = 0.082$), and 34 type III lesions (34/46, 74%, $P < 0.001$) were malignant. In terms of location, 22 lesions (22/85, 26%) were located in the contralateral breast from the index cancer, and 63 lesions (63/85, 74%) were located in the ipsilateral breast of the index cancer. Of the lesions located in the ipsilateral breast, 48 (48/85, 57%) were located in the same quadrant as the index cancer, and 15 (15/85, 18%) were located in another quadrant. Thirty-four lesions (34/48, 71%) in the same quadrant of the ipsilateral breast, two lesions (2/15, 18%) in the other quadrant of the ipsilateral breast (Fig. 1) and five lesions (5/22, 23%) in the contralateral breast were malignant (Fig. 2). The cancer rate was significantly higher in lesions with early enhancement and a delayed washout pattern on the kinetic curve (type III), located in the same quadrant as the breast cancer ($P < 0.001$). There was no statistically significant difference between the cancer rate and the size or type of lesions. Nine cases of non-mass-like enhancements were included in this study. Four were cancers, two were benign and three were negative on SLUS. All four cancers were located in the ipsilateral quadrant of the index cancer; three of them were type III and one was type II. Two benign non-mass-like enhancements represented fibrocystic change and sclerosing adenosis. Fibrocystic changes were located in the contralateral breast and exhibited a type II enhancement pattern. The sclerosing adenosis was located in another quadrant of the ipsilateral breast and exhibited a type I enhancement pattern. All three negative lesions exhibited type I enhancement pattern; two lesions were located in the contralateral breast and one was located in another quadrant of the ipsilateral breast. Non-mass-like enhancements also yielded the same conclusion as masses.

In our study, no cancer was diagnosed in 13 negative cases that underwent follow-up for at least two years (Fig. 3).

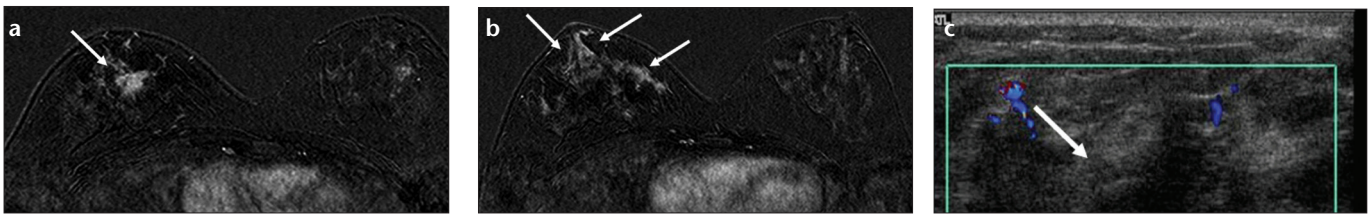

Figure 1. a–c. A 39-year-old woman with invasive ductal carcinoma (IDC) in the right breast. Axial dynamic contrast-enhanced and subtracted T1-weighted images **(a, b)** show biopsy-proven IDC in the right upper central breast with type II enhancement pattern *(***a,** *arrow)* and another non-mass-like enhancement with type II pattern *(***b,** *arrows)* in the lower portion of the index cancer. Second-look ultrasound **(c)** shows another malignant looking mass *(arrow)* at subareolar region of the right breast which was diagnosed as IDC on pathologic exam. Subsequently, surgical plan was changed from breast conserving surgery to mastectomy.

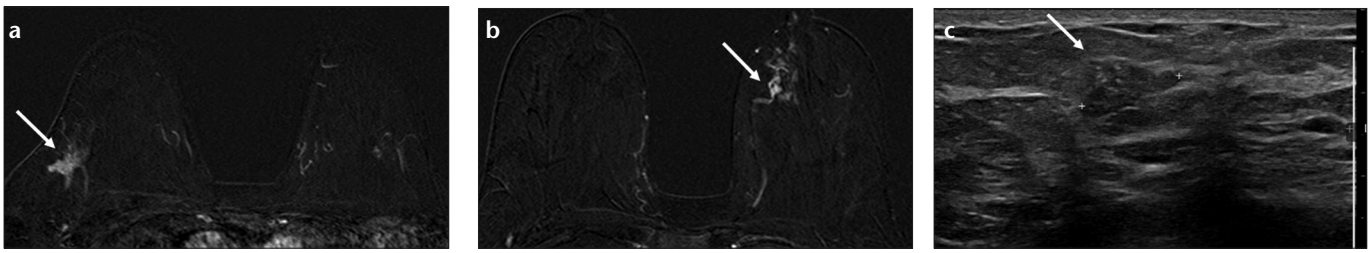

Figure 2. a–c. A 68-year-old woman with invasive ductal carcinoma (IDC) in the right breast. Axial dynamic contrast-enhanced and subtracted T1-weighted images **(a, b)** show biopsy-proven IDC in the right upper outer quadrant with type III enhancement pattern **(a,** *arrow)*. Another enhancing mass **(b,** *arrow)* with similar enhancement kinetic curve as the index cancer is detected in the left inner central breast. Second-look ultrasound **(c)** shows partially indistinct isoechoic mass that was not detected on the initial US exam in the left breast, 9 o'clock direction *(arrow)*. The pathology result of core needle biopsy of this lesion revealed ductal carcinoma in situ.

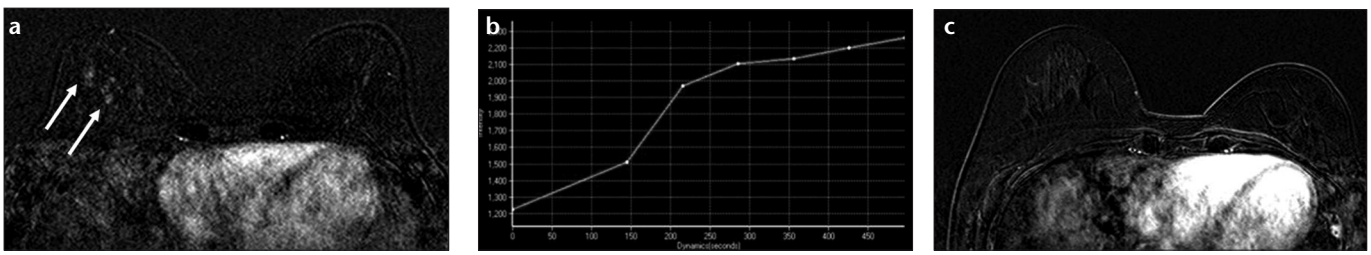

Figure 3. a–c. A 60-year-old woman with known left invasive ductal carcinoma. Axial dynamic contrast-enhanced and subtracted T1-weighted image **(a)** and enhancement kinetic curve **(b)** show several enhancing masses with type I enhancement pattern at the contralateral breast *(arrows)*. However, there were no matching lesions on second-look ultrasound. Axial dynamic contrast-enhanced MRI **(c)** performed one year later, shows that the enhancing lesions have disappeared.

Discussion

Second-look US, also known as targeted US or MRI-directed US, was shown to be highly useful in identifying lesions initially detected on MRI. In a previous study, targeted US identified 65 of 73 additionally detected enhancing lesions (89%), and eight lesions (11%) were not visible on targeted US (14). Shin et al. (11) reported that the detectability rate of SLUS was 71% (27/38), and Abe et al. (10) reported that US correlation was made in 115 of 202 additionally detected enhancing lesions (57%). In this study, 72 of 85 unexpected enhancing lesions (85%) were detected on SLUS, demonstrating a relatively high level of detectability compared with the previous studies. We routinely performed US twice on all patients, which contributed to the increased detectability. In addition, because Asian females have relatively small breasts, it was assumed that breast US would lead to easier detection and management of small lesions.

Our results showed a higher probability of cancer in unexpected enhancing lesions with a type III enhancement pattern that are located in the same quadrant as the index cancer. In a previous report, Schnall et al. (15) showed that 76% of lesions with type III enhancement pattern were associated with cancer. The type II enhancement pattern was reported to have 42.6% sensitivity and 75% specificity for detection of malignancy (16). In this study, the malignancy rates were 9% for type I, 29% for type II and 74% for type III enhancement patterns. Although there was some overlap in the enhancement characteristics of benign and malignant lesions, type III enhancement pattern is a significant indicator of cancer, and our experience with unexpected enhancing lesions also supports this conclusion.

We evaluated unexpected enhancing lesions according to their location with respect to the index cancer as follows: the same quadrant in the ipsilateral breast, another quadrant of the ipsilateral breast, and the contralateral breast. Depending on location, breast cancer can be defined as multifocal, multicentric, or synchronous bilateral tumor in case of multiple lesions confirmed to be malignant. According to

previous studies the mean prevalence is 30% for multifocal cancer, 13.4% for multicentric cancer, and approximately 1.0% for synchronous bilateral breast cancer (17–20). The incidence of unexpected enhancing lesions characterized as cancer is quite different; however, our results demonstrate that unexpected enhancing lesions located in the same quadrant of the index cancer have a higher probability to be another separate cancer.

There was no statistically significant correlation between the cancer rate and the mass size. In addition, detectability was not higher in larger lesions. Commonly, the larger the masses are, the easier they can be detected. However, with SLUS, it is more difficult to detect lesions with negative results on the initial US. Also, most lesions larger than 16 mm were non-mass-like enhancements that were more difficult to detect than masses (10). There was no statistically significant correlation between the cancer rate and the lesion type. Nine cases of non-mass-like enhancement yielded similar results as the masses; but further clinical studies are necessary due to the small number of cases.

On SLUS, 13 of 85 unexpected enhancing lesions (15%) were not correlated. These lesions did not exhibit any malignant features; therefore, we performed imaging follow-up. All lesions underwent annual mammography and US at six-month intervals for more than two years. Seven of 13 lesions underwent MRI follow-up once after the operation. On follow-up MRI, four unexpected enhancing lesions had disappeared. We speculate that these enhancing lesions represent the uptake of gadolinium by normal tissue due to hormonal fluctuations in premenopausal women. Three of these four patients did not receive anticancer therapy after breast conserving surgery due to early stage cancer (less than 1 cm in size) and one patient stopped anticancer therapy early in the treatment due to noncompliance. Therefore, the possibility of anticancer treatment effect was excluded. Three lesions exhibited no interval changes. We confirmed these lesions as benign, without MRI-guided biopsy. There was no developing malignant looking lesion in the other six lesions.

The probability of cancer is significantly higher in MRI-detected breast lesions with US correlation compared with those without such correlation (5, 21, 22). Our experience also supports this conclusion. However, some reports did not demonstrate a correlation between SLUS and diagnosis of malignancy (23–25). Despite the differences, all reports indicate that the absence of a US correlation is not a sufficient condition for ruling out malignancy. Considering this, we recommend imaging follow-up at short intervals in cases where an experienced radiologist cannot detect any suspicious findings on SLUS, the enhancing lesion on preoperative MRI does not exhibit delayed washout pattern on kinetic curve, and the enhancing lesion is not located in the same quadrant as the index cancer.

Our study has several limitations. First, we did not perform MRI-guided biopsy in cases that were negative on SLUS, and it was not always possible to be confident of the exact MRI-US correlation. Second, we performed imaging follow-up for two years or more. This follow-up period is insufficient to detect slow growing cancers. Third, we performed follow-up MRI in only a small group of patients. There was no developing cancer in six patients with only mammography and US follow-up; however, we could not apply US-MRI correlation to these patients, therefore, diagnostic accuracy might be influenced.

In conclusion, unexpected enhancing lesions detected on preoperative MRI of breast cancer patients can be identified by SLUS, even if they were not detected on the initial breast US exam. We recommend cautious short-interval imaging follow-up for unexpected enhancing lesions that are not correlated on SLUS, do not exhibit type III enhancement pattern, and are not located in the same quadrant as the index cancer.

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Conflict of interest disclosure

The authors declared no conflicts of interest.

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