EJGO European Journal of Gynaecological Oncology

Transvaginal ultrasound intrauterine echo flow resistance index as predictor of lymphovascular space invasion in endometrioid adenocarcinoma

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Summary

Background: Lymphovascular space invasion (LVSI) is an independent factor that affects the survival of patients with endometrioid carcinoma (EEC). However, few preoperative methods that can predict LVSI. Transvaginal ultrasonography (TVS) is a routine examination performed in patients with EEC. Therefore, the authors sought to assess whether there is a correlation between uterine blood flow resistance index (RI), determined by TVS, and LVSI. *Materials and Methods:* The authors performed a case-control study to examine patients with LVSI-positive (n=30) and LVSI-negative (n=148) Stage I-III endometrial cancer (EC) who underwent hysterectomy-based surgical staging. The risk associated with TVS intrauterine echo flow RI was estimated based on LVSI patterns. *Results:* Among 178 patients, the mean RI of patients without LVSI was 0.486 ± 0.15 and that of patients with LVSI was 0.581 ± 0.18. Univariate analysis showed that RI was a risk factor for LVSI ($p = 0.027$). Multivariate logistic regression analysis indicated that RI was not related to BMI, endometrial thickness, or uterine length. Hypertension, endometrial thickness, and length of intrauterine echo may increase risk through changes in RI ($p < 0.05$). *Conclusion:* Increased RI in EEC can predict the presence of LVSI. History of hypertension, endometrial thickness, and length of intrauterine echo also influence RI. Preoperative RI measurement is a useful tool for guiding clinical and surgical treatment.

Key words: Endometrioid carcinoma; Lymphovascular space invasion; Transvaginal ultrasonography.

Instruction

Endometrial cancer (EC) is a common type of reproductive-tract malignancy in females of which endometrioid carcinoma (EEC) is the most common [1]. Although generally favorable, the prognosis of EC can range from excellent with a high curability to poor in highly aggressive tumors. According to recent research, lymphovascular space invasion (LVSI) is a significant and consistent poor prognostic factor that is predictive recurrence and survival. LVSI appears to be a better predictor than other risk factors, such as tumor stage, grade, histologic type, and depth of myometrial invasion. Furthermore, LVSI correlates with lymph node involvement, and is reported to be a predictor of prognosis. LVSI invasion is defined as the presence of tumor cells inside endothelium-lined channels of uterine specimens outside the main tumor. Importantly, this pathologic finding correlates directly with lymphatic tumor metastasis. Among patients with endometrial carcinoma, approximately 8-10% of those with early stage and 93.5% of those with advanced stage can have LVSI [2]. LVSI is known to be associated with an increased risk of lymph node metastasis and decreased survival outcomes in endometrial cancer [3-5]. However, LVSI can only be diagnosed intraoperatively or based on postoperative pathology, and there is no effective technique to evaluate LVSI preoperatively. Identification of an effective method of predicting LVSI would aide clinicians in evaluating the extent of lymph node involvement and guiding surgical and postoperative treatment strategies.

Transvaginal ultrasonography (TVS) is a routine examination performed to visualize genital masses. The principle of TVS is based on alterations in the frequencies of acoustic or ultrasonic waves, which are related to the distance between body tissues and the ultrasound probe [6, 7]. Resistance index (RI) is the ratio of the difference between systolic peak velocity and end-diastolic flow speed compared to the systolic peak velocity (RI= (Vsp-Ved)/Vsp), and reflects the distal vascular bed resistance at points of measurement. Due to the use of the velocity ratio value, results are not affected by beam and blood flow direction angle; thus, RI has high credibility, repeatability, and objectivity. It has been universally used for the preoperative evaluation of benign and malignant tumors.

Evaluation of RI is simple, fast, and reproducible. If RI can be proven to correlate with LVSI, RI could be used at the time of surgery as a surrogate marker of LVSI. Thereby enabling the identification of patients who may benefit

Revised manuscript accepted for publication October 4, 2018

from full surgical staging. The aim of the present study was to investigate the association of RI with other histologic factors and the impact of RI in patients with EEC.

Materials and Methods

In the present retrospective, cohort study, data from women who were treated for primary EEC at the Department of Obstetrics and Gynecology, Lanzhou University of the First Hospital between January2010 and January 2015, were reviewed and analyzed. This study was performed in accordance with the ethical standards of the Declaration of Helsinki and was approved by the institution ' s local ethics committee.The records of all patients who underwent surgical staging for EEC were reviewed, and demographic, clinical, and pathologic data were collected. Clinical and pathologic variables included patient age, BMI (calculated as weight in kilograms divided by the square of the height in meters), menopausal status, surgical procedure, FIGO Stage, and final pathological analysis (histology type, grade, myometrial invasion, lymph node metastasis, and LVSI). All patients with a EEC FIGO Stage reported according to the 2009 staging system who underwent primary surgery were included in this analysis. Appropriate surgical staging was performed by gynecologic oncologists, and histopathologic analysis was conducted by a single dedicated gynecologic pathologist.

LVSI was defined as the presence of tumor cells in the space lined by endothelial cells outside the immediate invasive border. microcystic, elongated and fragmented (MELF) type invasion was used in diagnosing foci as LVSI. Intratumoral LVSI foci were not considered. The supportive criteria used to define LVSI included foci near other vessels and the presence of a lymphocytic infiltrate around the involved vessel.

Patient, tumor, and treatment characteristics were analyzed using SPSS16.0. Univariate analysis exact tests were used to determine the association between RI and myometrial invasion, grade, and LVSI. Multivariate logistics regression analysis was performed to evaluate the influence of variables on RI. Variables included in the logistic regression were based on bivariate analysis findings and model selection. *P* values less than 0.05 were considered to be statistically significant.

Results

During the study period, 125 patients with EEC were treated for Stage I, 38 patients were treated for Stage II, and 15 patients were treated for Stage III. The mean patient age was 55.4 ± 9.8 years; 81.2% of the patients were postmenopausal. The mean BMI was 25.6 ± 4.6. The FIGO grade distribution was as follows: G1: 69 (38.7%) cases, G2: 75 (42.1%) cases, G3: 34 (19.1%) cases. Myometrial invasion involved less than half the myometrium in 128 (71.9%) cases and more than half the myometrium in 50 (28.1%) cases. Cervical involvement was present in 30 (16.8%) cases and LVSI was present in 30 (16.8%) cases (Table 1).

The mean RI of patients without LVSI was 0.486 ± 0.15 and that of patients with LVSI was 0.581 ± 0.18. Univariate analysis showed that RI was a risk factor for LVSI (p = 0.027) (Table 2). Multivariate logistic regression analysis showed that RI was independent of BMI, endometrial thickness, and uterine length. History of hypertension, endometrial thickness, and length of intrauterine echo may influence LVSI risk through changes in RI ($p < 0.05$) (Table 3).

Table 1. — *Patient characteristics and final pathologic analysis*

Characteristics	Value (n = 178)
Age (years)	55.4±9.8
BMI (kg/m^2)	25.6±4.6
Menopause status	
Yes	146 (82.1)
No	32 (17.9)
FIGO Stage	
I	125(70.2)
II	38(21.3)
III	15(8.5)
Grade	
G1	69 (38.7)
G2	75 (42.1)
G3	34 (19.1)
Myometrial invasion	
< 1/2	128 (71.9)
≥ 1/2	50 (28.1)
LVSI	
Yes	30 (16.8)
No	148 (83.2)
Cervical involvement	
Yes	30 (16.8)
No	148 (83.2)
Lymph node metastasis	
Yes	8 (4.5)
No	170 (95.5)

FIGO: Federation International of Gynecology and Obstetrics; LVSI: lymphovascular space invasion.

Discussion

Surgery is the preferred treatment method for EEC. However, a subset of patients, who are difficult to identify, can benefit from full lymphadenectomy. Thus, pelvic lymph node excision is still controversial, particularly in patients with early-stage disease [8]. This controversy is reflected by the various recommendations of different authorities. For example, the most recent FIGO guidelines suggest that women with low-risk EEC (well-differentiated with less than 50% myometrial invasion) do not require full surgical staging. PORTEC-1/2,GOG-99, SEPAL, and ESMO have suggested that, for risk stratification and prognosis, the existence of LVSI is an important factor that can indicate the need for pelvic lymph node excision [9].

LVSI refers to presence of tumor cells inside endothelium-lined channels of uterine specimens outside the main tumor. The standard for identifying LVSI is based on the presence of tumor nests along the edges of the tumor, but separate from the tumor itself, that are surrounded by endothelial cells and exhibit a nearby stroma reaction. Ac-

Table 2. — *Univariate analysis of risk characteristics and LVSI*

Characteristics	Without LVSI (n=148)	With LVSI (n=30)	*p* value
Age, years	53.4 (8.3)	54.1 (8.6)	0.675
BMI (kg/m^2)	25.3 (2.6)	25.5 (3.8)	0.145
Menopause			
Yes	118 (79.7)	22 (73.3)	0.312
No	30 (20.3)	8 (26.7)	
FIGO Stage			
I	120 (81.0)	5 (16.7)	0.034*
II	26 (17.5)	12 (40)	
III	2 (1.5)	13 (43.3)	
Grade			
G1	67 (45.2)	2 (6.7)	0.019*
G2	64 (43.2)	11 (36.7)	
G3	17 (11.6)	17 (56.6)	
Myometrial invasion			
< 1/2	123 (83.1)	5 (16.7)	0.043*
≥ 1/2	25 (16.9)	25 (83.3)	
TVS of uterus (cm)			
Length	0.7 (0.56)	0.66 (0.82)	0.235
Width	0.42 (0.31)	0.39 (0.51)	0.285
Endometrial thickness	0.068 (3.2)	0.078 (1.2)	0.171
Intrauterine echo			
Length	1.3 (0.82)	1.5 (0.52)	0.723
Width	1.1 (0.83)	1.4 (0.18)	0.570
RI	0.486 (0.15)	0.681 (0.18)	0.027*

FIGO: Federation International of Gynecology and Obstetrics; LVSI: lymphovascular space invasion. *$p < 0.05$ indicates a significant difference between the two groups.

Table 3. — *Multivariable logistic regression for predicting LVSI using RI.*

Variables	OR (95% CI)	*p* value
Hypertension history	1.1 (1.0, 1.1)	0.0091 *
Endometrial thickness	1.51 (0.94, 2.42)	0.0472 *
Length of intrauterine echo	3.07 (1.76, 5.35)	0.0033 *

*$p < 0.05$.

cordingly, pathological analysis is the gold standard for diagnosing LVSI [10]. However, diagnosing LVSI based on frozen or paraffin sections exhibits great variability due to technical issues, position, and time required for evaluation [11, 12]. It is reasonable to consider that this variability might be amplified in frozen section analysis when time constraints and sampling errors are taken into consideration. Therefore, identification of an easily accessible tumor characteristic and auxiliary indicator that can be used to predict LVSI should be integrated into the intraoperative algorithm for risk stratification.

Zhi-Zhang Xu first demonstrated that RI was useful for the diagnosis of liver cancer and for the identification of benign or malignant liver tumors. If a putative tumor mass has an RI > 0.5, the chance of malignancy is higher [13]. Uggowitzer found that RI was higher in primary liver cancer and metastatic liver cancer compared to focal nodular hyperplasia [14]. Meanwhile, Gaiani concluded that an RI of 0.65 was the cut-off between malignant and benign tumor identification. This cut-off value was found to be accurate in nearly 83.8% of cases; however, the accuracy improved that were greater than 2 cm in diameter [15]. Similarly, breast tumors were most likely malignant if the RI was greater than 0.7.Moreover, RI combined with tumor markers can improve diagnostic sensitivity and decrease the incidence of misdiagnosis of ovarian cancer[16].

Positive LVSI is associated with a high-risk of lymph node metastasis and para-aortic recurrence. The Mayo Clinic group verified that LVSI can be used to evaluate the risk of pelvic lymph node metastasis [17]. Weinberg also suggested that LVSI was the only significant factor predictive of recurrence and survival. Indeed, the presence of LVSI is associated with a five-fold risk of microscopic pelvic lymph node metastases.

The diagnosis of LVSI requires intraoperative or postoperative pathological evaluation. Time constraints and the need to save tissue for a definitive diagnosis on permanent section assessment might lead to erroneous interpretation and inadequate sampling during frozen section analysis. In addition, rapid freezing of the specimen produces technical artifacts that can be misleading [18]. Therefore, based on clinical findings that can be used to aid in the diagnosis of LVSI in patients who would benefit from full surgical staging, different algorithms have been proposed.

The use of RI has been applied to the diagnosis of cancer, and was shown to be useful in differentiating between benign and malignant tumors [19]. The present univariate analysis showed that intrauterine echo flow RI was associated with LVSI. Interestingly, the present authors found that RI was a risk factor for LVSI ($p = 0.027$). Multivariate logistics regression analysis showed that RI was independent of BMI, endometrial thickness, and uterine length. History of hypertension, endometrial thickness, and length of intrauterine echo may influence LVSI risk through changes in RI. None of the previous studies showed a correlation between RI and LVSI. The present authors speculate that, in EEC, a higher RI correlates with an increased risk of LVSI.

In attempts to diagnose LVSI without permanent section and frozen section analysis, Joel Laufer proposed that tumor diameter can be used to predict LVSI. However, the above methods for evaluating LVSI all have notable shortcomings. Permanent section and frozen section analysis cannot be performed preoperatively, and poor agreement between permanent and frozen section diagnoses influences clinicians' use of these methods. When RI was abnormal, it was significantly and independently associated with LVSI in patients with EEC. Given the present results and the difficulties in diagnosing LVSI intraoperatively, it seems that preoperative RI measurement could be used to aid intraoperative LVSI determination and to guide the selection of an appropriate surgical strategy.

Importantly, determining RI is limited during routine

clinical use. Indeed, in practice, the performance of the instrument used during TVS, tumor location, integrity of the Doppler blood flow curve, experience of the physician, and patient cooperation, directly impact the accuracy of RI values. Yet, in this study, all patients underwent operations performed by gynecologic oncologists and all pathologic analyses were performed by a single, dedicated gynecologic oncology pathologist. This minimized the potential biases associated with the procedure and histological assessment. This is particularly important when analyzing data on LVSI, given its inconsistent pathologic identification.

Conclusion

In summary, the present authors found that a higher RI is significantly associated with LVSI, which is a key predictor of lymph node metastasis. LVSI is difficult to diagnose preoperatively and the accuracy of diagnosis is restricted by the tumor diameter. RI should be integrally reported during intraoperative assessment and included in the decision-making algorithm. In clinical preoperative practice, the use of RI to predict LVSI may influence the decision to perform full surgical staging, particularly for early-stage disease. Additionally, history of hypertension, endometrial thickness, and length of intrauterine echo should be considered when evaluating RI for predicting LVSI. The intraoperative use of RI as a marker for LVSI and its potential incorporation into the definition of LVSI in EEC should be further investigated.

Acknowledgement

This study was supported by the Foundation of Gansu natural science grant 18JR3RA340, the Foundation of Lanzhou science grant 2017-4-56, the Foundation of the First Hospital of Lanzhou university grant ldyyn 2017-13.

References

[1] Creutzberg C.L., van Putten W.L., Wárlám-Rodenhuis C.C., van den Bergh A.C., de Winter K.A., Koper P.C., *et al.*: "Outcome of high-risk stage IC, grade 3, compared with stage I endometrial carcinoma patients: the postoperative radiation therapy in endometrial carcinoma trial" *J. Clin. Oncol.*, 2004, *22*, 1234.

[2] Marnitz S.: "Current therapy of patients with endometrial carcinoma. A critical review". *Strahlenther. Onkol.*, 2012, *188*, 12.

[3] Mahdi H, Jernigan A., Nutter B., Michener C., Rose P.G.: "Lymph node metastasis and pattern of recurrence in clinically early stage endometrial cancer with positive lymphovascular space invasion". *Gynecol. Oncol.*, 2015, *26*, 208.

[4] AlHilli M.M., Podratz K.C., Dowdy S.C., Bakkum-Gamez J.N., Weaver A.L., McGree M.E., *et al.*: "Risk-scoring system for the individualized prediction of lymphatic dissemination inpatients with endometrioid endometrial cancer". *Gynecol. Oncol.*, 2013, *131*, 103.

[5] Weinberg L.E., Kunos C.A., Zanotti K.M.: "Lymphovascular space invasion (LVSI) is an isolated poor prognostic factor for recurrence and survival among women with intermediate- to high-risk early-stage endometrioid endometrial cancer". *Int. J. Gynecol. Cancer*, 2013, *23*, 1438.

[6] Mannelqvist M., Stefansson I.M., Bredholt G., Hellem Bø T., Oyan A.M., Jonassen I., *et al.*: "Gene expression patterns related to vascular invasion and aggressive features in endometrial cancer". *Am. J. Pathol.*, 2011, *178*, 861.

[7] Kumar S., Bandyopadhyay S., Semaan A., Shah J.P., Mahdi H., Morris R., *et al.*: "The role of frozen section in surgical staging of low risk endometrial cancer". *PLoS One*, 2011, *6*, e21912.

[8] Tsuruchi N., Kaku T., Kamura T., Tsukamoto N., Tsuneyoshi M., Akazawa K., Nakano H.: "The prognostic significance of lymphovascular space invasion in endometrial cancerwhen conventional hemotoylin and eosin staining is compared to immunohistochemicalstaining". *Gynecol. Oncol.*, 1995, *57*, 307.

[9] Ito K., Noro K., Yanagisawa Y., Sakamoto M., Mori S., Shiga K., *et al.*: "High accuracy Ultrasound Contrast Agent Detection Method for Diagnostic Ultrasound Imaging Systems". *Ultrasound Med. Biol.*, 2015, *41*, 3120.

[10] Uggowitzer M., Kugler C., Machan L., Gröll R., Stauber R., Mischinger H.J., *et al.*: "Power Doppler imaging and evaluation of the resistive index in focal nodular hyperplasia of the liver". *Abdom. Imaging*, 1997, *22*, 268.

[11] GaianiS., Casali A., Serra C., Piscaglia F., Gramantieri L., Volpe L., *et al.*: "Assessment of vascular patterns of smallliver mass lesions: value and limitation of the different Doppler ultrasoundmodalities". *Am. J. Gastroenterol.*, 2000, *95*, 3537.

[12] Mousavi A.S., Borna S., Moeinoddini S.: "Estimation of probability of malignancy using a logistic model combining color Doppler-transvaginal ultrasonography, serum CA125 level in women with a pelvic mass". *Int. J. Gynecol. Cancer*, 2006, *16*, 92.

[13] Green R.W., Valentin L., Alcazar J.L., Chiappa V., Erdodi B., Franchi D., *et al.*: "Endometrial cancer off-line staging using two-dimensional transvaginal ultrasound and three-dimensional volume contrast imaging: Intermethod agreement, interrater reliability and diagnostic accuracy". *Gynecol. Oncol.*, 2018, *150*, 438.

[14] Colombo N., Preti E., Landoni F., Carinelli S., Colombo A., Marini C., *et al.*: "Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up". *Ann. Oncol.*, 2011, *22*, vi35.

[15] Wright J.D., BarrenaMedel N.I., Sehouli J., Fujiwara K., Herzog T.J.: "Contemporary managementof endometrial cancer". *Lancet*, 2012, *379*, 1352.

[16] Amant F., Mirza M.R., Creutzberg C.L.: "Cancer of the corpus uteri". *Int. J. Gynecol. Obstet.*, 2012, *119*, S110.

[17] Creutzberg C.L., van Putten W.L., Koper P.C., Lybeert M.L., Jobsen J.J., Wárlám-Rodenhuis C.C., *et al.*: "Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: Multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma". *Lancet*, 2000, *355*, 1404.

[18] Keys H.M., Roberts J.A., Brunetto V.L., Zaino R.J., Spirtos N.M., Bloss J.D., *et al.*: "A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: A Gynecologic Oncology Group study". *Gynecol. Oncol.*, 2004, *92*, 744.

[19] Todo Y., Kato H., Kaneuchi M., Watari H., Takeda M., Sakuragi N.: "Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis". *Lancet*, 2010, *375*, 1165.

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