Gynecology and Obstetrics Clinical Medicine 1 (2021) 148–152

Contents lists available at ScienceDirect

Gynecology and Obstetrics Clinical Medicine

journal homepage: www.keaipublishing.com/en/journals/gynecology-and-obstetrics-clinical-medicine

Use of contrast-enhanced ultrasound during preoperative evaluation of endometrial carcinoma

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ARTICLE INFO

Keywords:
Contrast-enhanced ultrasound
Diagnosis
Endometrial carcinoma
Myometrial invasion

ABSTRACT

Objective: To explore the clinical role of contrast-enhanced ultrasound (CEUS) in a preoperative evaluation of early endometrial carcinoma.

Methods: This study included 14 patients who underwent preoperative CEUS and contrast-enhanced magnetic resonance imaging (CEMRI) and were ultimately diagnosed with stage I endometrial carcinoma from December 2019 to December 2020. The parameters of the time-intensity curve (TIC) were compared with the endometrial carcinoma group, the invaded myometrium group, and the normal myometrium group.

Results: TIC parameters between the endometrial carcinoma group and the invaded myometrium group were similar. Compared with the normal myometrium group, the time to peak (TTP) was significantly shorter and the ascending slope (AS) was significantly higher in the endometrial carcinoma group. The TTP of the invaded myometrium group was shorter than that of the normal myometrium group and the peak intensity (PI) was higher than that of the normal myometrium group. We then compared the TIC parameters between the endometrial carcinoma group and the invaded myometrium group after adjusting for the normal myometrium group, and the results still did not show any difference. Of the 14 cases of endometrial carcinoma, 9 cases were diagnosed by CEMRI and were consistent with the pathology results, 1 case was underestimated, and 4 cases were overestimated; while 11 cases diagnosed were diagnosed by CEUS and were consistent with the pathology results, 1 case was underestimated, and 2 cases were overestimated.

Conclusions: The contrast pulse sequencing technique used in the CEUS examinations performed well in evaluating the extent of the endometrial carcinoma. Future studies with larger sample sizes are needed to determine the applicability and value of this new procedure during preoperative assessments of early endometrial carcinoma.

1. Introduction

Endometrial carcinoma is one of the most common gynecological malignancies and typically occurs in postmenopausal women.[1,2] With the development of modern medicine, the survival rate of endometrial carcinoma has been improved, while morbidity rate is still gradually increasing.[3,4] A timely diagnosis and early intervention are essential for improving patient prognosis. Preoperative assessments, particularly imaging evaluations, are crucial to clarify both the stage and scope of endometrial carcinoma. At present, common evaluation methods include traditional transvaginal ultrasounds,[5] MRIs,[6,7] PET/CTs,[8] curettage scraping,[9] and hysteroscopy.[10] All have advantages and disadvantages, though none of these methods can accurately identify the perfusion status of endometrial carcinoma.

Angiogenesis and perfusion are closely related to the growth and metastasis of malignant tumors. Contrast-enhanced ultrasound (CEUS) utilizes contrast agents to highlight the macro- and micro-vasculature and has been widely used to diagnose and manage malignancies.[11]

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Publishing services by Elsevier on behalf of KeAi

https://doi.org/10.1016/j.gocm.2021.07.005
Received 26 March 2021; Received in revised form 3 July 2021; Accepted 22 July 2021
Available online 19 August 2021

Although there has not been recommended clinical gynecological application, CEUS has greatly improved the ability of ultrasounds to examine gynecological diseases. In recent years, CEUS in gynecological carcinoma has received increasing attention[12] and some studies have reported that CEUS can identify myometrium invasions and the carcinoma staging of endometrial carcinoma,[13–16] however, these studies are still inadequate. In this study, we quantitatively assessed the perfusion characteristics of endometrial carcinoma and invasive myometrium via CEUS and compared the ability of CEUS and CEMRI to assess the depth of the endometrial carcinoma invasion. The purpose of this research is to analyze how CEUS can be used in the preoperative evaluation of early endometrial carcinoma.

2. Materials and methods

2.1. Patients

This study included 14 patients who underwent preoperative CEUS and contrast-enhanced magnetic resonance imaging (CEMRI) and were ultimately diagnosed with stage I endometrial carcinoma from December 2019 to December 2020. The retrospective study was approved by the Institutional Review Board of the Peking University People's Hospital.- The participants all provided informed consent to participate in the study. Endometrial carcinoma was previously diagnosed via hysteroscopy and was surgically confirmed within 2 weeks of the CEUS and CEMRI examinations (the CEMRI examination was performed within 3 days of the CEUS examination). Patient inclusion criteria are as follows: (i): The diagnosis was first confirmed via hysteroscopy, while the staging operation was performed within 2 weeks of the preoperative imaging evaluation (CEUS and CEMRI); (ii): Patients were diagnosed with a malignant disease for the first time and did not receive estrogen and progesterone drugs, radiotherapy, chemotherapy, or other interventions before the examination; (iii): Postoperative pathological diagnosis of stage I endometrial adenocarcinoma; (v): The clinical, imaging, and pathological data were made available after the operations were complete. All CEUS was performed by a single experienced sonographer and the final diagnosis was based on the histopathological examination of specimens from at least two experienced pathologists, according to the Federation International Gynecology and Obstetrics (FIGO) classification.[17] Stage I endometrial carcinoma is defined as a tumor confined to corpus uteri; Stage Ia is defined as having no myometrial invasion or invasion of less than half of the myometrium, and Stage Ib is defined as having an invasion of half or more than half of the myometrium.

2.2. Contrast-enhanced ultrasound examinations

We first performed a traditional two-dimensional ultrasound to obtain the sagittal and coronal planes of the uterus on a Mindray-Resona 8 ultrasound machine. The area where the standard sagittal and coronal planes can be observed and the maximum scope of the endometrial lesion can be seen in the sectional plane were identified for the CEUS examination. CEUS was performed on the same ultrasound machine and patients were scanned with a 5- to 9-MHz transvaginal transducer after obtaining the patient's informed consent. The equipment was run under auto-contrast quantification and the ultrasound image software was used to analyze the contrast enhancement, while the region of interest was manually selected based on the blood supply of the lesion and the perfusion of the contrast agent. The contrast agent was purchased from SonoVue (Bracco, Imaging B.V, Switzerland), and a dose of 1.8–2 ml of the agent was used in each examination according to the patient's BMI. The contrast agent was administered parallel to the needle via the antecubital vein using a rapid intravenous bolus way, after which an additional 5 ml of physiologic saline solution was injected perpendicular to the needle to flush the cannula. The inspection lasted for at least 90 s, while the image data were stored in the machine's hard drive for subsequent analysis. The following parameters of the time-intensity curve (TIC) were observed in the endometrial carcinoma lesion, invaded myometrium, and normal myometrium groups: arrival time (AT), time to peak (TTP), ascend slop (AS), peak intensity (PI), and area under the curve (AUC).

2.3. Statistical analysis

Statistical analysis was performed using the SPSS 22.0 software. Continuous variables that conform to the normal distribution are presented as mean ± standard deviation (SD) and were compared by Student's t-test. Continuous variables that do not conform to the normal distribution used the median (interquartile range) for statistical description and the Mann-Whitney *U* test for comparison. $P < 0.05$ (two-sided) was considered statistically significant.

3. Results

3.1. Clinicopathologic characteristics of the patients

The clinicopathologic characteristics of the 14 patients are displayed in Table 1. Of the 14 patients, 10 were postmenopausal and 4 patients were premenopausal; 2 cases were nulliparity and 12 cases had abnormal uterine bleeding. The TIC derived from the CEUS of the endometrial carcinoma, invaded myometrium, and normal myometrium groups are displayed in Fig. 1. The enhancement order of the normal uterus was the uterine artery and outer myometrial layer, the inner myometrial layer, and the endometrial layer. The intensity of enhancement of the normal endometrium was always lower than in the myometrium. The enhancement features of endometrial carcinoma were as follows: 1) the contrast agent first arrived at the feeding vessels and then branched into endometrial cancer; 2) the enhancement order of the endometrial carcinoma was earlier and enhancement intensity was higher than that of the normal myometrium group, while the boundary between the normal myometrium and endometrial lesion groups was clear.

3.2. Parameter comparisons from TIC of the endometrial carcinoma, invaded myometrium, and normal myometrium groups

The analytical results of TIC parameters for the endometrial carcinoma, invaded myometrium, and normal myometrium groups are displayed in Table 2. TIC parameters between the endometrial carcinoma and invaded myometrium groups were similar. Compared with the normal myometrium groups, the TTP (33.54 ± 3.52 vs. 40.12 ± 4.27, $P < 0.001$) was significantly shorter and the AS [1.19 (1.02–1.45) vs. 0.89 (0.72–1.07), $P = 0.011$] was significantly higher in the endometrial carcinoma group. The average TTP (35.93 ± 4.74 vs. 40.12 ± 4.27, $P = 0.012$) of the invaded myometrium group was shorter than that of the normal myometrium group and the average PI [51.61 (46.09–56.33) vs. 43.89 (40.77–50.58), $P = 0.027$] was higher than that of the normal myometrium group. We then compared the TIC parameters between the endometrial carcinoma and the invaded myometrium after adjusting for the normal myometrium group, and there was still no difference (Table 3). However, significant differences were observed between the endometrial carcinoma/invaded myometrium groups and the endometrial carcinoma/normal myometrium groups for AT (1.018 ± 0.065 vs. 0.913 ± 0.091, $P = 0.001$), TTP (0.942 ± 0.101 vs. 0.841 ± 0.091,

Table 1
Baseline characteristics of 14 patients with endometrial carcinoma.

Characteristics	All patients (n = 14)
Age (years), X ± SD	55.43 ± 6.12
Body mass index (kg/m^2), X ± SD	24.33 ± 1.88
Nulliparity, n (%)	2 (14.29)
Postmenopausal status, n (%)	10 (71.43)
Abnormal uterine bleeding, n (%)	12 (85.7)

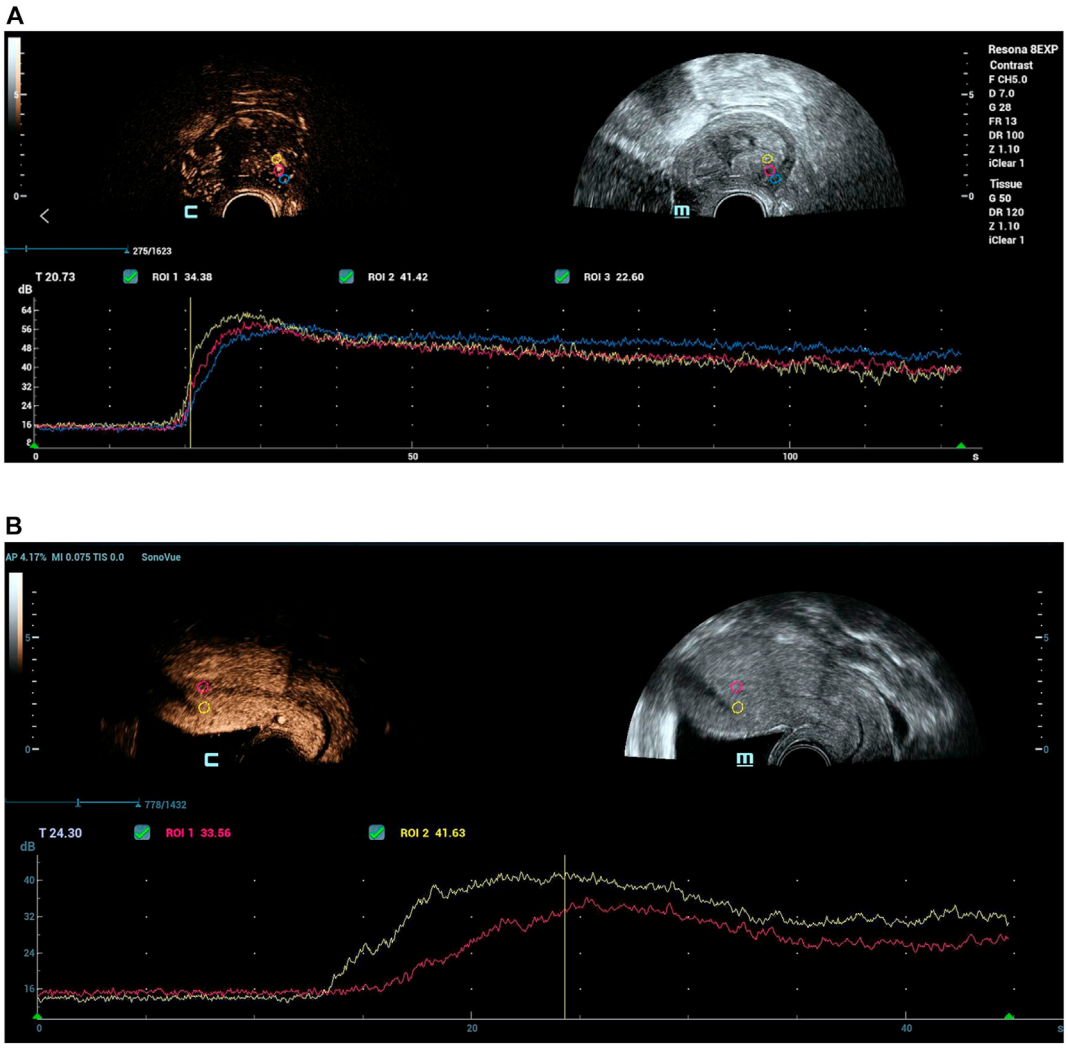

Fig. 1. Time-intensity curves derived from contrast-enhanced ultrasonography. Fig. 1A Time-intensity curves derived from contrast-enhanced ultrasonography of the region where there is an endometrial invasion. (Yellow: endometrial carcinoma lesion, pink: invaded myometrium, blue: normal myometrium). **Fig. 1B Time-intensity curves derived from contrast-enhanced ultrasonography of regions with no endometrial invasions.** (Pink: normal endometrium, yellow: normal myometrium).

P = 0.009), AS (1.025 ± 0.178 vs. 1.382 ± 0.346, P = 0.002), and AUC [0.929 (0.852–1.005) vs. 1.236 (1.106–1.509), P < 0.001] (Table 3).

3.3. Comparison of CEMRI and CEUS of myometrial invasion for endometrial carcinoma

The endometrial carcinoma grades of the CEMRI, CEUS, and pathology results are displayed in Table 4. Of the 14 cases of stage I endometrial carcinoma, 10 cases were confirmed by pathological analysis to be Stage Ia and four cases were confirmed to be Stage Ib; CEMRI diagnosed seven women with Stage Ia endometrial carcinoma and seven women with Stage Ib endometrial carcinoma. Nine cases were consistent with the results of the pathological analysis, while 1 case was underestimated and 4 cases were overestimated. Stage Ia and Ib endometrial carcinoma were diagnosed by CEUS in 9 and 4 women respectively, while 11 cases were consistent with the results of the pathological analysis, while 1 case was underestimated and 2 cases were overestimated.

4. Discussion

Previous studies have demonstrated that more than half of the confirmed endometrial carcinoma patients are in stage I, and the size of the lesion and the depth of endometrial carcinoma infiltration is directly related to disease prognosis. The metastasis rate of the lymph nodes is less than 5 % in stage Ia endometrial carcinoma, making it unnecessary to dissect the lymph node, while lymph node dissection is typically necessary for patients with stage Ib endometrial carcinoma.[18] Therefore, in the preoperative evaluation of endometrial carcinoma, lesions must be identified and the depth of the myometrial invasion in the endometrial carcinoma must be accurately determined. In this retrospective study, we demonstrated that the contrast pulse sequencing technique used in CEUS examinations can identify lesions near normal tissue, distinguish the invasive myometrium from the normal myometrium, and determine the depth of the myometrial invasion. In this present study, the diagnosis coincidence rate by CEUS (11/14) exceeded that of CEMRI (9/14), indicating that CEUS can play a role in preliminarily determining the depth of the myometrial invasion in patients with endometrial carcinoma.

Current evaluation methods commonly used include traditional transvaginal ultrasounds,[5] MRIs,[6,7] curettage scraping,[9] and hysteroscopy.[10] Curettage scraping and hysteroscopy can confirm the diagnosis of endometrial carcinoma but cannot identify the depth of the myometrial invasion in patients with endometrial carcinoma. Despite its high accuracy, the intraoperative frozen section is time-consuming and cannot be

Table 2
Parameter comparisons from TIC among endometrial carcinoma, invaded myometrium, and normal myometrium groups.

Parameters	Groups			*P* values		
	EC	IM	NM	P1	P2	P3
AT	15.41 ± 3.19	15.12 ± 2.85	17.03 ± 3.8	0.815	0.205	0.135
TTP	33.54 ± 3.52	35.93 ± 4.74	40.12 ± 4.27	0.37	<0.001*	0.012*
PI	50.05 (44.57–54.58)	51.61 (46.09–56.33)	43.89 (40.77–50.58)	0.839	0.114	0.027*
AS	1.19 (1.02–1.45)	1.1 (0.93–1.39)	0.89 (0.72–1.07)	0.531	0.011*	0.106
AUC	2041.00 ± 1082.27	2256.42 ± 1185.64	1617.63 ± 794.94	0.585	0.578	0.29

Data are presented as mean ± standard deviation or median (interquartile range). EC: endometrial carcinoma; IM: invaded myometrium; NM: normal myometrium; PI: peak intensity; AT: arrival time; TTP: time to peak; AS: ascend slope; AUC: area under the curve. *P < 0.05 was considered statistically significant, P1 was compared between the endometrial carcinoma group and the invaded myometrium group; P2 was compared between the endometrial carcinoma group and the normal endometrial group; P3 was compared between invaded myometrium group and the normal endometrial group.

Table 3
Parameter comparisons from TIC between endometrial carcinoma and invaded myometrium group adjusted for the normal myometrium group.

Parameters	Groups			*P* values	
	EC/IM	EC/NM	IM/NM	P1	P2
AT	1.018 ± 0.065	0.913 ± 0.091	0.898 ± 0.081	0.001*	0.623
TTP	0.942 ± 0.101	0.841 ± 0.091	0.898 ± 0.099	0.009*	0.126
PI	0.984 (0.950–1.054)	1.137 (0.979–1.225)	1.133 (0.100–1.224)	0.056	0.839
AS	1.025 ± 0.178	1.382 ± 0.346	1.358 ± 0.315	0.002*	0.829
AUC	0.929 (0.852–1.005)	1.236 (1.106–1.509)	1.398 (1.183–1.652)	<0.001*	0.194

Data are presented as mean ± standard deviation or median (interquartile range). EC: endometrial carcinoma; IM: invaded myometrium; NM: normal myometrium; PI: peak intensity; AT: arrival time; TTP: time to peak; AS: ascend slope; AUC: area under the curve. P1 was compared between EC/IM group and EC/NM group; P2 was compared between EC/NM group and IM/NM group. *P < 0.05 was considered statistically significant.

Table 4
Comparison of endometrial carcinoma grade by CEUS, CEMRI, and pathology results.

Grade	Pathology(n)	Coincident cases(n)	
		CEMRI	CEUS
Ia	10	6	8
Ib	4	3	3
Total	14	9	11

CEMRI: magnetic resonance imaging; CEUS: contrast-enhanced ultrasound.

planned.[19] MRIs are currently the most commonly used preoperative imaging technique in endometrial carcinoma patients and clearly show the uterus and pelvic lymph nodes with the accuracy of estimating the depth of myometrial invasion up to 73 %–97 %.[20,21] However, MRIs are relatively expensive, and patients with obesity, certain allergies, and metal inserts cannot receive an MRI scan. As such, there is still a need for a more convenient and relatively accurate diagnostic method. Transvaginal ultrasound examinations are one of the most commonly used methods since they provide fast results, are inexpensive, subject the patient to no radiation, and are non-invasive. However, these examinations can only provide information within the macroscopic assessment of the lesions. Rapidly advancing CEUS technology has made it possible to diagnose diseases at the tissue level of microcirculation perfusion, greatly improving the accuracy of traditional ultrasonic diagnoses.[22,23] Quantitative TIC analysis is an important part of CEUS, while the perfusion time parameters of AT, TTP, and AS can reflect the blood flow velocity and the intensity parameters basis intensity (BI) and PI directly show the volume of the lesion perfusion.[13,24]

The endometrial carcinoma group displayed a perfusion curve that quickly increased and then decreased, with lower perfusion time parameters and higher intensity parameters, while the blood flow curve in the normal myometrium group and benign endometrial lesion group increased slowly and then decreased slowly.[13,25] In a recent meta-analysis, we identified the ability of CEUS to accurately diagnose endometrial carcinoma and demonstrated that the pooled sensitivity of CEUS in the diagnosis of endometrial carcinoma was 84 % and its pooled specificity was 90 %, indicating that CEUS can help diagnose endometrial carcinoma.[26] Liu et al.[13] and Su et al.[14] compared the ability of CEUS to diagnose endometrial carcinoma and endometrial hyperplasia (EH) and found that all of the CEUS parameters in patients with endometrial carcinoma were lower than those of EH. Su et al.[14] also detected the diagnostic accuracy of CEUS during myometrial invasion for endometrial carcinoma and demonstrated that the total diagnostic accuracy of CEUS is 82.62 % (33/39). However, few studies have analyzed the enhancement characteristics of invasive myometrium. In this study, we found that all TIC parameters were comparable between the endometrial carcinoma group, while the TTP (35.93 ± 4.74 vs. 40.12 ± 4.27, P = 0.012) was significantly shorter and the PI [51.61 (46.09–56.33) vs. 43.89 (40.77–50.58), P = 0.027] was significantly higher in the invaded myometrium group compared with the normal myometrium group. We also compared the TIC parameters between the endometrial carcinoma group and the invaded myometrium group after adjusting for normal myometrium, and the results still did not show any difference. A significant difference in AT, TTP, AS, and AUC was observed between the endometrial carcinoma and invaded myometrium groups and the endometrial carcinoma and normal myometrium groups (Table 3).

This study has several limitations. First, a single-center design study with a small sample size produces results that are not comprehensive. While this study found that the accuracy of CEUS exceeded that of CEMRI, the accuracy of these results could be compromised due to the limited sample size and differences in the experience and level of imaging physicians. An MRI exam is still considered the most accurate imaging method, though CEUS is promising for the preoperative assessment of endometrial lesions; future large-scale, multi-center, prospective studies are needed to confirm these results. While the CEUS method is a promising technique, other factors must be considered before implementing it widely, including the safety of the contrast solution, a steep learning curve, and lack of patient coverage by medical insurance.

5. Conclusion

The contrast pulse sequencing technique used in the CEUS examinations was able to evaluate the invasive nature of endometrial carcinoma.

Future studies with larger sample sizes are needed to further determine the applicability and value of this new procedure during preoperative assessments of early endometrial carcinoma.

Author contributions

Zhao Tian and Hui-Min Yao both contributed to the study design and equally contributed to this article. Yi-Qin Wang and Na-Ze Chen contributed to the discussion and reviewed and edited the manuscript. Jun Tang and Jing Geng directed the project. Jing Geng is the corresponding author, had full access to all of the information in the study, and decided to submit this study for publication.

Funding

None.

Declaration of competing interest

All of the authors included in this study declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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