Correlation of color Doppler ultrasound and pathological grading in endometrial carcinoma

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Abstract

Introduction: Given the role of angiogenesis in tumor growth, the evaluation of tissue vascularization by Doppler ultrasound has been thought to be useful in the prediction of malignant endometrial changes. The aim of this study was to evaluate the efficacy of transvaginal color Doppler ultrasound (TV-CDU) findings in the differentiation between endometrial hyperplasia and endometrial carcinoma and its relation with pathologic findings. **Methods:** This observational study included 48 women with either endometrial hyperplasia ($n = 10$) or endometrial carcinoma ($n = 38$) that had been diagnosed by endometrial biopsy. The intratumoral blood flow characteristics including resistance (RI), pulsatility (PI) and peak systolic velocity (PSV) index were analyzed using TV-CDU before surgery. Endometrial thickness and myometrial invasion also was assessed in all patients using gray-scale ultrasound. Then the relationship between these ultrasound findings and histologic results was evaluated with EC. **Results:** RI, PI, and PSV indices in endometrial carcinoma were significantly higher than endometrial hyperplasia ($P < 0.0001$). There was also a significant difference between the mean endometrial thickness between the two groups of endometrial hyperplasia and endometrial carcinoma ($P < 0.0001$). Intratumoral blood flow index were higher in high grade tumors than in low grade tumors ($P < 0.05$). **Conclusion:** TV-CDU may be useful to show a difference the difference in tumor angiogenesis between endometrial hyperplasia and endometrial carcinoma and therefore be used in differentiation of endometrial hyperplasia and carcinoma. Evaluation of intratumoral blood flow using RI, PI, and PSV indices in patients with endometrial carcinoma may be helpful distinguishing between low-grade and high-grade tumors as well as preoperative tumor invasion before surgery.

Keywords: Blood flow index, endometrial carcinoma, hyperplasia, transvaginal Doppler ultrasound

Introduction

Endometrial carcinoma is the most common malignancy of the female reproductive system.[1] The incidence of endometrial cancer is estimated at 320,000 people worldwide, causing 7,600 deaths each year, with mortality rates ranging from 0.9 to 3.8 per 100,000 people in different countries.[2] Therefore endometrial carcinoma is one of the most important diseases that should be considered in women with abnormal vaginal bleeding. Studies have shown that 75–80% of endometrial carcinomas occur in postmenopausal women.[3] Vaginal bleeding is the first symptom in 75–90% of endometrial cancers.[4] Early detection of this disease can have a 5-year survival of patients because early treatment improves myometrial tissue health; it is worth noting that 40–60% of endometrial cancers lead to deep myometrial invasion.[5] Timely and accurate diagnosis of disease specifies treatment strategy (medical or surgical), which is another reason for the need for early diagnosis of malignancy.[6]

Nowadays preoperative evaluations using advanced imaging techniques have become more common, but little has been done on the best imaging technique for routine use and preoperative evaluations of endometrial carcinoma. The accuracy of

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transvaginal ultrasound has been reported in different studies[7] and some results are comparable to MRI.[8] Many studies have shown that findings, such as intra-tissue color flow, indicate the likelihood of malignancy of the tissue if elevated along with a decrease in blood flow resistance.[9] Concerning endometrial tissue in spite of the many theoretical differences, some studies advocate that transvaginal Doppler ultrasound can distinguish endometrial malignancies.[9] The importance of this imaging technique is in identifying myometrial tissue invasion. In addition, screening for lymph node metastasis and tumor grading are also advantages of this technique.[10] In a study aimed at evaluating tumor blood flow by transvaginal color Doppler ultrasound in endometrial cancer reported that transvaginal Doppler ultrasound evaluation in women with endometrial cancer is a reliable method for evaluating endometrial angiogenesis and can be a good predictor for tumor progression and metastasis in women with endometrial cancer. It was also concluded that performing TVS reduces the need for curettage and endometrial biopsy.[11] However, few studies have investigated the efficacy of this method in the evaluation of endometrial cancer, tumor grade and its tissue invasion. Given the role of angiogenesis in tumor growth, it seems that evaluation of tissue vascularity via Doppler ultrasound may be useful in predicting malignant endometrial changes since malignancy is associated with increased blood flow.[12] The aim of the present study was to evaluate the efficacy of transvaginal color Doppler ultrasound (TV-CDS) for the diagnosis and differentiation of endometrial hyperplasia from endometrial carcinoma, as well as predicting tissue proliferation and tissue invasion, and comparing the results of Doppler ultrasound with pathologic results and final surgical findings of patients.

Methods

The present study is a prospective observational study performed on patients with definitive diagnosis of carcinoma or endometrial hyperplasia referred to educational centers of Ahvaz University of Medical Sciences during 2018. The sample size was calculated using the results of the same study,[9] considering the significance level of 0.05, using the following formula (equals 48 persons):

$\alpha = 0.05 \rightarrow Z_{(1-\alpha/2)} = 1.96$

$\beta = 0.02 \rightarrow Z_{(1-\beta)} = 1.28$

d = 3

$$n = \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 S_d^2}{d^2} = 48$$

In this study we evaluated all data which were related to transvaginal Doppler ultrasound of patients referred to educational centers of Ahvaz University of Medical Sciences for various reasons, such as abnormal vaginal bleeding. Women with definitive diagnosis for endometrial hyperplasia or carcinoma by histology and endometrial biopsy were chosen and underwent transvaginal Doppler ultrasound. Patients with known endometrial

problems were evaluated on the basis of biopsy and pathology results in two groups of hyperplasia and endometrial carcinoma. All patients with definitive and proven diagnosis of hyperplasia and endometrial carcinoma by biopsy and pathology findings were first subjected to transvaginal ultrasound by an experienced radiologist using GE (General Electric LOGIC, USA). Common transvaginal gray-scale ultrasound was performed using a 5.0 MHz endovaginal probe. Ultrasound was performed at the lithotomy position after bladder emptying. Tumor size and maximum of endometrial thickness were measured in sagittal plane. Myometrial invasion was also assessed.

To do transvaginal color Doppler ultrasound (TV-CDU) the wall filters were set to 100 Hz, and pulse repetition frequency ranged from 2 to 32 kHz. After vascular identification, Doppler waveforms were identified from intra-tumor or intra-endometrial vessels within or around of the abnormal endometrium. The intra-tumor blood flow indices were measured automatically as follows:

1. Resistance Index (RI): The vascular resistance index is derived from the difference between the systolic frequency change and the diastolic end divided by the systolic frequency change.
2. Pulsatility Index (PI): The pulsatility index is the difference between the peak systolic flow velocity and the diastolic end divided by the mean flow rate.
3. Peak Systolic Velocity (PSV): peak systolic velocity was calculated per cm/sec in each tumor.

For each patient, these markers were measured in two vessels of each endometrial lesion and then the lowest RI, lowest PI, and highest PSV in each sample were selected and recorded.[9] Subsequently, the carcinoma patients underwent hysteroscopic surgery and a tissue specimen from suspected endometrial sites was removed and examined pathologically. Grading of endometrial carcinoma was performed as follows.[7]

Grade 1: Well-differentiated endometrial carcinoma

Grade 2: Moderately differentiated endometrial carcinoma

Grade 3: Poorly differentiated endometrial carcinoma (undesirable histologic type, penetration to more than half myometrial depth, penetration into the cervix)

Finally, pathologic grading findings were compared with previous Doppler ultrasound findings.

SPSS software version 22 was used for statistical analysis. Mean, standard deviation, amplitude, frequency, and percentage indices were used to describe the data. Spearman correlation test was used to examine the agreement between the data obtained from both methods. Significance level was considered at 0.05 ($P < 0.05$).

Results

The mean age of patients was 63 ± 9 years and mean weight was 66 ± 6 kg. In this study baseline characteristics including

age, weight, BMI, underlying disease, smoking, pregnancy history, and breast cancer history were similar between the two groups. The results of pathology and gray-scale ultrasound before surgery are presented in Table 1. As shown, there was a significant difference between the hyperplasia and endometrial carcinoma groups in terms of invasion, tumor type, tumor grade, endometrial thickness, and invasion to myometrium ($P < 0.05$). But there was no significant difference in tumor size between the two groups ($P > 0.05$).

Results of transvaginal Doppler ultrasound are presented in Table 2. As can be seen, intra-tumor blood flow indices in endometrial carcinoma were significantly higher than endometrial hyperplasia.

Results on the concordance of TV-CDS findings with pathologic and surgical findings are presented in Tables 3-6. According to the results presented in Table 3, intra-tumor blood flow indices including RI, PI, and PSV in invasive tumors were higher than non-invasive tumors, but this difference was significant only in PI and PSV parameters. There was also a significant relationship between PI and PSV indices with the invasive mass but no significant relationship was observed for RI index.

According to the results presented in Table 4, intra-tumor blood flow indices in malignant tumors were more than benign tumors. But this difference was significant only in PI and PSV parameters. There was also a significant relationship between PI and PSV indices with type of mass but no significant relationship was observed for RI.

According to the results presented in Table 5, intra-tumor blood flow indices were significantly higher in high grade tumors than in low grade tumors. There was also a significant relationship between RI, PI, and PSV indices with tumor grade [Figure 1].

According to the results presented in Table 6, intra-tumor blood flow indices in myometrial invasion tumors were higher than non-myometrial invasion tumors. But this difference was significant only in the PSV parameter. There was also a significant relationship between PSV index and myometrial invasion, but the other two indices had no significant relationship with myometrial invasion.

Discussion

The results of this study showed that intra-tumor flow rate parameters including RI, PI, and PSV in endometrial carcinoma were significantly higher than endometrial hyperplasia. Kurjak *et al.* (1993) reported a significant difference between RI and PSV intra-tumor blood flow indices between the two groups of endometrial hyperplasia and endometrial carcinoma.[10] Consequently, the difference in angiogenesis between hyperplasia and endometrial carcinoma can be observed due to evaluation of intra-tumor blood flow by TV-CDU and these parameters are useful in differentiating between hyperplasia and carcinoma. The results of Aboul-Fotouh *et al.*'s (2012) study of Doppler sonography of post-menopausal women with vaginal bleeding showed that PI and PSV indices in postmenopausal women with endometrial carcinoma were significantly higher than endometrial hyperplasia. But RI was lower in carcinoma cases. It was also concluded that Doppler sonography is useful in the diagnosis of carcinoma in women with post-menopausal hemorrhage.[13] Similar results have been reported in other studies by Chan *et al.* (1999), Sheth *et al.* (1994) and Sladkevicius *et al.* (1994).[14-16]

In the present study, intra-tumor blood flow indices increased with increasing tumor grade and tumor invasion, and grade 3 tumors had the highest PI, RI, and PSV indices. It has also been reported in the past that the rate of angiogenesis increases with tumor invasion.[17] Tumor grading as an indicator of tumor invasion is an important part of the endometrial cancer classification system. Tumor grade is one of the most important prognostic factors for predicting overall survival as well as the most common factor that can be assessed preoperatively. On the other hand, the surgeon has to rely on the tumor grade determined by endometrial biopsy, which is often not very accurate and may differ from the final grade of tumor in the hysterectomy specimen.[18] In a study histologic grade determined by preoperative biopsy had 89% accuracy, 75% sensitivity, and 95% specificity.[19] But another study reported 35.2% accuracy for preoperative histologic grading.[20] In another study, Alcazar *et al.* (2002) examined the association between intra-tumor blood flow analysis and tumor characteristics in women with endometrial carcinoma showed PSV index in grade three tumors, cervical involvement tumors, myometrial invasion, lymph

Table 1: The results of pathology and Gray-scale ultrasound				
Variable	Group	Endometrial hyperplasia (*n*=10)	Endometrial carcinoma (*n*=38)	*P*
Mass nature	Invasive	6 (60%)	38 (100%)	0.001
	Non-invasive	4 (40%)	0	
Mass type	Malignant	6 (60%)	38 (100%)	0.001
	Benign	4 (40%)	0	
Tumor Grade	Grade 1	4 (40%)	10 (26.31%)	0.0001
	Grade 2	2 (20%)	22 (57.89%)	
	Grade 3	0	6 (15.78%)	
Tumor size, mm		3.58±0.83	4.10±1.23	0.460
Endometrial thickness, mm		1.20±0.06	2.17±0.74	0.0001
Myometrial invasion, yes		0	36 (94.73%)	0.0001

node metastasis, and tumors with a high risk of recurrence are significantly more than other tumors.[21]

Precision preoperative grading is essential for careful preoperative planning to reduce excessive or inappropriate procedures, especially in older patients.[22] For example, lymphadenectomy may increase morbidity that can cause lymphocysts, vascular damage, and gastrointestinal-urinary complications. Even the incision rate varies by tumor grade.[18] In this regard, studies have shown the use of advanced imaging tools are increasing to evaluate preoperative tumor grading.[23] However, according to the obtained results, transvaginal ultrasound is not only a diagnostic tool but can also be used as a prognostic tool. Another finding of this study was that endometrial thickness in endometrial carcinoma was significantly higher than endometrial hyperplasia. These results suggest that endometrial thickness measurement by gray-scale ultrasound can aid in the differentiation of carcinoma and endometrial hyperplasia. However, some studies have confirmed this results,[24,25] but Emoto *et al.* (2002) and some other studies did not show a significant difference between endometrial thickness in the two groups of hyperplasia and endometrial carcinoma.[9,26]

The differences in the results of the present study with other studies may be partly due to differences in the study population and study design. Tumor blood flow can be measured by non-invasive color and power Doppler ultrasound. But power Doppler imaging is more sensitive than color Doppler in detecting low-speed flows, and thus provides a better image of small vessels.[13] The discrepancy in results between different studies may be due to differences in ultrasound equipment, device settings, radiologist experience, and the absence of standardized criteria for subjective vascular endometrial evaluation.

Conclusion

The results of this study showed that evaluation of PI, RI, and PSV vascular resistance indices by transvaginal Doppler ultrasound can show angiogenesis differences between endometrial hyperplasia and endometrial carcinoma and thus this method can be used in differentiation of endometrial hyperplasia and carcinoma. In addition, evaluation of intra-tumor blood flow using RI, PI, and PSV indices in women with endometrial carcinoma can help to identify high and low grade tumors as well as preoperative tumor invasion.

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Conflicts of interest
There are no conflicts of interest.

Table 2: Doppler ultrasound parameters of women with hyperplasia and endometrial carcinoma

Parameter	Endometrial hyperplasia	Endometrial carcinoma	*P*
RI	0.27±0.23	0.33±0.18	0.0001
PI	0.24±0.28	0.42±0.22	0.0001
PSV	10.00±8.67	19.74±11.07	0.0001

RI: resistance index; PI: pulsatility index; PSV: peak systolic velocity

Table 3: Correlation of TV-CDS findings with mass tissue invasion

Ultrasound parameter	Invasive (*n*=44)	Non-invasive (*n*=4)	Correlation*
RI	0.32±0.18	0.24±0.28	Sig=0.033, *r*=0.824
PI	0.41±0.23	0.03±0.03	Sig=0.319, *r*=0.027
PSV	18.68±11.08	7.00±8.08	Sig=0.297, *r*=0.041

*Spearman correlation test to investigate the relationship between ultrasound parameters and the invasive tumor.

Table 4: Correlation of TV-CDS findings with tumor pathologic findings

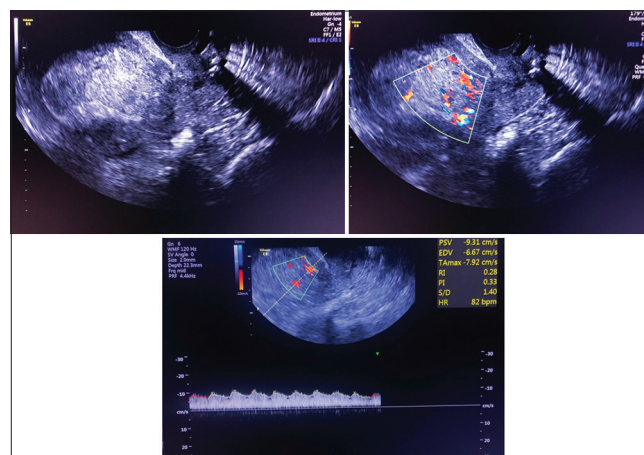| Parameter	Benign (*n*=4)	Malignant (*n*=44)	Spearman Correlation
RI	0.24±0.28	0.32±0.18	Sig=0.033, *r*=0.824
PI	0.03±0.03	0.41±0.23	Sig=0.319, *r*=0.027
PSV	7.00±8.08	18.68±11.08	Sig=0.297, *r*=0.041

Figure 1: Endometrial carcinoma: (a) transvaginal ultrasound examination of the uterus showed grossly thickened heterogeneous endometrium, and endometrial thickness measured about 29 mm. (b) Color Doppler imaging showed increased vascularity of the lesion. (c) Doppler examination showed its blood flow velocity waveform with high diastolic flow, RI = 0/28, and PI = 0/33. The patient underwent hysterectomy and histopathological study of the lesion confirms the diagnosis of endometrial carcinoma

Table 5: Correlation of TV-CDS findings with surgical findings (tumor grade)

Parameter	Grade 1 (*n*=14)	Grade 2 (*n*=24)	Grade 3 (*n*=6)	Spearman Correlation
RI	0.25±0.22	0.34±0.16	0.42±0.04	Sig=0.300, *r*=0.038
PI	0.32±0.29	0.44±0.20	0.52±0.06	Sig=0.484, *r*=0.0001
PSV	10.14±9.33	21.67±10.44	26.67±2.25	Sig=0.651, *r*=0.0001

Table 6: Correlation of TV-CDS findings with myometrial invasion findings			
Parameter	Yes (*n*=36)	No (*n*=12)	Spearman Correlation
RI	0.33±0.18	0.29±0.21	Sig=0.033, *r*=0.824
PI	0.41±0.22	0.29±0.28	Sig=0.319, *r*=0.027
PSV	19.56±11.36	11.33±8.87	Sig=0.297, *r*=0.041

References

1. De Haydu C, Black JD, Schwab CL, English DP, Santin AD. An update on the current pharmacotherapy for endometrial cancer. Expert Opin Pharmacother 2016;17:489-99.

2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, *et al.* Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:359-86.

3. Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J Clin 2016;66:7-30.

4. Rizzo S, Femia M, Buscarino V. Endometrial cancer: An overview of novelties in treatment and related imaging keypoints for local staging. Cancer Imaging 2018;18:45.

5. Batool S, Manzur S, Raza S. Accuracy of Doppler ultrasound in diagnosis of endometrial carcinoma. J Pak Med Assoc 2013;63:28-31.

6. Larson DM, Connor GP, Broste SK, Krawisz BR, Johnson KK. Prognostic significance of gross myometrial invasion with endometrial cancer. Obstet Gynecol 1996;88:394-8.

7. Epstein E, Van Holsbeke C, Mascilini F, Måsbäck A, Kannisto P, Ameye L, *et al.* Gray-scale and color Doppler ultrasound characteristics of endometrial cancer in relation to stage, grade and tumor size. Ultrasound Obstet Gynecol 2011;38:586-93.

8. Savelli L, Ceccarini M, Ludovisi M, Fruscella E, De Iaco PA, Salizzoni E, *et al.* Preoperative local staging of endometrial cancer: Transvaginal sonography vs. magnetic resonance imaging. Ultrasound Obstet Gynecol 2008;31:560-6.

9. Emoto M, Tamura R, Shirota K, Hachisuga T, Kawarabayashi T. Clinical usefulness of color Doppler ultrasound in patients with endometrial hyperplasia and carcinoma. Cancer 2002;94:700-6.

10. Kurjak A, Shalan H, Sosic A, Benic S, Zudenigo D, Kupesic S, *et al.* Endometrial carcinoma in postmenopausal women: Evaluation by transvaginal color Doppler ultrasonography. Am J Obstet Gynecol 1993;169:1597-603.

11. Sawicki V, Spiewankiewicz B, Stelmachów J, Cendrowski K. Color Doppler assessment of blood flow in endometrial cancer. Eur J Gynaecol Oncol 2005;26:279-84.

12. Runner GJ, Gerscovich EO, Fodor A, Shakeri S, Oswal H, McGahan JP, *et al.* Practical utility of color Doppler sonography in the evaluation of endometrial pathology. J Diagn Med Sonography 2014;30:281-7.

13. Aboul-Fotouh ME, Mosbeh MH, El-Gebaly AF, Mohammed AN. Transvaginal power Doppler sonography can discriminate between benign and malignant endometrial conditions in women with postmenopausal bleeding. Middle East Fertil Soc J 2012;17:22-9.

14. Sheth S, Hamper UM, McCollum ME, Caskey CI, Rosenshein NB, Kurman RJ. Endometrial blood flow analysis in postmenopausal women: Can it help differentiate benign from malignant causes of endometrial thickening? Radiology 1999;195:661-5.

15. Chan FY, Chau MT, Pun TC, Lam C, Ngan HY, Leong L, *et al.* Limitations of transvaginal sonography and color Doppler imaging in the differentiation of endometrial carcinoma from benign lesions. J Ultrasound Med 1994;13:623-8.

16. Sladkevicius P, Valentin L, Marsal K. Endometrial thickness and Doppler velocimetry of the uterine arteries as discriminators of endometrial status in women with postmenopausal bleeding: A comparative study. Am J Obstet Gynecol 1994;171:722-8.

17. Folkman J. Angiogenesis in cancer, vascular, rheumatoid and other disease. Nature Med 1995;1:27-31.

18. Çakıroğlu Y, Doğer E, Yıldırım Kopuk ğ, Özcan C, Nalbant B, Çorakçı A, Yücesoy İ. Prediction of tumor grade and stage in endometrial carcinoma by preoperative assessment of sonographic endometrial thickness: Is it possible? Turk J Obstet Gynecol 2014;11:211-4.

19. Sanjuán A, Cobo T, Pahisa J, Escaramís G, Ordi J, Ayuso JR, *et al.* Preoperative and intraoperative assessment of myometrial invasion and histologic grade in endometrial cancer: Role of magnetic resonance imaging and frozen section. Int J Gynecol Cancer 2006;16:385-90.

20. Wang X, Zhang H, Di W, Li W. Clinical factors affecting the diagnostic accuracy of assessing dilation and curettage vs frozen section specimens for histologic grade and depth of myometrial invasion in endometrial carcinoma. Am J Obstet Gynecol 2009;201:194.e1-10.

21. Alcazar JL, Galan MJ, Jurado M, Lopez-Garcıa G. Intratumoral Blood Flow Analysis in Endometrial Carcinoma: Correlation with Tumor Characteristics and Risk for Recurrence. Gynecologic Oncology 2002;84:258-62.

22. Akbayir O, Corbacioglu A, Numanoglu C, Guleroglu FY, Ulker V, Akyol A, *et al.* Preoperative assessment of myometrial and cervical invasion in endometrial carcinoma by transvaginal ultrasound. Gynecol Oncol 2011;122:600-3.

23. Barwick TD, Rockall AG, Barton DP, Sohaib SA. Imaging of endometrial adenocarcinoma. Clin Radiol 2006;61:545-55.

24. Gull B, Carlsson S, Karlsson B, Ylostalo P, Milsom I, Granberg S. Transvaginal ultrasonography of the endometrium in women with postmenopausal bleeding: Is it always necessary to perform an endometrial biopsy? Am J Obstet Gynecol 2000;182:509-15.

25. Vuento MH, Pirhonen JP, Makinen JI, Tyrkkö JE, Laippala PJ, Gronroos M, *et al.* Screening for endometrial cancer in asymptomatic postmenopausal women with conventional and colour Doppler sonography. Br J Obstet Gynaecol 1999;106:14-20.

26. Lindgren R, Mattsson LA, Andersson K, Lagrelius A, Sandin K, Karisson K, *et al.* Transvaginal ultrasonography and endometrial histology in peri- and postmenopausal women on hormone replacement therapy. Br J Obstet Gynaecol 1999;106:421-6.