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## Characterization of Adnexal Masses Using Contrast-Enhanced Subharmonic Imaging: A Pilot Study.

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Characterization of Adnexal Masses Using Contrast-Enhanced Subharmonic Imaging: A  
Pilot Study

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1 **Abstract**

2           This pilot study evaluated whether contrast-enhanced subharmonic imaging (SHI)  
3 could be used to characterize adnexal masses prior to surgical intervention. Ten women  
4 (with 12 lesions) scheduled for surgery of an ovarian mass underwent a SHI examination  
5 of their adnexal region using a modified Logiq E9 scanner (GE, Waukesha, WI) with an  
6 endocavitary probe, where digital clips were acquired using pulse  
7 destruction/replenishment SHI imaging across the lesion. Time intensity curves were  
8 created off-line to quantitatively evaluate SHI parameters (fractional tumor perfusion,  
9 peak contrast intensity, time to peak contrast enhancement, and area under the time  
10 intensity curve), which were compared to pathological characterization of the lesion. Of  
11 the 12 masses, 8 were benign and 4 were malignant. Qualitative analysis of the SHI  
12 images by an experienced radiologist resulted in a diagnostic accuracy of 70%, compared  
13 to 56% without contrast, while an inexperienced radiologist improved from 50% to 58%  
14 accuracy, demonstrating the benefit of SHI. Quantitative analysis of SHI parameters  
15 produced diagnostic accuracy as high as 81%. Peak contrast intensity was significantly  
16 greater in malignant than benign masses ( $0.109 \pm 0.088$  AU vs.  $0.046 \pm 0.030$  AU,  $p =$   
17  $0.046$ ). Malignant masses also demonstrated significantly greater perfusion than benign  
18 masses ( $24.79 \pm 25.34\%$  vs.  $7.62 \pm 6.50\%$ ,  $p = 0.045$ ). When the radiologist reads were  
19 combined with the most predictive quantitative SHI parameter (% perfusion), diagnostic  
20 accuracy improves to 84% for the experienced radiologist and 96% for the novice  
21 radiologist. Results indicate SHI for pre-surgical characterization of adnexal masses may  
22 improve the determination of malignancy and diagnostic accuracy; albeit based on a small  
23 sample size.

24 **Keywords:**

25 Subharmonic imaging, adnexal masses, diagnostics, contrast agents

26

## 27 **Introduction**

28           Ovarian cancer is the seventh most commonly diagnosed cancer in women  
29 worldwide, with approximately 240,000 new cases diagnosed and 152,000 deaths each  
30 year (representing a 64% mortality rate) [1]. Ovarian cancer is also the fifth most common  
31 cause of cancer death in women in the United States, and an estimated 1 in 71 women  
32 in the United States will develop ovarian cancer in their lifetime [2, 3]. If caught early  
33 enough that disease is confined to the ovary (stage I), patients require less morbid  
34 surgical intervention, have significantly improved quality of life, and most importantly have  
35 a 5-year survival rate of approximately 90% [2, 4, 5]. Unfortunately, roughly 75% of new  
36 diagnoses are late-stage cancers, bringing the mortality rates up as high as 80% [5]. The  
37 prevalence of late-stage diagnoses clearly highlights the inadequacy of conventional  
38 endovaginal ultrasound (US) imaging and pelvic examinations as the first-line in detecting  
39 adnexal masses [6-8]. Additionally, once detected, many adnexal masses are deemed  
40 clinically indeterminate with first-line US imaging, and follow-up magnetic resonance  
41 (MR), and computerized tomography (CT) imaging cannot always definitively  
42 characterize them as benign or malignant [9, 10]. Therefore, up to 80% of presenting  
43 patients undergo surgery out of an abundance of caution, in response to the  
44 aforementioned mortality rates for late-stage disease [11-13]. Thus, there is a clear  
45 clinical need for earlier and accurate characterization of adnexal masses to improve  
46 patient survival.

47           Imaging techniques can play a critical role in improving detection and diagnosis of  
48 ovarian masses, especially in the assessment of angiogenesis and blood perfusion in the  
49 lesion [6, 7, 14, 15]. One of the earliest changes that differentiates cancerous tissues from

50 normal tissues is tumor angiogenesis [16, 17]. Additionally, the morphology of these  
51 angiogenic vessels can serve as a predictor of malignancy in cancerous masses [18, 19],  
52 including those in the adnexal region [20, 21]. Angiogenic vessels form a substantial  
53 portion of the mass of malignant lesions (up to 10% of total tumor volume) [22], providing  
54 a strong opportunity for noninvasive imaging to improve on the classification of these  
55 adnexal lesions compared to purely anatomical imaging modes. While contrast-enhanced  
56 MR and CT can be up to 90% accurate in classifying adnexal masses that were deemed  
57 indeterminate with first-line US [6, 23], these secondary modalities are costly and utilize  
58 contrast agents associated with marked adverse reactions, and CT also exposes patients  
59 to significant ionizing radiation. However, contrast-enhanced US (CEUS) imaging has  
60 great potential to provide clinically relevant information related to measuring angiogenesis  
61 and blood flow in adnexal lesions. Specifically, CEUS imaging using gas microbubbles  
62 greatly improves the ability to visualize tumor angiogenesis and quantify blood flow within  
63 tumors, including adnexal masses, without the marked adverse reactions and  
64 contraindications of MR and CT contrast [14, 24-26]. Several studies have shown that  
65 CEUS imaging can be useful in classification of adnexal masses as benign or malignant  
66 [14, 26-29], and characterizing blood flow kinetics in these masses [30]. However, these  
67 techniques fall short of clinically viable accuracy in diagnosis, likely due to image  
68 degradation and reduction in blood-to-tissue contrast in tissue [31].

69 In an effort to address this clinical need, we have been developing a contrast-  
70 specific imaging modality known as subharmonic imaging (SHI). SHI transmits the  
71 ultrasound signal at twice the resonance frequency ( $2f_0$ ) of the ultrasound contrast agent  
72 (UCA) and receives at half of the transmit frequency ( $f_0$ ), which allows for excellent

73 suppression of tissue echoes relative to other US contrast modes [32, 33]. Although other  
74 modes, such as contrast pulse sequences (CPS), pulse inversion, and flash-  
75 replenishment, can be used for tissue suppression, SHI combines the ability to specifically  
76 suppress tissue echoes while also providing quantitative data. Our group, as well as  
77 others, have performed extensive SHI feasibility studies [25, 34-47]. We have also  
78 demonstrated that SHI can detect the slow, small volume blood flow associated with  
79 tumor angiogenesis in a first-in-humans study of women with breast lesions [34, 40-42].  
80 Moreover, UCAs are pure intravascular tracers and enable CEUS to depict tumor  
81 vascularity differently from MR, which uses gadolinium chelates as contrast agents. Given  
82 these advantages, CEUS utilizing SHI could help address the critical clinical need by  
83 providing a more accurate imaging technique at earlier stages, and may ultimately  
84 improve patient survival. Therefore, the objective of this pilot study was to evaluate  
85 whether contrast-enhanced SHI could help characterize adnexal masses prior to surgical  
86 intervention.

87

## 88 **Materials and Methods**

### 89 *Patient Recruitment and Clinical Pathology*

90 Twenty-eight women scheduled for surgery of suspicious ovarian lesions at  
91 Thomas Jefferson University between August 2017 and August 2018 who met the  
92 inclusion criteria for this IRB-approved study were approached to participate. Twelve  
93 women agreed to enroll, and signed informed consent to participate in the study and  
94 undergo a contrast-enhanced SHI exam of the adnexal region prior to surgery. Two  
95 women declined to participate and withdrew consent prior to contrast administration, for



96 a total of ten participants who completed the study. Inclusion criteria included diagnosis  
97 with an adnexal mass, plan for surgical resection of adnexal mass, at least 21 years of  
98 age, and clinically stable. Pre-menopausal subjects had to have a negative pregnancy  
99 test to be enrolled in the study, since pregnancy was one of the exclusion criteria for study  
100 participation. Other exclusion criteria included pulmonary hypertension, cardiac shunts,  
101 or unstable cardiopulmonary conditions, current systemic chemotherapy regimen, clinical  
102 instability or terminal illness with a life expectancy of less than 1 month, and history of  
103 anaphylactic allergy to ultrasound contrast agents. Study subjects ranged in age from 34  
104 to 76 years old, with an average age of 55.5 years. Tumor marker CA-125 and risk of  
105 malignancy (RMI) were determined by pathological evaluation. Following surgery,  
106 excised lesions were classified by clinical pathology as part of standard of care.

#### 107 *Contrast-Enhanced SHI Evaluation*

108 Contrast-enhanced SHI scanning was performed using a Logiq E9 scanner (GE  
109 Healthcare, Waukesha, WI) equipped with an IC5-9-D endocavitary probe, using three  
110 pulse coded excitation SHI mode with a transmit frequency of 7.0 MHz and receiving at  
111 3.5 MHz. Using coded excitation will have marked improvements in signal-to-noise ratio,  
112 due to suppression of tissue signals [48]. Imaging was optimized on an individual basis,  
113 using a mechanical index (MI) below 0.18 in all cases (ranged from 0.10 – 0.18, average  
114 0.13). Patients first received a 1.5 mL intravenous bolus injection of Definity® (Lantheus  
115 Medical Imaging, N Billerica, MA), while digital clips of the lesion in the area with the most  
116 flow seen using power Doppler were acquired for up to 5 minutes after injection. Patients  
117 then rested for 10 minutes to ensure contrast clearance before receiving an infusion of  
118 1.5 mL of Definity diluted in 25 mL of sterile saline over 5 minutes, where digital clips were

119 acquired during flash-replenishment SHI imaging across the lesion, including the same  
120 areas that were previously imaged. These sequences consisted of destructive US pulses  
121 at an average mechanical index (MI) of 0.6 (ranged from 0.5 – 0.8), which ruptured the  
122 UCA within the imaging plane, followed by nonlinear SHI imaging at a lower intensity (MI  
123 of 0.07) to allow monitoring of the UCA re-perfusion into the lesion. An average of 6 pulses  
124 per lesion were collected, with at least 4 per lesion, as the number of pulses collected  
125 was subjective on a case-by-case basis.

126 Time-intensity curves (TICs) and parametric maps were generated offline using  
127 Matlab (MathWorks, Natick, MA) to quantitatively evaluate SHI parameters from the flash-  
128 replenishment sequences. These curves estimate perfusion over the adnexal lesion by  
129 calculating the slope of the curve from the time contrast was first visualized to the peak  
130 intensity. Data from TICs were used to calculate estimated fractional tumor perfusion  
131 (PER), peak contrast intensity (PI), area under the TIC (AUC), and time to peak contrast  
132 enhancement (TTP), which is defined as the time from contrast infusion to the point at  
133 which maximum pixel intensity is reached [25, 40]. The TIC was also fit with a two-  
134 parameter exponential recovery curve:  $VI = \alpha(1 - e^{-\beta t})$ , in which VI represents video  
135 intensity,  $\alpha$  (dB) represents the asymptotic plateau correlative of the microvessel cross-  
136 sectional area, and  $\beta$  (mm/s) represents the blood velocity [49-51]. The product  $\alpha \times \beta$  is  
137 an estimate of perfusion or blood flow per tissue unit (mL/(s\*mg)).

138 Additionally, qualitative assessment of the SHI images was performed by two  
139 radiologists, one who was experienced with CEUS (more than 10 years of experience)  
140 and one who was not (around 6 months of experience). The radiologists were blinded to  
141 the pathological classification of the lesions, and were given both grayscale and contrast-

142 enhanced SHI clips for evaluation. After reviewing each case, the radiologists provided a  
143 qualitative score for diagnosis based purely on their assessment of the images using a 5-  
144 point visual analog scale, with 1 representing benign and 5 malignant, and their  
145 confidence in that diagnosis (on a percent scale).

#### 146 *Statistical Analysis*

147 Statistical analysis was performed with Stata 15 (StataCorp, College Station, TX),  
148 using t-tests ( $\alpha < 0.05$ ) to compare the data between response groups. Receiver  
149 operating characteristics (ROC) curves were used to determine diagnostic accuracies as  
150 the area under the ROC curve [52]. Reverse stepwise logistical regression was used to  
151 combine qualitative and quantitative results to test for improved accuracy. Results were  
152 collected in triplicate, and error is reported as standard deviation (SD).

153

## 154 **Results**

### 155 *Clinical Evaluation of Adnexal Masses*

156 Two patients withdrew their consent and did not complete the study, while ten  
157 patients completed their ultrasound scans. Of these ten patients, two had two adnexal  
158 lesions; for a total of 12 lesions analyzed in this study. Clinical pathology determined that  
159 8 (67%) of the lesions were benign and 4 (33%) were malignant. Benign lesions were  
160 classified as mucinous cystadenoma (3), hydrosalpinx (2), mature cystic teratoma (1),  
161 mixed epithelial neoplasm (1), and endometriosis (1). Malignant lesions were classified  
162 as carcinosarcoma (2), serous adenocarcinoma (1), and adenocarcinoma from colonic  
163 metastasis (1). In the two patients presenting with two lesions, the pathological finding  
164 was consistent for both lesions (i.e. both were benign or both were malignant). Tumor

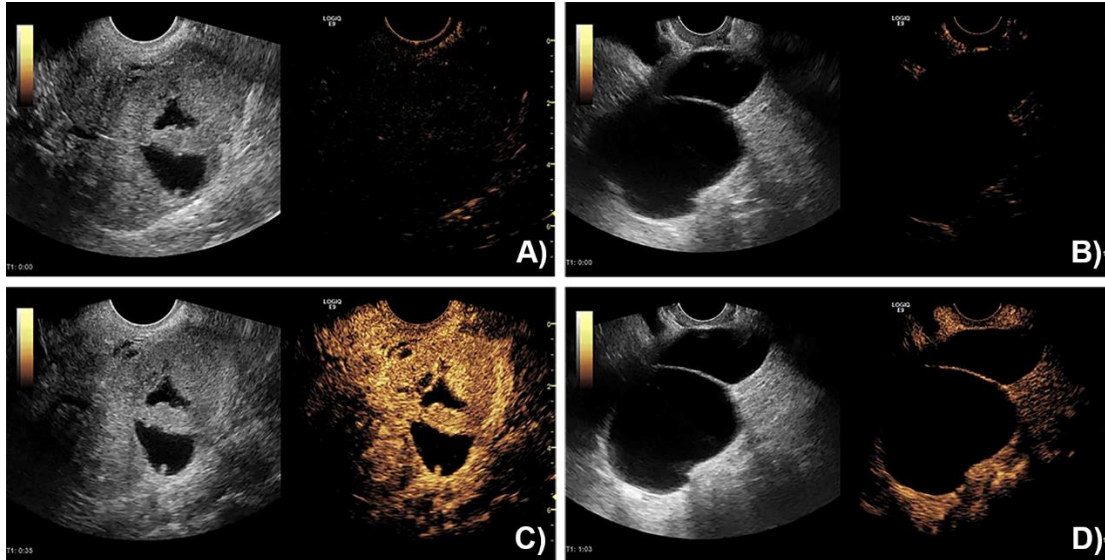
165 marker CA-125 and risk of malignancy index (RMI) were collected for 8 of the 12 lesions,  
166 including 5 of the 8 classified as benign and 3 of the 4 classified as malignant. CA-125  
167 levels in benign lesions ( $17.46 \pm 8.42$  nL) were statistically similar to levels in malignant  
168 lesions ( $56.20 \pm 75.17$  nL,  $p = 0.27$ ). CA-125 had a diagnostic accuracy of 60% in this  
169 pilot study. There was also no statistical difference in the RMI between benign and  
170 malignant lesions ( $104.00 \pm 95.67$  vs.  $505.67 \pm 676.65$ ,  $p = 0.22$ ). The diagnostic accuracy  
171 for RMI was 73%.

172

### 173 *Quantitative Analysis of Contrast-Enhanced SHI*

174 Representative images of lesions classified as malignant and benign are shown in  
175 Figure 1. Malignant lesions (Figs. 1A and C) typically presented with hyperechoic regions  
176 that demonstrated increased blood flow on SHI, while benign lesions (Figs. 1B and D)  
177 typically presented with hypoechoic and/or anechoic regions that indicated fluid-filled  
178 cysts.

179



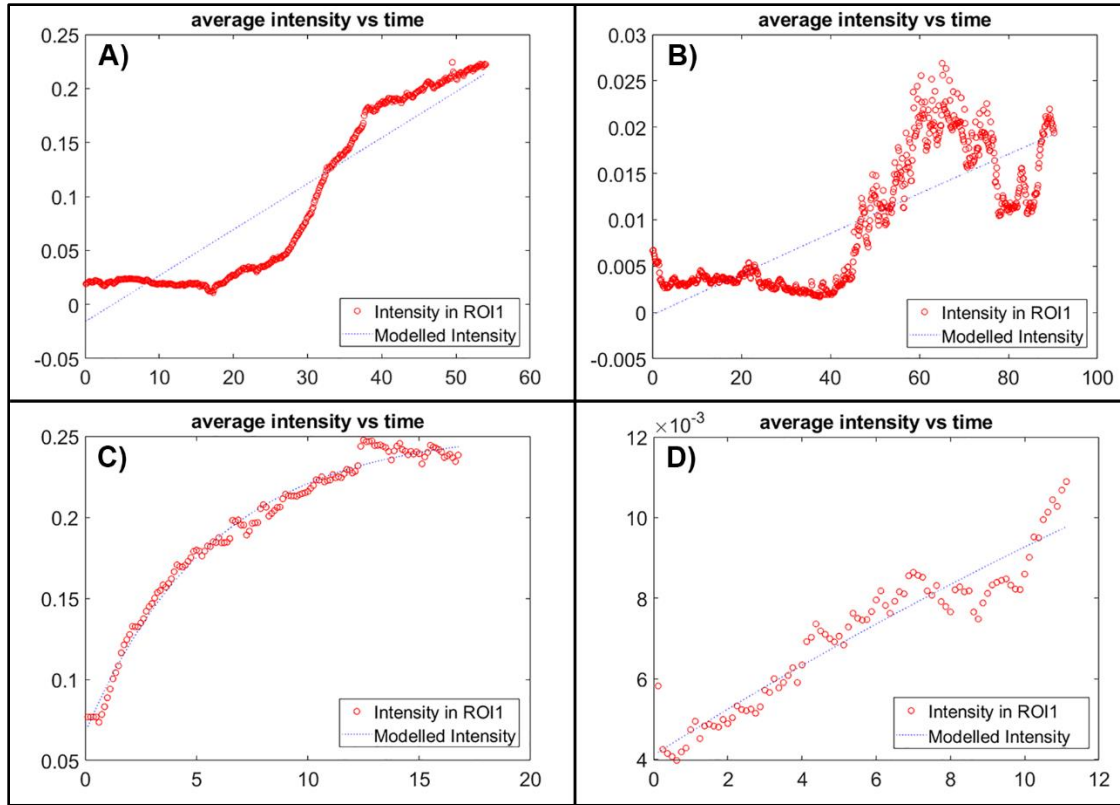
180

181 *Figure 1: Representative SHI images from study patients. A) Pre-contrast image of a*  
 182 *lesion later classified as malignant by pathology. B) Pre-contrast image of a lesion later*  
 183 *classified as benign by pathology. C) SHI of the malignant lesion shown in panel A. D)*  
 184 *SHI of the benign lesion shown in panel B.*

185

186 The outcomes of the quantitative SHI analysis are summarized in Table 1, and  
 187 representative time-intensity curves are shown in Figure 2. Peak contrast intensity (PI)  
 188 was significantly greater in malignant than benign masses ( $0.109 \pm 0.088$  vs.  $0.046 \pm$   
 189  $0.030$ ,  $p = 0.046$ ). Malignant masses also demonstrated significantly greater PER than  
 190 benign masses ( $24.79 \pm 25.34\%$  vs.  $7.62 \pm 6.50\%$ ,  $p = 0.045$ ). There were no significant  
 191 differences between benign and malignant lesions in TTP ( $p = 0.52$ ) or AUC ( $p = 0.06$ ).  
 192 Additionally, the two-parameter exponential recovery model did not yield any significant  
 193 differences between benign and malignant masses for any of the three parameters ( $p =$   
 194  $0.72$  for  $\alpha$ ;  $p = 0.19$  for  $\beta$ ; and  $p = 0.07$  for  $\alpha \times \beta$ ).

195



196

197 *Figure 2: Representative time-intensity curves from study patients. A) Initial wash-in of*  
 198 *contrast within a lesion later classified as malignant by pathology. B) Initial wash-in of*  
 199 *contrast within a lesion later classified as benign by pathology. C) A representative flash-*  
 200 *replenishment sequence from the malignant lesion shown in A. D) A representative flash-*  
 201 *replenishment sequence from the benign lesion shown in B. NOTE: The y-axis values*  
 202 *are scaled to the data in each curve for better visualization.*

203

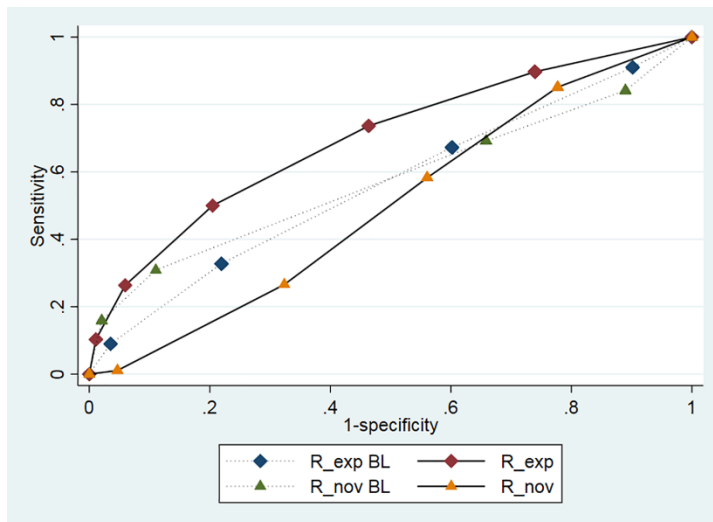
204 Diagnostic accuracy was calculated for each SHI parameter. The fraction of the  
 205 lesion showing perfusion had the highest diagnostic accuracy at 81%. The rest of the  
 206 parameters ranged in accuracy from 52% (TTP) to 79% (model parameter  $\alpha$ ). All  
 207 diagnostic accuracies are presented in Table 1.

208

### 209 Radiological Scoring of CEUS and SHI Clips

210 The performance of the radiologists on the qualitative assessment of the contrast-  
211 enhanced SHI clips demonstrates the importance of familiarity and experience with  
212 CEUS. The diagnostic confidence of the experienced radiologist significantly increased  
213 when reviewing the SHI imaging ( $86 \pm 28\%$ ) compared to grayscale only ( $68 \pm 23\%$ ,  $p =$   
214  $0.042$ ). There was no change in the diagnostic confidence for the novice radiologist  
215 between SHI ( $86 \pm 15\%$ ) and grayscale ( $83 \pm 15\%$ ,  $p = 0.27$ ). The ROC curves associated  
216 with pre- and post-contrast diagnostic confidence for both radiologists are shown in Figure  
217 3.

218



219

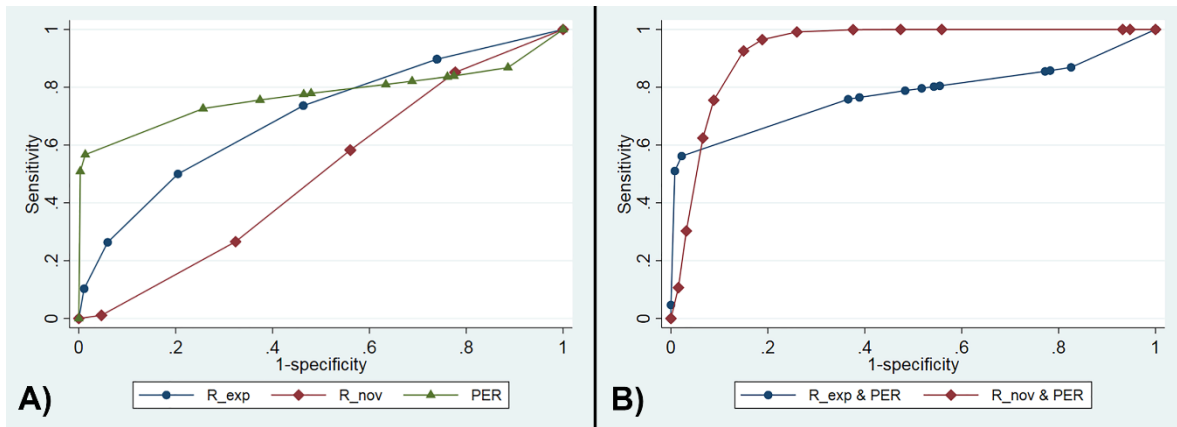
220 *Figure 3: ROC curves for diagnostic confidence for both novice ( $R_{nov}$ ) and experienced*  
221 *( $R_{exp}$ ) radiologists before (BL for baseline) and after contrast-enhanced SHI.*

222

223 There was also no difference in diagnostic confidence between the experienced  
224 and novice radiologists when reviewing the SHI clips ( $p = 0.50$ ). Additionally, as shown in

225 Figure 4, qualitative analysis of the SHI images by the experienced radiologist resulted in  
226 a diagnostic accuracy of 70%, compared to 56% without contrast, while the novice  
227 radiologist only saw a 7% improvement (from 50% to 58%, Fig. 4A). When the radiologist  
228 reads are combined with the most predictive quantitative SHI parameter (% perfusion;  
229 PER), diagnostic accuracy improved to 84% for the experienced radiologist and 96% for  
230 the novice radiologist (Fig. 4B); this difference was not significant ( $p = 0.32$ ). However,  
231 given that both radiologists saw improvement in diagnostic accuracy once the quantitative  
232 parameter (PER) was included in the ROC model, these results suggest that the PER  
233 parameter adds diagnostic value.

234



235  
236 *Figure 4: ROC curves of diagnostic data. A) Analysis of the experienced radiologist ( $R_{exp}$ ),*  
237 *novice radiologist ( $R_{nov}$ ), and highest quantitative SHI parameter (perfusion %, PER). B)*  
238 *Combination of PER with radiologist reads.*

239

## 240 Discussion

241 Only 10-20% of all ovarian lesions surgically excised are malignant [53],  
242 highlighting the necessity for a more definitive pre-operative classification via imaging.



243 Such a modality could increase the pre-operative confidence for differentiating benign  
244 from malignant lesions, therefore diminishing the number of indeterminate lesions that  
245 necessitate surgery for classification.

246 This work represents, to our knowledge, the first study to investigate the use of  
247 endovaginal contrast-enhanced SHI imaging in women scheduled to undergo surgery for  
248 an adnexal mass as a potential tool for characterizing the malignancy of the lesion. We  
249 demonstrated that contrast-enhanced SHI imaging, particularly the quantitative  
250 parameters derived from subharmonic time-intensity curves, could achieve diagnostic  
251 accuracies up to 81%. Additionally, the diagnostic accuracy of the experienced radiologist  
252 improved by 14% with the addition of contrast-enhanced SHI imaging, suggesting that it  
253 is a valuable tool for clinical adaptation; albeit in a small sample size. Our findings suggest  
254 that noninvasive, endovaginal, contrast-enhanced SHI imaging may become a clinical  
255 imaging modality for evaluating adnexal masses with the potential to reduce both cost  
256 and risk to the patient, while also improving diagnostic accuracies. In this study, we  
257 specifically evaluated SHI imaging. It is conceivable that replacing or combining SHI with  
258 other tissue suppression methods, such as amplitude modulation (similar to CPS) or  
259 pulse inversion, would improve results further. However, establishing this will require  
260 further experiments.

261 Quantitative analysis of the contrast-enhanced SHI images showed that malignant  
262 adnexal masses had a significantly greater perfusion than those classified as benign. We  
263 expected that malignant tumors would demonstrate tumor angiogenesis and increased  
264 blood flow [16, 17, 19], and our findings that this is identifiable with endovaginal contrast-  
265 enhanced SHI is supported by other studies using CEUS imaging [15, 29].

266 We also found that clinical screening factors for malignancy were inconclusive in  
267 distinguishing benign from malignant masses in our limited study population; however,  
268 there was large deviation in the malignant group. CA-125 levels are only clinically relevant  
269 for later stage ovarian cancer, as this serum marker lacks sensitivity in early stage disease  
270 [54, 55]. One patient with a malignant mass presented with a CA-125 level of 143 U/mL,  
271 was staged as IIB high-grade serous ovarian cancer, and is now in remission, while  
272 another patient with malignancy presented with a CA-125 level of 12.8 U/mL and has  
273 since succumbed to disease. However, the average CA-125 level for patients with benign  
274 lesions was 19.3 U/mL, with only one patient below the 12.8 U/mL observed for a patient  
275 with malignancy. These cases highlight the insufficiency of CA-125 as a predictor for  
276 malignancy in ovarian masses.

277 RMI is calculated from CA-125, as well as patient age, menopausal status, and  
278 clinical impression [56], so inherently a lack of difference in CA-125 levels between the  
279 two pathological classifications would suggest that RMI would also be similar. We suspect  
280 that differences in CA-125 and RMI would appear between malignant and benign masses  
281 with increased sample sizes, as comparing 3 malignant lesions versus 5 benign lesions  
282 is hardly an ideal comparison. However, we did find that RMI had a higher diagnostic  
283 accuracy at 73% than CA-125 levels alone (60%), suggesting that the other factors used  
284 in calculating the RMI score (including an ultrasound score) [55, 56] provide a better  
285 overall assessment of the lesion. Given the high diagnostic accuracy provided by  
286 contrast-enhanced SHI, this modality could possibly be incorporated into the RMI  
287 calculation in the future, providing an even better ultrasound score and potentially further  
288 improving clinical classification of adnexal masses based on this modified RMI.

289 One limitation to this pilot study is the small sample size, with only ten patients  
290 completing the study at a single medical center. Therefore, we cannot definitely determine  
291 whether the observed differences between benign and malignant adnexal masses, as  
292 measured with contrast-enhanced SHI, can serve as an effective diagnostic tool.  
293 However, it is encouraging that all of the significant findings support this trend. Further  
294 investigation, with larger sample sizes at multiple centers, is necessary to determine  
295 whether contrast-enhanced SHI evaluation of adnexal masses could be a noninvasive,  
296 real-time, quantitative factor for determining malignancy and the need for surgical  
297 intervention (at least in high-risk populations [53]). Also, although *in vitro* and animal *in*  
298 *vivo* studies show that other UCAs are also effective in intermittent destruction-  
299 replenishment CEUS perfusion imaging [57, 58], we limited our pilot study to only use  
300 Definity contrast agent. Definity represents one of only three UCAs that are commercially  
301 available and FDA approved for use in humans in echocardiography, and we have  
302 previously had success with off-label use of Definity [25, 40, 59].

303 The potential clinical impact of these findings is promising, as there is no definitive  
304 noninvasive method for determining malignancy in ovarian lesions. Coupled with clinical  
305 standard of care evaluations, contrast-enhanced SHI for pre-surgical characterization of  
306 ovarian masses may improve the determination of malignancy, reducing cost and risk to  
307 patients, while improving diagnostic accuracy; albeit based on a small sample size.

308

### 309 **Acknowledgements**

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313 R21 CA190930 and F32 AR072491.

314

315

## 316 **Figure Captions List**

317 *Figure 1: Representative SHI images from study patients. A) Pre-contrast image of a*  
318 *lesion later classified as malignant by pathology. B) Pre-contrast image of a lesion later*  
319 *classified as benign by pathology. C) SHI of the malignant lesion shown in panel A. D)*  
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327 ***are scaled to the data in each curve for better visualization.***

328

329 *Figure 3: ROC curves for diagnostic confidence for both novice ( $R_{nov}$ ) and experienced*  
330 *( $R_{exp}$ ) radiologists before (BL for baseline) and after contrast-enhanced SHI.*

331

332 *Figure 4: ROC curves of diagnostic data. A) Analysis of the experienced radiologist ( $R_{exp}$ ),*  
333 *novice radiologist ( $R_{nov}$ ), and highest quantitative SHI parameter (perfusion %, PER). B)*  
334 *Combination of PER with radiologist reads.*

335 **Tables**

336 *Table 1: Summary of quantitative SHI analysis. \*p = 0.046, \*\*p = 0.045, ^ most predictive*  
 337 *quantitative SHI parameter.*

	Time to Peak Contrast, <b>TTP (s)</b>	Peak Contrast Intensity, <b>PI (AU)</b>	Fraction of Lesion with Perfusion, <b>PER (%)</b>	Area Under the Curve, <b>AUC (AU)</b>	Model $\alpha$ , correlative $\mu$ vessel cross- sectional area (dB)	Model $\beta$ , Blood Velocity (mm/s)	Model $\alpha \times \beta$ , Perfusion per Tissue (mL/s*mg)
Benign	142.79 $\pm$	0.05 $\pm$	7.62 $\pm$	0.72 $\pm$	0.76 $\pm$	0.10 $\pm$	5.84 x 10 <sup>-3</sup> $\pm$
(n=8)	122.26	0.03*	6.50**	0.50	1.97	0.07	5.73 x 10 <sup>-3</sup>
Malignant	140.35 $\pm$	0.11 $\pm$	24.79 $\pm$	1.61 $\pm$	0.16 $\pm$	0.14 $\pm$	1.89 x 10 <sup>-2</sup> $\pm$
(n = 4)	22.45	0.09*	25.34**	1.30	0.06	0.08	2.19 x 10 <sup>-2</sup>
Diagnostic Accuracy (Az)	52%	72%	81%^	75%	79%	71%	75%

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