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Prognostic Value of Quantitative Perfusion Parameters by Enhanced Ultrasound in Endometrial Cancer

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Background: Tumor perfusion is significantly associated with the development and aggressiveness of endometrial cancer. The aim of this study was to assess the prognostic value of quantitative perfusion parameters measured by contrast-enhanced ultrasonography (CEUS) in endometrial cancer before surgery.

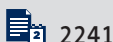
Material/Methods: A total of 223 patients with endometrial cancer were included between 1 May 1 2013 and 1 May 1 2017 for preoperative CEUS. The mean enhancement rate (ER) was calculated as enhancement intensity (EI)/rise time (RT) results from time-intensity curve (TIC) during CEUS. After a mean follow-up of 33.5±9.9 months, the correlation of ER and postoperative overall survival (OS) and disease-free survival (DFS) was analyzed using univariate and multivariate analysis.

Results: The optimal cutoff ER value predicting survival based on the ROC curve was 1.8 dB/s. Kaplan-Meier univariate analysis demonstrated that a patient with a high ER level had worse DFS and OS than those with a low ER (DFS, P<0.01; OS, P<0.05). In multivariate analysis, ER was confirmed as an independent predictor for both recurrence (HR, 1.68; 95% CI: 1.01–7.73) and OS (HR, 1.98; 95%CI: 1.01–7.83) for patients with endometrial cancer (both P<0.05).

Conclusions: Perfusion variables measured by CEUS are significantly useful predictive factor for postoperative survival in endometrial cancer.

MeSH Keywords: **Endometrial Neoplasms • Hemoperfusion • Prognosis • Ultrasonography**

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Background

Endometrial cancer is one of the most frequent gynecologic malignancy in China and worldwide [1,2]. Although survival outcome of endometrial cancer patients has been improved over recent decades, the incidence and mortality rates keep increasing [3,4]. Standard surgical approaches consisting of hysterectomy, bilateral salpingo-oophorectomy, and lymph nodes dissection have been considered as the preferred curative treatments for early endometrial cancer [5,6]. However, standard surgery is not effective for all types of endometrial cancer with heterogeneous perfusion, and staging, preoperative staging, and risk stratification are essential for surgery planning [7,8]. Therefore, a more accurate and practical indicator for guiding treatment planning of endometrial cancer is needed in clinical practice. Several clinicoradiopathologic parameters have been previously confirmed as predictors for prognosis of endometrial cancer, such as tumor differentiation and tumor staging. However, such indicators are most feasible after surgery and pathologic exams, and cannot be used to guiding treatment planning of endometrial cancer.

Contrast-enhanced ultrasonography (CEUS) has been successfully and widely applied in the diagnosis and management of malignancies [9,10]. In recent years, the value of CEUS in gynecological cancer has been increasingly recognized, and can provide the ability to identify endometrial diseases and to dynamically assess capillary perfusion [11,12]. Furthermore, quantitative perfusion assessments are enabled by using the time-intensity curve (TIC) analysis of CEUS [13]. Angiogenesis or perfusion are closely associated with the growth and metastasis of solid tumors, including endometrial cancer [14–16]. Therefore, accurate pretreatment quantification assessment of tumor perfusion may be useful for predicating postoperative outcome in endometrial cancer patients.

In previous studies, the pretreatment evaluations of endometrial cancer patients were mainly conducted by using conventional enhanced imaging examinations, which can be inaccurate due to subjective factors and are unable to directly, quantifiably, and in real time reflect the perfusion status [17,18]. Therefore, in the present study we quantitatively assessed the perfusion characteristics of endometrial cancer by CEUS, and evaluated the prognostic value of these perfusion parameters for endometrial cancer patients following surgery. These perfusion characteristics provided by CEUS can be used in planning treatment of endometrial cancer.

Material and Methods

Patients

This retrospective study was approved by the Ethics Committee of the Affiliated Hospital of the Academy of Military Medical Sciences. The study was conducted from 1 May 2013 to 1 May 2017 according to the principles of the Declaration of Helsinki and all patients provided signed informed consent. We enrolled 223 consecutive patients planned for surgery for primary endometrial cancer at the Affiliated Hospital of Academy of Military Medical Sciences from 1 May 2013 to 1 May 2017. The diagnosis of endometrial cancer was based on pathological evaluations. A number of patients were excluded due to the following conditions: metastatic cancer and other malignancies, preoperative acute and severe comorbidity, distant metastasis, preoperative adjuvant chemotherapy, unavailable clinical and histopathological data, and life expectancy less than 24 weeks. Patients who died due to causes unrelated to endometrial cancer during following-up were also excluded. All patients were treated according to the National Comprehensive Cancer Network (NCCN) clinical guidelines. The standard surgery protocol was performed for each participating patient. Postoperative adjuvant chemotherapy was administered according to NCCN guidelines, consisting of paclitaxel and carboplatin for 3 to 6 cycles. Clinical data of all patients were collected from the medical records, including demographic characteristics, serum CA125, tumor stage, histology and differentiation, maximum tumor size, myometrium invasion, cervical stromal invasion, lymphovascular space (LVS) involvement, and lymph node metastasis. Tumor clinical stages were evaluated according to International Federation of Gynecology and Obstetrics (FIGO) stage guidelines [19].

Contrast-enhanced ultrasound examinations

All patients underwent CEUS examination on the day immediately prior to surgery. After regular transvaginal ultrasound revealing two-dimensional gray-scale images of lesions, CEUS was performed using an ACUSON Sequoia™ 512 color ultrasound system (Siemens AG, Munich, Germany). A scanning plane showing the lesion's largest diameter or most abundant blood flow, the lesion, and surrounding tissues simultaneously, and the standard long and short axis planes whenever possible, was chosen as the most appropriate plane to display the lesion, then the imaging setting was defined as the contrast pulse sequences. We administered 2.4-ml SonoVue solution (Bracco, Milan, Italy) by bolus injection via the hand vein, followed by a 5-ml saline injection. The built-in timer within the ultrasound equipment was turned on, then the SonoVue uptake and washout and echo intensity within the region of interest were continuously evaluated in real time. All imaging data were stored for later analysis. The built-in auto-contrast

quantification software was used to select the appropriate region of interest to automatically scan and record the time-intensity curve (TIC) analysis. The following parameters were quantitatively evaluated in TIC analysis: time parameters, including arrival time (AT), time-to-peak (TTP), rise time (RT=TTP-AT), as well as intensity parameters, including basis intensity (BI), peak intensity (PI), and enhancement intensity (EI=PI-BI). Finally, enhancement rate (ER) calculated as the ratio of EI and RT was selected as a standing indicator of perfusion parameters.

Clinical evaluation and follow-up

After discharge, all patients were followed up with repeat ultrasound and CT/MRI every 3 months during the 1st year and every 4-6 months for subsequent years. Clinical follow-up lasted from the day of surgery to either death or May 2018. The primary outcome assessed was overall survival (OS), which was accurately defined as the duration from surgery to disease-specific death or study endpoint. The disease-free survival (DFS) was considered as the secondary outcome evaluation, which was defined from the day of surgery until recurrence or study endpoint.

Statistical analysis

Statistical analyses were conducted using SPSS 20.0 (IBM, USA). P <0.05 (two-sided) was considered as statistically significant. The optimal cutoff level for the ER predicting survival was determined through receiver operating characteristic (ROC) curve analysis. Categorical variables were compared using the χ^2 test or Fisher's exact test, while comparison of continuous variables was performed using the by independent-samples t test. The OS and DFS curve were evaluated using the log-rank test in Kaplan-Meier analyses. The Cox regression model was used to evaluate the hazard ratio and multivariate analysis.

Results

Clinicopathologic characteristics of the patients

Clinical and pathological characteristics of the 223 patients who underwent surgery for endometrial cancer are presented in Table 1. Mean age of all patients was 58.1±8.6 years (range, 33-81 years). The majority of patients were histologically diagnosed as having endometrioid adenocarcinoma (88.3%, n=197). Other pathological subtypes included serous adenocarcinoma (6.3%, n=14), clear cell carcinoma (3.1%, n=7), and mixed cell carcinoma (2.2%, n=5). The mean value of the maximum diameter of tumor was 3.2±1.8 cm. According to the FIGO staging methods, there were 191 (85.7%) patients with stage I or II tumors and 32 (14.3%) patients with stage III tumors. There were 79 (35.4%) patients with pathological grade G1,

Table 1. Baseline characteristics of 223 patients with endometrial cancer.

Characteristics	All patients (n=223)
Age (years)	58.1±8.6
CA-125 (U/mL)	34.7±6.3
Tumor maximum size (cm)	3.2±1.8
Histology	
Endometrioid	197 (88.3%)
Serous	14 (6.3%)
Clear cell	7 (3.1%)
Mixed	5 (2.2%)
Histologic grade	
G1	79 (35.4%)
G2	95 (42.6%)
G3	49 (22.0%)
FIGO stage	
I-II	191 (85.7%)
III-IV	32 (14.3%)
LN metastasis	
Absent	200 (89.7%)
Present	23 (10.3%)
Myometrial invasion	
≥1/2	157 (70.4%)
<1/2	66 (29.6%)
Cervical stromal invasion	
Absent	196 (87.9%)
Present	27 (12.1%)
LVS involvement	
Absent	182 (81.6%)
Present	41 (18.4%)
Perfusion parameters	
Arrival time (s)	11.8±1.5
Time-to-peak (s)	23.8±2.5
Rise time (s)	12.1±2.8
Enhancement intensity (dB)	25.2±3.2
Enhancement rate (dB/s)	2.3±0.8

95 (42.6%) with grade G2, and 49 (22.0%) with grade G3. lymph node involvement and cervical stromal invasion were observed in 23 (10.3%) and 27 (12.1%) patients, respectively. Forty-one (18.4%) patients were found to have lymphovascular space invasion. The mean values of AT, TPP, RT, EI, and ER of tumors were 11.8±1.5 s, 23.8±2.5 s, 12.1±2.8 s, 25.2±3.2 dB, and 1.6±0.8 dB/s, respectively (Table 1).

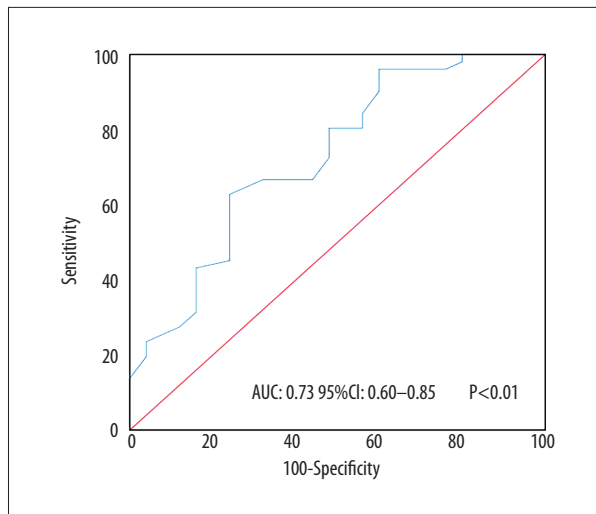


Figure 1. Receiver-operator characteristic curve for ER measured by CEUS. The areas under the curve were 0.73 with a 95% confidence interval (95% CI) for the area between 0.60 and 0.86, $p < 0.01$.

Determination of optimal cutoff level of ER

According to the ROC curve analysis, the optimal cutoff level of ER predicting survival was calculated as 1.8 (area under the curve, 0.73; 95%CI: 0.60–0.85; $p < 0.01$), with a sensitivity of 67.2% and a specificity of 76.7% (Figure 1).

Univariate and multivariate analysis of the parameters associated with survival

All 223 patients were followed up for a mean period of 33.5 ± 9.9 months. At the endpoint of follow-up, 195 patients were alive without disease (87.4%), 21 patients had died due to progression of the disease (9.4%), and 7 patients were alive with disease (3.1%). Figure 2 illustrates the Kaplan-Meier DFS and OS curves for the 223 patients who underwent surgery for

endometrial cancer, according to preoperative ER by CEUS. The log-rank test showed that the DFS and OS for endometrial cancer patients with a high ER were poorer than for patients with a low ER (DFS and OS: $P < 0.01$ and $P = 0.04$) (Figure 2).

The correlation between clinicopathological characteristics and OS of endometrial cancer patients was assessed by univariate and multivariate analyses. Univariate analysis for OS identified a significant difference in several clinicopathological variables: age, histologic type, FIGO stage, tumor size, lymph nodes metastasis, myometrial invasion, LVS involvement, and ER (all $P < 0.05$). In the multivariate Cox proportional hazards model, we found that FIGO stage (HR, 3.02; 95%CI: 1.03–12.61, $P = 0.04$), LN metastasis (HR, 5.37; 95%CI: 1.51–19.18, $P = 0.01$), LVS involvement (HR, 4.23; 95%CI: 1.06–16.22, $P < 0.01$), and ER (HR, 1.98; 95%CI: 1.01–7.83, $P < 0.01$) were independent prognostic factors for OS in patients underwent surgery for endometrial cancer (Table 2).

For DFS analysis, we found in univariate analysis that clinicopathological characteristics, including age, CA-125 levels, histologic type, FIGO stage, lymph nodes metastasis, myometrial invasion, cervical stromal invasion, LVS involvement, and ER, were significantly associated with DFS of patients with endometrial cancer (all $P < 0.05$). In multivariate analyses using Cox proportional hazards model for DFS, FIGO stage (HR, 3.68; 95% CI: 1.23–16.31, $P = 0.02$), lymph nodes metastasis (HR, 5.71; 95% CI: 2.03–18.18, $P < 0.01$), and ER (HR, 1.68; 95% CI: 1.01–7.73, $P < 0.01$) were significant and independent predictors for DFS in patients with endometrial cancer (Table 3).

Discussion

In this retrospective study we showed that preoperative ER value measured though CEUS was significantly associated with survival outcome of patients with endometrial cancer, with the optimal cutoff of ER value predicting survival determined as 1.8 dB/s.

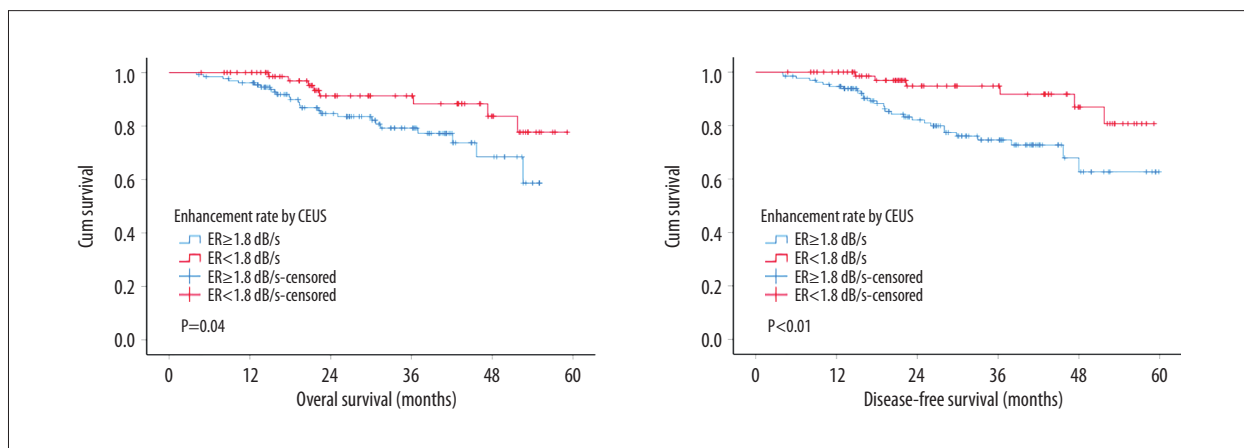


Figure 2. Kaplan-Meier estimates of overall survival and disease-free survival according to enhancement rate (ER) by CEUS.

Table 2. Overall survival analysis in 223 patients with endometrial cancer.

	Univariate			Multivariate		
	HR	95%CI	p	HR	95%CI	p
Age (years) (≥60 vs. <60)	4.82	1.23–16.22	0.01			
CA-125 (U/ml) (≥13.4 vs. <13.4)	5.31	0.93–12.75	0.07			
Tumor size (cm) (≥2 vs. <2)	3.29	1.02–9.51	0.04			
Histology (endometrioid vs. others)	3.41	1.01–11.23	0.05			
Histologic grade (G1+G2 vs. G3)	2.86	0.92–8.36	0.07			
FIGO stage	4.51	1.37–15.32	0.02	3.02	1.03–12.61	0.04
LN metastasis	6.86	1.93–22.35	<0.01	5.37	1.51–19.18	0.01
Myometrial invasion	4.62	1.38–15.51	0.01			
Cervical stromal invasion	2.48	0.68–8.57	0.19			
LVS involvement	5.67	1.72–19.38	<0.01	4.23	1.06–16.22	<0.01
ER(dB/s) (≥1.8 vs. <1.8)	2.57	1.05–8.21	0.02	1.98	1.01–7.83	<0.01

Hazard ratios (HRs) were obtained from Cox’s proportional hazard model. 95%CI – 95%confidence interval; CA-125 – cancer antigen 125; FIGO – International Federation of Gynecology and Obstetrics; LN metastasis – lymph node metastasis; LVS – lymphovascular space invasion; ER – enhancement rate.

Table 3. Disease-free survival analysis in 223 patients with endometrial cancer.

	Univariate			Multivariate		
	HR	95%CI	p	HR	95%CI	p
Age (years) (≥60 vs. <60)	4.61	1.64–13.02	<0.01			
CA-125 (U/ml) (≥13.4 vs. <13.4)	3.48	1.15–10.65	0.03			
Tumor size (cm) (≥2 vs. <2)	2.37	0.92–6.01	0.07			
Histology (endometrioid vs. others)	2.65	0.94–7.46	0.07			
Histologic grade (G1+G2 vs. G3)	1.56	0.91–2.76	0.11			
FIGO stage	2.59	1.57–4.32	0.01	3.68	1.23–16.31	0.02
LN metastasis	6.56	2.33–18.75	<0.01	5.71	2.03–18.18	<0.01
Myometrial invasion	3.72	1.41–9.57	<0.01			
Cervical stromal invasion	3.78	1.42–10.07	<0.01			
LVS involvement	5.21	1.62–8.37	<0.01			
ER (≥1.8 vs. <1.8)	2.23	1.02–7.36	<0.01	1.68	1.01–7.73	<0.01

Hazard ratios (HRs) were obtained from Cox’s proportional hazard model. 95%CI – 95%confidence interval; CA-125 – cancer antigen 125; FIGO – International Federation of Gynecology and Obstetrics; LN metastasis – lymph node metastasis; LVS – lymphovascular space invasion; ER – enhancement rate.

Furthermore, in multivariate analysis, ER measured by CEUS was still positively correlated with OS and DFS, independent of well-established prognostic factors for EC. The results of our study suggest that preoperative measurement of ER by CEUS can be used to identify patients at risk for poorer prognosis and disease recurrence and to plan a more patient-personalized treatment for each patient, in addition to currently used conventional clinical, pathological, and imaging diagnostic modalities.

Contrast-enhanced ultrasonography has been widely applied in gynecological cancer, mainly for tumor morphology, differential diagnosis, and TIC parameters evaluation [20,21]. Liu et al. evaluated the TIC parameters different between endometrial hyperplasia and endometrial cancer, and demonstrated that CEUS can indirectly reflect blood vessel changes inside the tumor and differentiate benign and malignant lesions [22]. Furthermore, in TIC analysis during CEUS examination, the perfusion time parameters of AT, TTP, and RT can

reflect the blood flow velocity, while the intensity parameters BI and EI directly show the lesion perfusion volume [22]. Endometrial malignancy with lower perfusion time parameters and higher intensity parameters displayed a quick rise-quick decline perfusion profile, whereas the benign endometrial lesions had a slow rise-slow decline blood flow profile, with longer AT and PT, and lower EI [12,22]. Therefore, CEUS can be a useful diagnostic tool for endometrial cancer, as well as preoperative evaluation. However, in the setting of CEUS, several issues need to be considered, such as safety of contrast solution, longer learning curve, and lack of coverage by medical insurance.

CEUS has important significance in perfusion evaluation of endometrial cancer, including detection of neo-vessels formation during tumor angiogenesis, and predicting intra-tumor vessel changes prior to morphological changes [23]. Furthermore, perfusion parameters obtained from the TIC analysis during CEUS examination were significantly associated with micro-vessel density (MVD) of endometrial cancer [22]. It was suggested that the MVD is an indirect marker of the intensity of tumor vascularization, which is known to be associated with the progression of endometrial cancer and survival outcome [24,25]. Therefore, perfusion parameters obtained from the TIC analysis during CEUS examination may be associated with prognosis of endometrial cancer. In our study, we confirmed this hypothesis and demonstrated the prognostic significance of ER obtained from CEUS in patients with endometrial cancer.

The present study also evaluated the predictive capacity of ER using ROC curve analysis. ROC curve analysis is a useful and common tool for evaluating diagnostic tests and is statistically simple, effective, and straightforward [26]. Meanwhile, the optimal cut-off value can also be calculated based on the ROC curve analysis. In the present study, the results of ROC curve analysis indicated that the cutoff value of ER was 1.8 dB/s,

which is consistent with previous studies [22,27]. Otherwise, the ER, as the ratio of EI to RT, is considered as a more precise and comprehensive indicator reflecting perfusion characteristic of tumor. Thus, ER may be a valuable indicator for predicting survival outcome of patients with endometrial cancer.

There are some limitations to this study. The single-center design study may have influenced accuracy of results, thus contributing to the disparity between our results and previous studies. A large-scale, multi-center, prospective study is required to confirm our results and reduce selection bias. Furthermore, our study did not enroll patients with recurrent and metastatic endometrial cancer, which potentially diminishes generalizability. Finally, a systemic review and meta-analysis with a high level of evidence and which enrolls various validation studies may be needed to confirm the significance of perfusion parameters measured by CEUS in predicting ablation efficacy in endometrial cancer.

Conclusions

We have demonstrated that quantitative perfusion parameters, including ER, are significantly correlated with the prognosis of patients with endometrial cancer, indicating that longer time parameters and lower intensity parameters were linked to a better treatment outcome. This study provides critical information and verification for the MVD-related factors in endometrial cancer. CEUS evaluation is easy to incorporate into clinical practical to evaluate the perfusion and MVD, thus predicting survival outcome and guiding treatment planning for endometrial cancer patients.

Conflict of interest

None.

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