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Characterization of Ovarian Masses using Contrast-Enhanced Subharmonic Imaging

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***Abstract*— This clinical pilot study evaluated whether contrast-enhanced ultrasound subharmonic imaging (CEUS SHI) could be used to characterize indeterminate ovarian masses prior to surgical intervention. Ten women (with twelve lesions) scheduled for surgery of an ovarian mass underwent CEUS SHI examination of their pelvis using a modified Logiq E9 scanner (GE Healthcare, Waukesha, WI, USA) with an endocavitary transducer. Patients first received a bolus injection of ultrasound contrast agent Definity (Lantheus Medical Imaging, N Billerica, MA, USA), while ultrasound imaging was continuously performed up to 5 minutes after contrast injection. Following a 10 minute wait to ensure contrast agent clearance from the circulation, patients received an infusion of 1.5 ml of Definity diluted in 25 ml of saline over 5 minutes. During this time, destruction/ replenishment CEUS SHI imaging was performed in multiple planes across the lesion. The contrast time intensity curves were created off-line to quantitatively evaluate CEUS SHI kinetic parameters, which were compared to the tissue histology of the lesion after surgery. Of the 12 lesions, 8 were benign and 4 were malignant. Qualitative analysis of CEUS SHI images by a radiologist with 15 years of CEUS experience demonstrated diagnostic accuracy (determined as the area under the ROC curve) of 70%, compared to 56% without contrast, while analysis by a radiologist with 6 months of experience only improved from 50% to 57%. Diagnostic accuracy of quantitative CEUS SHI kinetic parameters was as high as 81%. Malignant masses showed significantly higher peak contrast intensity ($p = 0.046$) and overall perfusion ($p = 0.045$) than benign lesions. These results suggest that CEUS SHI for pre-surgical characterization of ovarian lesions may improve determination of malignancy, albeit based on a small sample size.**

Keywords—subharmonic imaging, ovarian masses, contrast-enhanced ultrasound

I. Introduction

With approximately 240,000 new cases diagnosed annually, ovarian cancer is the seventh most commonly diagnosed cancer in women in the world [1]. In addition to this high incidence, ovarian cancer also carries an extremely high mortality rate of approximately 64%, with 152,000 deaths annually [1].

Unfortunately, approximately 75% of cases are diagnosed at late-stage, highlighting inadequacy in conventional endovaginal ultrasound (US) imaging and pelvic examinations for early ovarian cancer detection [2]. Furthermore, a large proportion of ovarian masses are deemed indeterminate upon detection. This results in up to 80% of women with indeterminate or suspicious adnexal masses undergoing surgical resection, primarily out of an abundance of caution, due to the high mortality rates associated with late-stage ovarian cancer [3, 4]. Therefore, there is a critical clinical need for a more accurate method for early characterization of adnexal lesions.

One of the features that differentiates malignant tissues from normal is tumor is neoangiogenesis, commonly resulting in increased blood flow in malignant lesions [5]. Neoangiogenesis is the growth of new blood vessels, and is a fundamental physiological process for reproduction, development and wound repair [5]. Abnormal rapid proliferation of blood vessels (so called pathologic angiogenesis) plays an essential role in the growth of tumors and development of metastases [5].

Contrast-enhanced US (CEUS) has a well-documented history for providing valuable information about blood flow and perfusion [6, 7]. CEUS utilizing subharmonic imaging (CEUS SHI) could help address this clinical need by providing a more accurate imaging technique at earlier stages, and may ultimately improve patient survival. CEUS SHI transmits at twice the resonant frequency of the contrast agent and receives at half of the transmit frequency, allowing for improved suppression of background tissue echoes compared to conventional CEUS [8, 9]. As a result, SHI has a potential to improve the detection of slow, small volume blood flow associated with early tumor angiogenesis [7, 10, 11]. Therefore, this pilot study evaluated whether CEUS SHI could be used to characterize ovarian masses prior to surgical intervention.

II. Materials and Methods

The Institutional Review Board of Thomas Jefferson University approved this study. Ten women (with 12 lesions) scheduled for surgery of an indeterminate or suspicious ovarian mass provided informed consent to be enrolled in this prospective FDA-approved (IND no 124,465) pilot study between August 2017 and August 2018.

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A. *Ultrasound Examination*

Patients underwent a CEUS SHI examination of their pelvis using a modified Logiq E9 scanner (GE Healthcare, Waukesha, WI, USA) with an IC5-9-D endocavitary transducer. Two contrast injections were performed during the examination. Patients first received a 1.5 ml bolus injection of Definity (Lantheus Medical Imaging, N Billerica, MA, USA) while the imaging was performed for up to 5 minutes after injection. After a 10 minute wait to ensure contrast clearance from the circulation, patients received an infusion of 1.5 ml Definity diluted in 25 ml saline over 5 minutes. During this time destruction/replenishment CEUS SHI imaging was performed in multiple planes across the lesion.

B. *Data Analysis*

Ultrasound contrast time-intensity curves were generated offline using Matlab software (MathWorks, Natick, MA, USA) to quantitatively evaluate CEUS SHI parameters, calculating the peak contrast intensity (PI), time to peak contrast enhancement (TTP), area under the curve (AUC), and estimated tumor perfusion (PER) derived from the slope of the wash-in portion of the time intensity curve related to the fractional blood volumes measured over the cine clips [7]. These parameters were compared to the tumor histology obtained after surgery, used as a clinical reference standard.

CEUS SHI images were also qualitatively assessed by two radiologists, one with more than 15 years of experience (R_exp) and one with only 6 months of experience (R_nov). The radiologists were blinded to the clinical reference standard, and were provided with randomized, matching grayscale and CEUS SHI clips. Cases were then scored using a 5-point visual-analog scale, with 1 representing benign, 2 probably benign, 3 representing an indeterminate mass, 4 probably malignant, and 5 representing malignant. The two readers also reported their confidence (in %) for each diagnosis made.

C. *Statistical Analysis*

Statistical analysis was performed with Stata 15 software (StataCorp, College Station, TX, USA), using t-tests to compare the data between groups, with p-values below 0.05 indicating statistical significance. Additionally, reverse stepwise logistical regression (ROC curves) was performed to determine diagnostic accuracies. Results were collected in triplicate, and error is reported as standard deviation (SD).

III. Results and Discussion

Only a small portion (approximately 15%) of all indeterminate ovarian lesions that are surgically removed are actually malignant [12], making the development of a more definitive pre-operative lesion classification a critical clinical need. This pilot study represents one of the first attempts to use transvaginal CEUS SHI in patients scheduled for surgical excision of an indeterminate or suspicious ovarian mass as a potential tool for preoperative characterization of the lesion.

Representative CEUS SHI images of both benign and malignant lesions are shown in Figure 1. Benign lesions typically presented with hypoechoic regions (Fig. 1B right), while malignant lesions typically presented with hyperechoic regions (Fig. 1D right) on the CEUS images that demonstrated increased blood flow.

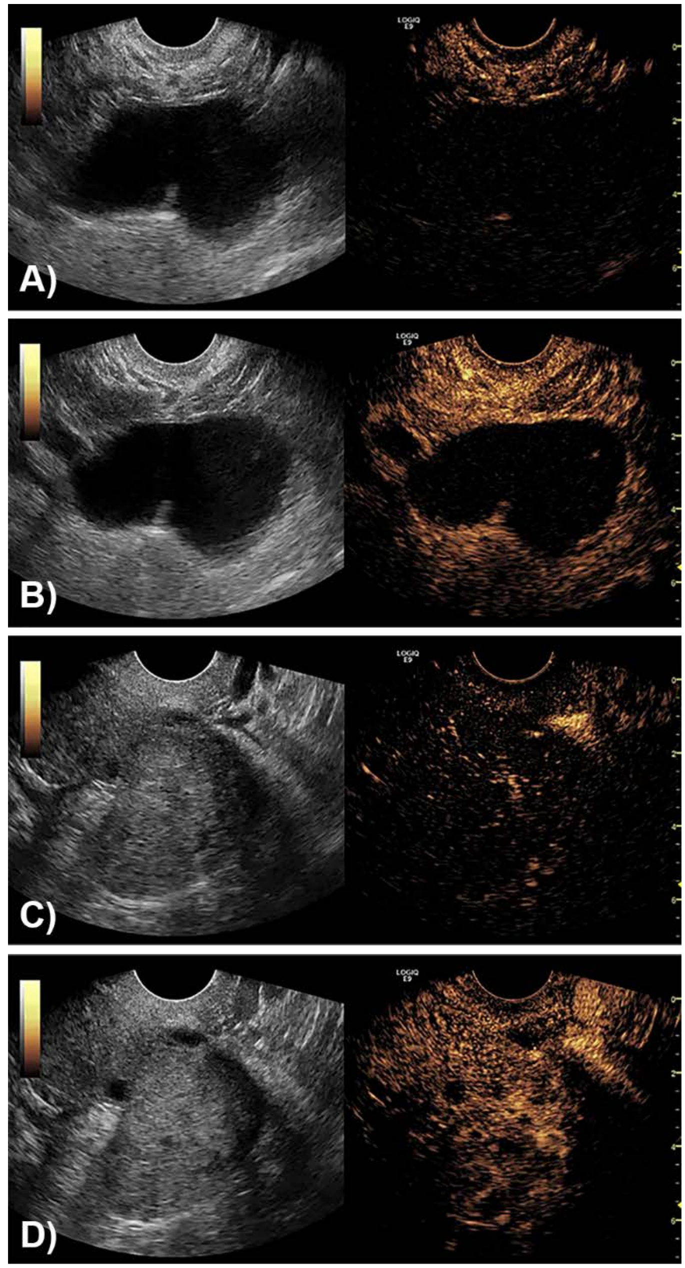

Fig. 1. Representative CEUS SHI images from study patients. A) Pre-contrast image of a benign lesion. B) Post-contrast image of a benign lesion; note the hypoechoic regions of the CEUS SHI image on the right. C) Pre-contrast image of a malignant lesion. D) Post-contrast image of a benign lesion; note the hyperechoic regions of the CEUS SHI image on the right.

Quantitative analysis showed that PI was significantly lower in benign lesions (0.05 ± 0.03 AU) than in malignant lesions (0.11 ± 0.09 AU, $p = 0.046$). Benign masses were also significantly less perfused (PER) (7.62 ± 6.50%) than malignant masses (24.79 ± 25.34%, $p = 0.045$). There was no difference in TTP and AUC between benign and malignant lesions ($p > 0.06$). PER had the highest diagnostic accuracy (defined as the area under the ROC curve) at 81%, as shown in Figure 2A. The rest of the parameters ranged in accuracy from 52% (TTP) to 75% (AUC).

The importance of familiarity with CEUS was highlighted by the diagnostic confidence reported by two radiologists with different levels of CEUS experience. There was a significant increase in diagnostic confidence for the experienced radiologist (68% with grayscale to 86% with SHI imaging, $p = 0.042$), but no improvement in confidence for the inexperienced radiologist (83% with grayscale to 86% with SHI imaging, $p = 0.27$). This corresponded to an improvement in diagnostic accuracy for the experienced radiologist (from 56% with grayscale to 70% with SHI imaging), but only a 7% change for the inexperienced radiologist (from 50% to 57%). When the qualitative reads are combined with the most predictive quantitative SHI parameter (PER), diagnostic accuracy improved to 84% for the experienced radiologist and 96% for the novice reader (Figure 2B).

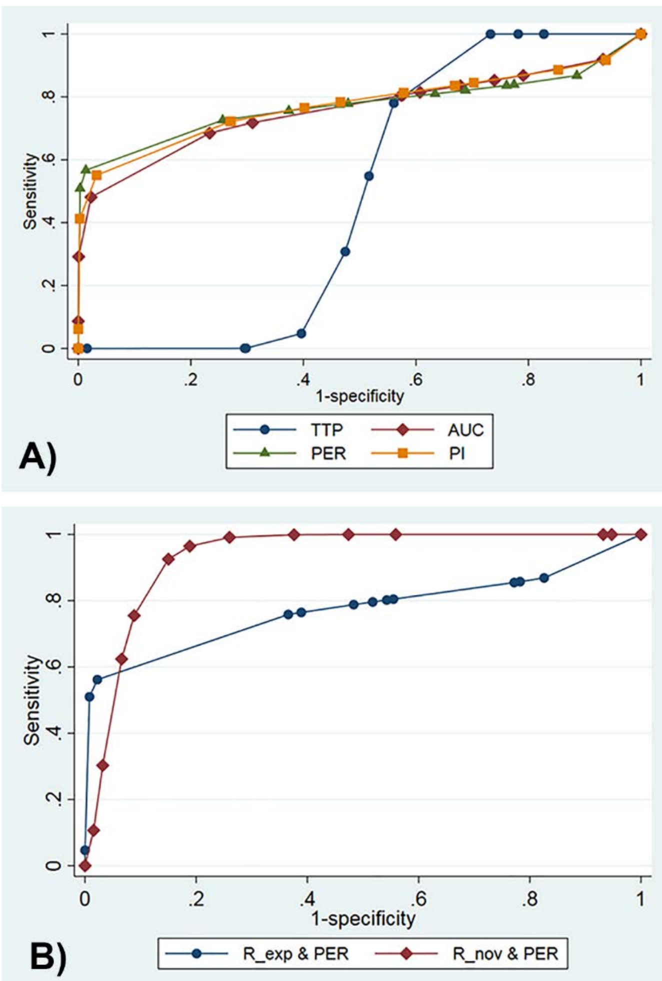

Fig. 2. ROC curves for parameters from CEUS SHI clips. A) Diagnostic accuracies for the four quantitative SHI parameters. B) Diagnostic accuracies of radiologist reads combined with PER.

Our findings suggest that noninvasive, transvaginal, CEUS SHI has the potential to improve pre-operative characterization of ovarian masses, albeit based on a small sample size. If successful, this modality could reduce both risk and cost to the patient by eliminating unnecessary surgical removal of definitely benign lesions, while also improving diagnostic accuracy of ovarian cancer diagnosis.

IV. Conclusion

These findings have potential to make a clinical impact, since there is currently no noninvasive method for definitively determining malignancy in ovarian masses. However, this is a pilot study, and a larger sample size from a high risk population (most likely across multiple medical centers) will be necessary to further substantiate any clinical translation of ovarian SHI.

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