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Ultrasonic shear-wave elastography: a novel method for assessing the tumor grade in endometrial cancer: a prospective study

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ABSTRACT

Aims: To evaluate the diagnostic performance of the real time shear-wave elastography in patients with endometrial cancer in terms of tumor grade and myometrial invasion depth preoperatively.

Methods: In this prospective observational study, forty-eight women who were diagnosed with endometrioid type endometrium cancer in our gynecologic oncology clinic of a tertiary hospital between September 2020-January 2021 in Turkey. All patients underwent an ultrasonographic shear-wave measurements. Mean shear-wave values were measured from the tumor itself. Mean elasticity values were assessed in terms of tumor grade and myometrial invasion depth.

Results: The median [%25-%75] shearwave value of the participants was 29.45kPa (5.02-167.21). Shear-wave value for grade 3 endometrial cancer showed a statistically significant difference compared to grade 1 and 2 shear-wave values ($p<0.001$). To determine the myometrial invasion depth, lymph node involvement, lympho-vascular stromal invasion and cervical stromal invasion statues, shear-wave measurements did not show a significant result ($p>0.05$). ROC curve analysis showed significant results to determine the myometrial invasion depth and grade 3 endometrial cancer with the mean shear-wave cut-off values of 28.29 kPa and 57 kPa respectively ($p<0.001$).

Conclusion: Real-time shear-wave elastography is a promising tool to predict the grade 3 tumors and deep myometrial invasion in endometrial cancer patients.

Keywords: Endometrial cancer, Shear-wave elastography, shear-wave, tumor grade, grade 3 endometrial cancer

INTRODUCTION

Endometrial cancer (EC) is the most common gynecologic cancer of women in developed countries.[1] Although the majority of diagnosis are made in the postmenopausal period, nearly 15% of patients are diagnosed at premenopausal ages.[2] With the increase in life expectancy, endometrial cancer has become more frequent.[3] Because of this rising incidence, accurate diagnostic evaluation of patient is essential. Fortunately, EC has a favorable prognosis and early detection rates compared to other genital malignancies. Nevertheless some patients have worse prognosis due to many factors, such as; tumor grade, histological type, the depth of myometrial invasion, the tumor size, lympho-vascular invasion and lymph node status that can affect the course of the disease.[4]

Tumor grade is one of the important prognostic factors. As the tumor grade increases mortality and morbidity rates rise and extent of the surgery differentiates for the treatment. Endometrioid ECs are graded using the International Federation of Gynecology and Obstetrics (FIGO) classification system, which assesses the architectural pattern and nuclear grade; Grade 1-Less than 5 percent solid growth patterns Grade 2-6 to 50 percent solid growth patterns Grade 3-Greater than 50 percent solid growth

As seen in the histologic grading system, alterations in the growth pattern result in an increase in solid component of the cells, which may cause change in the tissue elasticity. Recently a novel method, elastography,

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has been used to assess the tissue stiffness quantitatively. Although it was firstly introduced in the late 1980s and early 1990s[5-8] clinical use of the application become more common in the recent years with the improvements in technology. Shear-wave ultrasonography (SWE) is a type of elastography which measures the tissue hardness without applying any external pressure to the tissue. In this method, transducer-generated acoustic force causes a displacement in the targeted tissue. As a result of this displacement shear waves arise from the tissue vertical to the acoustic force. Tissue-originated shear waves' velocity is then calculated quantitatively and converted to Young's modulus as Kilopascal (kPa).[9] The method's reproducible, and easy-to-learn nature makes it popular among the researchers. Several studies investigated the clinical use of SWE in the field of malignant-benign breast lesions, thyroid, superficial lymph nodes,[10-13] and rectum.[14] Also, cervix, myometrium and ectopic pregnancy were investigated by the gynecologist.[15,16]

However, to our knowledge, no study evaluated the SWE of EC in terms of histologic tumor grade, depth of myometrial invasion and lymph node status. Therefore, we aimed to investigate the relationship between SWE values and EC prognostic factors affecting the operation type, mortality and morbidity.

METHODS

The study was carried out with the permission of by Adana City Training and Research Hospital Clinical Researches Ethics Committee (Date: 26.08.2020, Decision No: 1043). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study population of this research, consisted of women who were diagnosed with endometroid EC in our gynecologic oncology clinic of a tertiary hospital between September 2020-January 2021. Preoperative endometrial sampling was performed to diagnose endometrial cancer, and final pathology confirmed our preoperative diagnosis. Total of 48 patients were enrolled for the study. All patients' SWE measurements were performed 24 hours before the surgery. Relationship between the final pathology and SWE values of the patients were analyzed. Inclusion criteria of the patient were: 1) having the pathological confirmation of endometrioid type EC, 2) a minimum 1cm. endometrial mass that could be seen on the ultrasound examination, 3) Body mass index (BMI) between 20-25 kg/m², 4) No other gynecologic benign and malign disease, 5) no other co-existing malignancy. Exclusion criteria were: 1) Patients with gynecologic benign or malign diseases such as, myoma uteri, adenomyosis or ovarian cancer etc. 2) patients with connective tissue disease, 3) tumor diameter 4 cm or greater 4) patients who were treated before the surgery. 5) BMI>25.

Ultrasound Examination

Examination of the participants were performed via a high-resolution ultrasound (US) device (Philips EPIQ 7), with a transabdominal 1-5 MHz convex probe (Philips Health Care, Bothell, WA, USA). Endometrial stiffness of the patient during the supine position was measured with ElastoPQ technique which is a point shear-wave (pSWE) elastography evaluation during the US examination, possible minimum compression was applied with the probe, which was maintained in a constant position. Elastography was performed with breath hold to minimize motion artifacts. After obtaining the conventional US images, target area was determined, and the measurements from region of interest (ROI) were taken. To achieve an optimum SWE measurement, grayscale mode was used. Our study's maximum ROI target distance was 8 cm, with a constant ROI box dimension of 1-0.5 cm. To evaluate the endometrial stiffness ten valid measurements were obtained from each patient's endometrial lesion and their average was calculated. If SWE measurement had low reliability due to operator (overpressure, not holding the probe fixed) or patient (cough or moving etc.) the measurement was ignored and to get a reliable measurement examination was repeated. The results were expressed as kPa. All the examinations were performed by a radiologist who is well-experienced in conventional US and SWE measurements. The specialist performs 500 SWE procedures annually with more than 5 years of experience. The average time to obtain a reliable measurement was about 25-30 minutes.

Statistical Analysis

IBM SPSS V.23 program was used for data analysis. The Shapiro-Wilk test was utilized to determine whether or not the continuous data followed a normal distribution. ANCOVA analysis was used to examine the effect of parameters on the mean shear-wave value by removing the effect of some variables. Roc Analysis was used to determine the cut-off value for the mean shear-wave value for the determination of grade 3 tumor and depth of myometrial Invasion. Analysis results were presented as frequency (percentage) for categorical variables and continuous variables were summarized as mean±standard deviation when it provided the assumption of normal distribution and as median [25%-75%] if it did not. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 48 patients were enrolled for this study. Table 1 summarizes the demographic features and tumor characteristics of the participants. The mean age (mean±SD) of the participants was 59.88±9.29 and the

median (%25-%75) tumor diameter of the patients was 2.75 cm. (1cm-3.7cm). Patients had a median (%25-%75) body mass index (BMI) of 22.66 kg/cm² (20.6-24.62) (Table 1). Main effect of tumor grade on mean shear-wave values was statistically significant (p<0.001). Shear-wave values of grade 1, 2 and 3 were 13.52 kPa, 33.24 kPa and 101.89 kPa respectively (Table 2). The shear-wave value for grade 3 EC showed a statistically significant difference compared to grade 1 and 2 shear-wave values (p<0.001) (Table 2). Main effect of myometrial invasion depth, lymph node involvement, lympho-vascular stromal invasion and cervical stromal invasion statues, on mean shear-wave values did not show a significant result. (p>0.05).

Table 1. The demographic features of patients and tumor characteristics

	n=48
Age (years) (mean ±SD)	59.88±9.29
Body mass index (kg/m²) (median [25%-75%])	22.6 [20.6-24.62]
Parity (median [25%-75%])	3 [0-12]
Tumor diameter (median [25%-75%])	2.75 [1-3.7]
Tumor grade (n, %)	
Grade 1	16 (33.3%)
Grade 2	17 (35.4%)
Grade 3	15 (31.3%)
Tumor stage (n, %)	
Stage I	25 (52.1%)
IA	20 (41.7%)
IB	5 (10.4%)
Stage II	9 (18.8%)
Stage III	12 (24.9%)
IIIA	5 (10.4%)
IIIB	1 (2.1%)
IIIC1	2 (4.2%)
IIIC2	4 (8.3%)
Stage IV	2 (4.2%)
IVA	1 (2.1%)
IVB	1 (2.1%)
Lymph node involvement (n, %)	
Yes	15 (31.3%)
No	33 (68.8%)
Myometrial invasion depth (n, %)	
<1/2	24 (50%)
>1/2	24 (50%)
Cervical stromal invasion (n, %)	
Yes	22 (45.8%)
No	26 (54.2%)
Lympho-vascular invasion (n, %)	
Yes	14 (29.2%)
No	34 (70.8%)

Table 2. Mean shearwave values of the prognostic factors

	Mean Shearwave Values	
	Mean±SD	p
Tumor grade		<0.05
Grade 1	13.52±7.2[b]	
Grade 2	33.24±18.48[b]	
Grade 3	101.89±33.13[a]	
Total	48.12±43.24	
Myometrial invasion depth		0.294
Invasion less than 1/2	23.2±23.66	
Invasion more than 1/2	73.04±44.33	
Total	48.12±43.24	
Lymph node involvement status		0.639
No	26.38±24.21	
Yes	95.96±37.04	
Total	48.12±43.24	
Cervical stromal invasion status		0.225
No	18.29±14.4	
Yes	83.37±39.18	
Total	48.12±43.24	
Lympho-vascular invasion status		0.639
No	29.79±27.62	
Yes	92.65±42.54	
Total	48.12±43.24	

a,b: There is no significant difference between the groups with same letter

A ROC curve was constructed to determine the tumor grade. The mean shear-wave value was used and the AUC was 0.994 (p<0.001). The mean shear-wave cut-off value of 57 kPa was used to diagnose grade 3 EC with 100% sensitivity and 96.97% specificity. Positive predictive value and negative predictive value were 93.75% and 100% respectively (Table 3) (Figure 1).

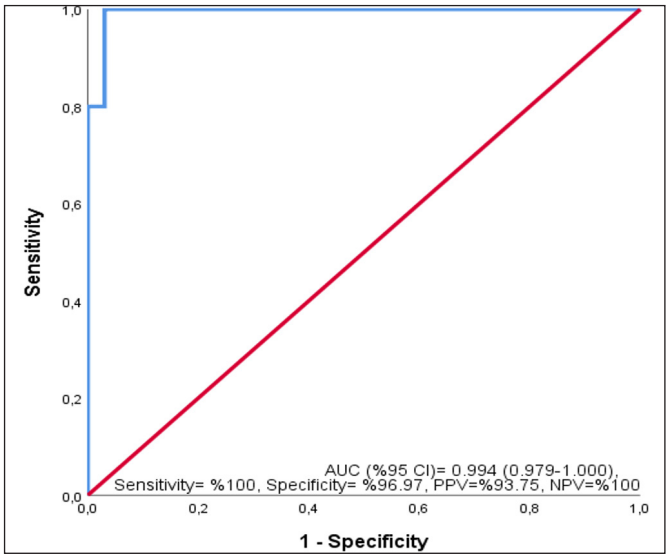

Figure 1. ROC curve to determine the grade 3 endometrial cancer

Table 3. Cut-off points analysis of the mean shearwave values to determine the grade 3 tumor and myometrial invasion depth

	Cut point	AUC	p	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Grade 3	≥57	0.994 (0.979-1.000)	<0.001	100%	96.97%	93.75%	100%
MID	≥28.29	0.853 (0.740-0.996)	<0.001	83.33%	79.17%	80%	82.61%

MID: Myometrial invasion depth

To determine the myometrial invasion depth another ROC analysis performed using mean shear-wave value. And AUC was 0.853 (p<0.001). The mean shear-wave cut-off value was 28.29 kPa with 83.33% sensitivity and 79.17% specificity. Positive predictive and negative predictive values were 80% and 82.61% respectively (Table 3) (Figure 2).

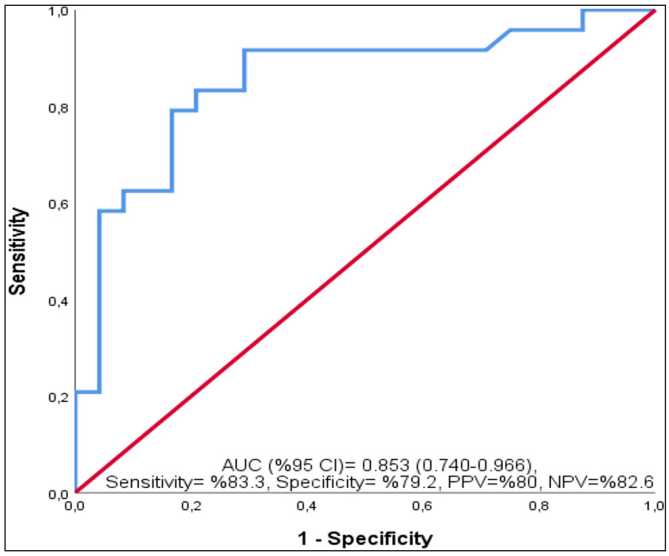

Figure 2. ROC curve to determine the myometrial invasion depth

DISCUSSION

So far, several researchers have investigated the diagnostic accuracy of shear-wave elastography in various malign and benign lesions of the organs including; breast, rectum, thyroid, liver and cervix.[13,14,17-19] Also a recent meta-analysis showed that SWE may have high diagnostic accuracy for the differential diagnosis of benign and malignant endometrial diseases.[20] In our study we also investigated the diagnostic performance of the shear-wave elastography in endometrial cancer patients in terms of the histologic grade of the tumor. In our study, we found that patients with grade 3 EC had higher shear-wave values compared to grade 1 and 2 patients 101.89 kPa, 13.52 kPa, 33.24 kPa, respectively (p<0.001). We think this difference may arise from the nature of the cancer cells. As far as we know, an increase in the tumor grade means an increase in solid component of the cells, which may cause a hardness in the tissue, and may result with a higher SWE value in high-grade lesion.[21] In addition, since the fibrous and vascular structure of the tissue is changed by the tumor, the tissue architecture is disrupted. Thus, cancerous tissue has more dens, fibrous structure with abnormal angiogenetic capillary vessels than normal tissue. These alterations may also contribute to the tissue stiffness.[22,23]

In 2020 European Society of Gynecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP) updated the guidelines for the management of the patients with endometrial carcinoma. In this guideline the grade 3 EC patients were underlined as a high-risk group.[24] Grade 3 EC shows more aggressive behavior, with more local and distant relapse and poorer survival rates compared to low grade EC (Grade 1 and grade 2).[25-27] The National comprehensive cancer network (NCCN) also categorizes the grade 3 endometroid type tumor as a high risk. So even if it is an early-stage endometroid type endometrial cancer, NCCN recommends comprehensive surgery and adjuvant treatment for these patients.[28] In a study conducted by Gungorduk et al.[29] in 2021 they stated, comprehensive surgery with adequate lymphadenectomy with optimal cytoreductive approach is the key point for the grade 3 EC despite its poor prognosis. These results show us the importance of accurate evaluation of the patients preoperatively. Even though pathologist may define the grade of the tumor in EC patients, study of the M.-H. Baek et al.[30] found the preoperative pathological assessment is unreliable compared to final pathology in tumor grading. In 2017, a review also showed, preoperative sampling may be discordant with final pathology in tumor grade.[31] In this context, our study may contribute to the preoperative determination of the EC grade. This cheap and non-invasive method may be a helpful tool for clinicians' Current study revealed a 0.994 AUC value (p<0.001), while SWE measurement cut-off to determine the grade 3 EC was 57 kPa with 100% sensitivity and 96.97% specificity. Positive predictive value and negative predictive value were 93.75% and 100% respectively (Figure 1).

Myometrial invasion depth is another important prognostic factor that can change type of surgery in EC. Therefore, preoperative evaluation of myometrial depth is also an important issue. Magnetic resonance imaging (MRI) and transvaginal ultrasonography (TVS) are being used so far. In 2017 a meta-analysis that Alcazar et al.[32] studied, found an overall pooled 75% sensitivity and 86% specificity for detecting the deep myometrial invasion via TVS, while MRI revealed an 83% sensitivity and 82% specificity for deep myometrial invasion detection. In 2020 Zhao et al.[15] investigated the applicability of SWE in the preoperative diagnosis of deep myometrial invasion. Unlike our study, while they measured myometrial tissue stiffness with SWE, we measured the tumoral mass itself shear-wave value. They found a significant difference between patients with deep myometrial invasion and patients with superficial myometrial invasion. In that study, mean SWE cut off values were, to determine deep myometrial invasion of endometrial cancer, 28.17 kPa with a 92.9% sensitivity, 94.6% specificity and positive predictive value was 86.7%, negative predictive value was

97.2%. They attributed this difference to pathological changes caused by the tumoral cells invasion in myometrial tissue. We also found a 28.29 kPa cut-off value in the current study to determine the myometrial invasion depth (AUC= 0.853, p<0.001). This cut-off value has 83.33% sensitivity and 79.1% specificity with 80% positive predictive and 86.61% negative predictive value (**Figure 2**).

Study Strengths and Limitations

First of all, our study has a prospective design. For an accurate measurement of tissue elastography, operator needs to have certain training and operation experience.[33] In the study of Zhao et al.[15] the operator conducted 30 cases of training first to improve data repeatability. In our study SWE measurements were performed by an experienced radiologist with more than 5 years of experience in SWE studies. Conducting the study with a small sample size of the grade 3 EC group was a limitation of the study. However, grade 3 EC patients with BMI<25 are rare. In the literature many studies conducted with transvaginal probe.[20,34] In this study we used abdominal real-time shear-wave elastography. Abdominal wall fat has impact on measurement, so the impact of BMI on patients has not been studied, and it will be further explored in subsequent studies.[34,35]

CONCLUSION

Because of its poorer prognosis, grade 3 EC deserves extra attention for preoperative evaluation and optimal treatment strategy. World Health Organization and FIGO recommend identifying the risk groups for optimal treatment because of the prognostic relevance for tumor grade. Therefore, real-time shear-wave elastography may help the clinician with its high diagnostic accuracy regarding tumor grade and myometrial invasion depth. Hereby, SWE may be a valuable tool for deciding the treatment method and making a judgment about the future prognosis of the disease.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of by Adana City Training and Research Hospital Clinical Researches Ethics Committee (Date: 26.08.2020, Decision No: 1043).

Informed consent: Written consent was obtained from the patient participating in this study.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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