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FULL PAPER

Quantified ultrasound elastography in the assessment of cutaneous carcinoma

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The results of this study were originally presented at the press conference of the Radiological Society of North America Annual Meeting on 1 December 2009.

Objective: To evaluate the feasibility of high-frequency ultrasound and ultrasound elastography (USE) in discriminating benign from malignant skin lesions in a prospective cohort study and to introduce the use of a “strain ratio” for evaluation of skin lesions.

Methods: A commercial ultrasound system with a 14-MHz transducer was used to visualize skin lesions requiring biopsy on clinical evaluation. Anatomic ultrasound and USE imaging of the skin lesions was performed using 2- to 4-mm gel stand-off pads. A region of interest was manually selected over the area of each lesion with the lowest strain. The concept of a strain ratio of the compressibility of the normal skin at the corresponding layer to that of the least compressible region of a lesion in question was created and applied. This ratio was

subsequently correlated with blind histopathological evaluation for malignancy.

Results: 55 patients were included in the study with a total of 67 lesions evaluated. 29 lesions were malignant and 38 benign. All malignant lesions had strain ratios ≥ 3.9 . All benign lesions had strain ratios ≤ 3.0 . A diagnostic value between 3.0 and 3.9 would result in 100% sensitivity and specificity in the characterization of these lesions as malignant.

Conclusion: This pilot study demonstrated that USE plus strain ratio appears to be a promising modality in providing diagnostic determination between cancerous and benign primary solitary skin lesions prior to biopsy.

Advances in knowledge: This is the first reported study applying an original mathematical elastographic ratio, or strain ratio, to evaluate primary solitary skin lesions.

INTRODUCTION

The reported incidence of skin cancer has increased precipitously in recent decades.¹ The method of diagnosing skin cancer, however, has remained virtually unchanged for the past 100 years. Diagnosis is still made almost exclusively by visual inspection and palpation of lesions. Because benign and malignant cutaneous lesions can be difficult to distinguish visually or by palpation, dermatologists tend to biopsy any questionable or concerning lesion. However, skin lesions that lack visual or tactile criteria typically associated with malignancy may remain undiagnosed.^{2–4} The diagnostic accuracy based on physical examination is considerably lower than the gold standard of biopsy with histopathological analysis.⁵ Visual inspection is also associated with a high false positive rate

for skin cancer,⁶ and atypical or deeper cancerous lesions can be difficult to diagnose with physical examination alone.^{7–12}

Technologies such as MRI, MR spectroscopy, among others can provide functional and physiological information about skin lesions as well as information about size, depth and location.^{13–18} While optical coherence tomography and other optical techniques, including elastography, show promise given their ability to provide high-resolution skin imaging and flow data,^{19–21} they are not readily available in imaging or dermatology departments. Optical imaging can only penetrate to the level of the dermis and not to deeper structures, which is a major limitation in staging, evaluation of the extent of disease and lesion characterization.^{22,23}

Conventional ultrasound imaging has been used to image and characterize normal skin, as well as benign and malignant skin lesions.^{24–27} However, this technique has not been widely used in clinical practice. High-frequency ultrasound may offer tremendous advantages given its potential to provide highly detailed anatomic information as well as penetration through and below all skin layers. It has also shown great potential for primary skin imaging because of its relatively low cost, availability, portability, lack of ionizing radiation and ease of use.^{28–31}

High-frequency ultrasound also offers an intriguing analog to traditional skin palpation; it can provide information about the stiffness of a lesion at and below the skin surface, using the functional image processing technique known as ultrasound elastography (USE).^{32–37} In strain elastography, a single relatively small compression made by the transducer allows determination of the rate of change in displacement of tissue as a function of distance from the transducer (strain). The strain value is an indirect measurement of elasticity. Tissue stiffness cannot be quantified precisely from the strain value, despite the relationship of stiffness to strain.³⁸ The addition of the strain ratio has been studied in aiding in the detection of pressure ulcers which show elasticity changes deep to the surface of the skin when clearly diagnostic features are not present superficially; however, its application to lesions suspicious for skin cancer has not been reported.³⁹

The purpose of this study was to evaluate the potential feasibility of the combination of high-frequency ultrasound (analogous to visualization) with USE (analogous to palpation) to distinguish benign from malignant cutaneous lesions with the use of the strain ratio of a region of interest (ROI) within a lesion to a ROI in healthy skin within the same field of view.

METHODS AND MATERIALS

This study protocol was designed as a feasibility analysis to evaluate the potential viability of high-frequency ultrasound and USE in the discrimination of benign from malignant skin lesions. It was performed prospectively after receiving approval from the Institutional Review Board at Wayne State University School of Medicine (Detroit, MI). Informed consent was obtained. Dermatologists affiliated with the department of Dermatology at Wayne State University enrolled patients in the study.

All USE images were obtained using a Hitachi Hi Vision® system (Hitachi Medical Corporation, Tokyo, Japan) with a 2- to 4-mm thick stand-off gel pad centred over each skin lesion. The various solitary skin lesions were imaged in B mode (2 Dimensional image) without colour Doppler at 14 MHz because it was the maximum frequency commercially available and FDA approved for human use by the vendor in the United States when this study was performed, and it is within the range previously reported as acceptable for the task.^{5,33,34} At this frequency, the maximum depth of penetration is 40 mm. In this study, the frame of view for the ultrasound transducer was kept between 7.5 and 10 mm. This allowed an image to be obtained in which the epidermis, dermis and subcutaneous tissues could be adequately resolved.⁴⁰

Patients included in the study were ≥ 18 years of age with at least one suspicious skin lesion ≥ 2 mm in diameter, on any part of the body that is clinically recommended for biopsy. Patients with lesions < 2 mm in diameter, lesions determined clinically benign, previously diagnosed, or recurrent in the same location were excluded. The patients were evaluated per established routine clinical practice using visual inspection of the lesions. Those patients who had lesions that were determined by visual inspection alone to be clinically benign were ineligible to participate in the study and were not invited to receive ultrasound imaging and analysis because no biopsy was clinically indicated in the standard of care. When biopsy was determined to be clinically indicated by a board certified dermatologist, patients with lesions meeting inclusion criteria were invited to participate in the study. Lesions in participating patients were then imaged, and USE was performed by a dermatologist with 5 years' experience and training in diagnostic imaging of the skin, and further training in the use of the specific machine used in this study for elastography.

First, the ultrasound gel and a 2- to 4-mm thick stand-off gel pad were placed on the surface of the lesion and surrounding healthy skin. Thicker, 4-mm gel pads were used when the thinner, 2 mm gel pads did not provide adequate contact. With the transducer at the centre of the skin lesion, strain elastography was performed with manual, low frequency, vertical compressions of the tissue by the operator using the transducer.³⁸ The Hitachi Hi Vision system software is able to assess the degree of compression and indicate to the operator when the appropriate displacement is achieved in order to assure reproducibility of compressions. Elastographic properties of the skin were displayed on the monitor as a colour-coded spectrum ranging from blue to red, corresponding to a range from low strain (less deformable with echopalpation and thus less elastic) to high strain (more deformable with stress, more elastic). This technique has shown promising results in characterizing malignancies in other parts of the body such as breast cancer.⁴¹

For each participant, a pathologic lesion was identified in real-time using USE to obtain a hemisection of the lesion plus flanking healthy tissue in the same field of view. This allowed an image of the lesion to be obtained corresponding to the best approximation of the slice that would be interpreted on histopathology. The strain of a region was quantified using software that allowed the dermatologist performing elastography to manually draw a ROI guided by the anatomy of the lesion in B mode and the colour-coded spectrum in elastography, which was displayed as an overlay on the image. Care was taken to draw each ROI approximately the same size to the best of the operator's ability. A ROI was drawn within the image of the pathologic lesions and marked as ROI "A" (ROI-A) by manually selecting the region of the lesion that was observed to have the lowest strain value (e.g. dark blue), which indicates the greatest relative stiffness.

A region of adjacent normal and uninvolved tissue (e.g. green average relative stiffness) within the same field of view at the level of the target lesion and within the corresponding layer of epidermis, dermis and/or subcutaneous tissues was then manually selected as ROI "B" (ROI-B). Normalcy of tissue was

Table 1. Type of lesions observed

Lesions	Histopathology	Total
Malignant		29
	Basal cell carcinoma	17
	Squamous cell carcinoma	12
Benign		38
	Pilar and epidermoid cyst	5
	Keloid scar	3
	Seborrhoeic keratosis	11
	Hyperkeratotic actinic keratosis	7
	Benign nevus	6
	Skin tag	5
	Angiokeratoma	1

determined by the absence of a lesion on the surface, the homogeneity of the elastograph below the surface and the presence of well-defined epidermal and dermal layers. This region was selected to serve as a control to signify an area outside of the lesion representing what was believed to be normal adjacent skin.

The software built into the system then determined an average of the values of the pixels (picture elements) within the ROIs. The ratio of the average strain value of ROI-B (normal skin) to that of ROI-A (average strain value of the portion of the lesion with minimum strain) was then computed as a strain ratio. This ratio represents the average compressibility of the normal comparable adjacent skin layer to that of the minimum compressibility of the skin lesion (usually less compressible). It was predicted that a low strain or less compressible skin lesion, such as a malignancy, would have a low average value in the ROI compared with surrounding normal skin, which would result in a relatively high strain ratio, which was defined as the average value of ROI-B/ROI-A.

Lesions that were not able to be imaged with an elastograph and corresponding strain ratio that was reproducible without artefact at least three times were excluded from the analysis. All images and calculations were stored on the Hitachi Hi Vision system for subsequent comparison with histopathology. The operator was blind to the histopathology results until completion of the study when results were compared retrospectively to evaluate the usefulness of the strain ratio.

After imaging was complete, a shave biopsy was performed according to the standard of care in the shape of an ellipse with the axis of the longest dimension corresponding to the footprint of the transducer. Histopathological analysis was subsequently performed by a team of dermatopathologists (Pinkus Dermatopathology Laboratory, Monroe, MI) who were unaware of the ultrasound or elastography findings. Tissue was processed by sectioning along the axis of the longest dimension of the elliptical specimen.

RESULTS

There were a total of 55 participants and 69 lesions initially included in the study. There were two lesions from one patient that were excluded from the analysis owing to the inability to obtain a reproducible elastograph without artefact. This left a total of 67 lesions that were included in the analysis, all of which had biopsy-proven disease. Of the 67 lesions, 29 (43%) were diagnosed as malignant and 38 (57%) were diagnosed as benign. Malignant skin lesions were basal cell carcinomas and squamous cell carcinomas. Benign epidermal and dermal skin lesions included seborrhoeic keratosis, actinic keratosis, keloid scar, and epidermoid cyst, and others (Table 1).

In all patients, the ultrasound images at 14 MHz were of sufficient resolution to distinguish the layers of the epidermis from the dermis and the dermis from the subcutaneous tissue. The entire skin lesion and surrounding normal tissue were imaged in a single field of view for all lesions imaged.

There was a clear separation among the B/A ratios between benign and malignant lesions, and there was no overlap in B/A ratios between benign and malignant lesions. The strain ratio of the 29 malignant lesions ranged from 3.9 to 32.2, whereas that of the 38 benign lesions ranged from 0.01 to 3.0 (Table 2). As expected, malignant lesions were less elastic (or more “stiff”) than corresponding healthy skin in the same region (Figures 1 and 2; Supplementary Figure A). All malignant lesions in this study were found to have a strain (compressibility) at least 3.9 times lower than that of corresponding normal skin. Benign lesions had a strain value of at most 3.0 times less than normal corresponding skin (Figure 3). The strain ratio provided clear differentiation of malignant from benign lesions with no overlap between the lowest elastic ratio of the malignant lesions (3.9) and the highest elastic ratio of the benign lesions (3.0) (Figure 4).

The ability of the USE strain ratio to differentiate benign from malignant tissue was highly significant ($p = 0.0007$). A student's t -test was used to determine the p -value. For the lesions included in this study, the distinct separation provided by the B/A ratio would result in an effective 100% sensitivity and 100% specificity for this USE technique if a strain ratio of ≥ 3.0 were selected for malignant lesions and a strain ratio of ≤ 3.0 were established for benign lesions.

Table 2. Maximum and minimum strain ratios for benign and malignant lesions

Lesions	Maximum strain ratio	Minimum strain ratio
Malignant	32.2	3.9
Benign	3	0.01

The minimum strain ratio of malignant lesions was uniformly higher (B/A range 3.9^a to 32.2) than the maximum strain ratio of benign lesions (B/A range 0.01 to 3.0).

^aOnly one malignant lesion was found to have a strain ratio <4.7.

Figure 1. A sample of a basal cell carcinoma. An example of a malignant lesion (a) that appears hypoechoic on B mode imaging with a convex, relatively hyperechoic border pushing down from the dermis with a $B/A = 6.36$. The hardest area within the lesion (marked "A") is compared to the region of healthy adjacent skin at the same level (marked "B") to calculate the B/A strain ratio. The harder areas, depicted in blue, on the elastography image (a) at the deeper portion of the lesion on elastography imaging appear to correlate with increased cellularity on (b) corresponding histopathology, which confirmed basal cell carcinoma. For colour image see online.

(a)

(b)

In one interesting case, the echotexture of the B mode image of the lesion appeared homogeneous while the addition of elastography highlighted heterogeneity that was not appreciated in the B mode image alone ([Supplementary Figure B](#)). When later compared with the histopathological findings, the differences in tissue laxity observed on elastography were consistent with cellular organization within the lesion. It is possible that functional information provided by elastography allowed detection of tissue heterogeneity that could not be well characterized at this resolution by B mode imaging alone.

There was one “colliding” neoplasm observed in the study that was oriented such that only the superficial lesion (later diagnosed as benign seborrheic keratosis) was observed clinically on the epidermis ([Figure 5](#)). Colliding lesions show no distinct border on dermatopathological analysis. Immediately deep to and colliding with the benign lesion, a basal cell carcinoma was identified by histopathology. For this case, a strain ratio in the malignant range was determined on USE despite the malignant lesion not being clinically visible on the surface of the skin.

Figure 2. A sample of a squamous cell carcinoma. An example of a raised lesion that is observed on the B mode image with hypoechoic echotexture superficially (a). The deeper border of the lesion is relatively more hyperechoic and is more easily differentiated on elastography as a relatively stiff (blue) region (marked A) from adjacent uninvolved tissue (marked B) with a B/A = 32.2. (b) The corresponding histopathology showed squamous cell carcinoma. For colour image see online.

(a)

(b)

23 (79%) of the malignant lesions had a strain ratio between 3.9 and 12.0, and there were five lesions (17%) that clustered around a 5.0 strain ratio. The lowest strain ratio for malignant lesions was 3.9 (Figure 6). On histopathology, this lesion was found to be a squamous cell carcinoma invading into the dermis. The lesion contained a region of central necrosis that correlated with the elastography finding of a relatively soft (yellow-green) central region. Although the B/A ratio of 3.9 for this lesion containing necrosis was less than the other malignant lesions, it was still greater than the benign lesions.

DISCUSSION

This study demonstrates the application of skin USE with strain ratio in evaluation of basal cell carcinomas and squamous cell carcinomas and several types of benign solitary skin lesions. When the strain ratio of ROI-B to ROI-A was compared with histopathology, malignant lesions were found to have a higher strain ratio than do benign lesions suggesting decreased elasticity among malignant lesions. These results suggest that USE plus strain ratio may help distinguish malignant from benign skin lesions. Although this pilot study found that only 43% of the clinically suspicious lesions included for evaluation were

Figure 3. A sample of a benign lesion. On B mode, the lesion is seen as a thickened hypoechoic area in the dermis. The least elastic area (blue) within the lesion (marked A) is compared with adjacent normal tissue at the same level (marked B) resulting in a $B/A = 1.92$ (a). The corresponding histopathology confirmed a benign lesion, seborrhoeic keratosis (b). For colour image see online.

(a)

(b)

malignant, this study was not designed to assess the clinical utility of USE with strain ratio compared to clinical evaluation in routine dermatology practice. However, future studies with larger number of subjects at multiple centres may offer the potential to substantially impact clinical practice if the results of this study are reproducible.

The maximum benign (3.0) and minimum malignant (3.9) strain ratios were defined without a priori reference criteria for

such a differentiation. Instead, this ratio was established retrospectively. Although this study showed 100% correlation between skin USE and histology, the total number of patients was limited and the number of cases per pathological entity was relatively small. The lack of strain ratio values between 3.0 and 3.9 also suggest that more lesions need to be analysed before diagnostic criteria can be chosen. There was a large subgroup of malignant lesions relatively close in strain ratio to the benign group, which suggests that more overlap may occur in a larger

Figure 4. Strain ratio of malignant vs benign skin lesions. Ordered lesions and their respective B/A strain ratios are graphed as a scatter plot with malignant lesions in blue and benign lesions in red. A clear separation was observed in the B-to-A ratio of malignant vs benign lesions with a p -value of 0.0007 calculated using a student's t -test. For colour images see online.

sample set. The lesion with a strain ratio nearest to the benign range was noted to contain significant central necrosis; however, specific factors that may contribute to the strain ratio of malignant lesions were not evaluated and require further study. If potentially more aggressive lesions consistently demonstrate lower strain ratios, it would be important to minimize the potential for the most dangerous lesions registering as false negatives. Therefore, it is important for future studies to consider the polychotomy of cancerous lesions with respect to strain ratio and other features. The performance of the strain ratio to distinguish cancerous from healthy skin lesions would be best evaluated prospectively after more lesions are analysed and diagnostic criteria for using the strain ratio is proposed.

Variability of results between operators and different elastography systems was outside the scope of this feasibility study and thus was not evaluated. Before any criteria are established for USE strain ratio differentiation of solitary benign from malignant skin carcinomas, a significantly larger number of patients should be scanned, ideally with multiple operators across several institutional settings. This approach could help to evaluate operator dependence and variability

using different USE systems and a broader range of skin lesions. Nonetheless, the proof of concept is supported by our results.

The higher B/A strain ratio of basal and squamous cell carcinomas may be the result of the inherently stiff (or less compressible) nature of malignancy and greater adherence of malignant lesions to surrounding tissue. This has previously been shown in USE to correlate with increased cellularity in cancerous lesions.⁴² Or it may be the result of a disruptive impact of malignant lesions on surrounding tissue with a tendency for greater extracellular matrix change and/or deposition.^{43–47} These changes affect the elastic modulus of the tissue, which is proportional to measured tensile strain. The elasticity of the tissue and therefore the strain ratio is not related to the size or depth of the lesion. Small lesions can be less elastic with higher strain ratios, large lesions can be more elastic with lower strain ratios and the inverse is also true. The goal of this study is not to determine the physiological mechanism of decreased elasticity in malignant skin tumours, but instead to use this observation diagnostically.

Although cancerous lesions were relatively well demarcated macroscopically using conventional ultrasound in combination

Figure 5. A sample of a colliding neoplasm with a malignant lesion deep to a benign lesion. (a) The elastographic image shows a benign lesion seen as a hyperechoic focus at the top of the image. Underlying the epidermal growth there is also an area with decreased elasticity in dark blue (marked A) and adjacent normal tissue (marked B) with a calculated $B/A = 17.65$. A microhistograph showing a benign lesion (seborrheic keratosis) involving the epidermis (b). Just deep to this benign lesion is a malignant basal cell carcinoma colliding neoplasm (black arrowheads) which correlates with the area of decreased elasticity on ultrasound elastography. On clinical evaluation, only the lesion involving the epidermis was appreciated, and the underlying cancer could not be seen. For colour image see online.

(a)

(b)

with USE, all lesions manifest some degree of heterogeneity. It is possible that there could be an extension of cancerous tissue that was not visualized qualitatively into ROI-B. If this occurred, tissue selected as healthy adjacent tissue could actually contain cancer. If this occurred, instead of comparing the cancerous lesion to

adjacent uninvolved tissue, the ROI-B could be misregistered comparing the cancer to an area of mixed composition cancerous and healthy tissue. This could result in a false negative where the cancerous tissue would inappropriately appear to have a lower strain ratio similar to benign lesions. There were

Figure 6. The most elastic of the malignant lesions contained necrosis. An elastographic image (a) showing the malignant lesion with the lowest strain ratio in this study ($B/A = 3.91$), depicted as deep blue and marked A, adjacent to normal tissue at the same level, marked B. A microhistograph showing an invasive squamous cell carcinoma involving the dermis (b), with large areas of necrosis (black arrowheads). For colour image see online.

no false negatives encountered in this study. Therefore, either this type of misregistration did not occur or the effect was not significant enough to lower the strain ratio to the range of benign lesions.

Lesions located in sharply curved parts of the body, such as the fingers or nose were more difficult to evaluate elastographically because of problems in applying evenly propagated compressions on those surfaces. This results in distorted images and

renders the strain ratio less reliable. Non-uniform compressions and poor contact with tissue results in falsely depressed elasticity (blue) (Figure 7).

Limitations

A limitation of the current study was the resolution provided by the ultrasound transducer and the ultrasound system utilized. Although at the time of publication there are commercial transducers in the 18–20 MHz range available in the United

Figure 7. Samples of artefacts that could affect the B/A ratio if not recognized. An image of a lesion located on the curvature of the neck (a). The neck curvature resulted in inaccurate detection of decreased elasticity (blue) in the normal epidermis, dermis and subcutaneous tissue (left) of the target lesion (marked B) on elastographic imaging, which would be expected to register similar on the elastograph as the area of normal tissue (marked A) on the B mode image. This could have resulted in a false positive if the artefact was not identified. (b) The corresponding histology showed benign cephalic histiocytosis. (c) Another lesion located on the flat surface of the back of the same patient. This image shows artificially decreased laxity of normal tissue to the far left of the lesion (blue) compared with healthy tissue directly adjacent to the lesion (green). The red colour (as seen to the right of the image) is an artefact indicating an area of the healthy tissue depressed too forcefully to be properly resolved. Together, these artefacts represent a non-uniform depression with significantly more pressure delivered on the right side of the lesion than the far left. For colour image see online.

States and Europe, the 14-MHz transducer was the highest frequency available for use on the Hitachi Hi-Vision USE commercial system in the United States at the time this study was performed. The limited resolution of the 14-MHz transducer resulted in difficulty in imaging small or thin lesions of actinic keratosis, squamous cell carcinoma *in situ* (Bowen disease) and superficial basal cell carcinomas. Although the use of ultrahigh-frequency ultrasound has been reported in the literature in the 20–100 MHz range, these studies typically use proprietary or custom-built transducers that are not FDA approved for routine clinical use. According to the literature, one may achieve a resolution as high as 40 microns per pixel with high-frequency ultrasound at 50 MHz.⁵ At these frequencies the basement membrane, which is an important landmark to determine the invasive nature of epidermal skin cancers, could potentially be evaluated reliably *in vivo* before biopsy. To our knowledge, there are no technical limitations that would preclude the use of USE or shear elastography at these high frequencies.

The initial method for application of skin USE with strain ratio described in this study relied on the existing, readily available hardware and software. This meant significant user input to

image acquisition and analysis. Strain elastography is subject to interuser and intrauser variabilities requiring a sufficient level of proficiency and technical ability by the user. For instance, the user must be able to generate consistent compressions, to identify the lesion, and its least compressible region, then select the ROIs without any guidance from the software. In this study, an individual operator performed all strain elastography and image analysis, which improved reproducibility, but could have the potential to introduce bias. Therefore, care was taken to follow a defined protocol for image analysis in the same fashion for each image. The operator performed USE and image analysis prior to biopsy and was blind to histopathological analysis until completion of the study. It is possible that software or hardware modifications that allow a similar approach with less user input could make the technique described in this study more accessible, generally reproducible and less prone to bias. Indeed, shear elastography is one technique that shows promise in improving performance through transducer-generated compression.^{48–51}

CONCLUSION

This pilot study demonstrates that USE plus strain ratio may be a promising modality in providing diagnostic determination between cancerous and benign primary solitary skin lesions prior to

biopsy. The fact that skin is easily accessible to biopsy and excise has made skin imaging a relatively unexplored frontier in diagnostic imaging. To effectively augment or supplant the invasive, time consuming and expensive practice of biopsies of skin lesions, a diagnostic imaging procedure will need to be highly accurate and precise in the detection of neoplasms. Although these pilot results are promising, they should be followed by larger studies with multiple systems and different operators to better assess real world impact. Standardization among manufacturers of the evolving technology and software, particularly including minimization of user dependence, would potentially increase reproducibility of results and lead to a reliable diagnostic criteria. Users need to be well trained and practiced in the use of the technology and in the interpretation of the results. A future study comparing USE to the assessment of a clinician blinded to the

results of the technique in selecting concerning lesions for biopsy is needed before the clinical utility of USE can be assessed.

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