

# Assessment of myometrial invasion of endometrial carcinoma with preoperative transvaginal sonography

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**Objective:** Routine pelvic and para-aortic lymphadenectomy up to the level of the renal veins is controversial in endometrial cancer as the complication rate and prolonging the operation time is considerable. Intraoperative frozen section analysis of the uterus is the mainstay for the decision of performing a staging lymphadenectomy. Preoperative estimation of myometrial invasion may be useful for surgical planning. Our objective is to assess the accuracy of preoperative transvaginal ultrasound for identifying myometrial invasion. **Methods:** 80 consecutive patients operated between August 2017 and December 2019 with a histologically confirmed diagnosis of endometrial carcinoma evaluated within two weeks before surgery by transvaginal ultrasound are the subject of this study. Myometrial invasion estimation is documented and intraoperative frozen section analysis and final pathologic diagnosis as the reference standard was recorded. **Results:** Preoperative TVUS had 76.5% sensitivity, 91.3% specificity, whereas frozen section analysis had 85.3% sensitivity and 93.5% specificity, and they correlate well with each other ( $P < 0.01$ ). Agreement between these two methods was substantial according to Cohen's kappa index ( $\kappa$ ) = 0.74 ( $P < 0.01$ ) and percentage of agreement was 88%. Increasing tumor diameter decreased the prediction accuracy of preoperative ultrasound ( $P < 0.01$ ). **Conclusion:** There is good correlation of preoperative transvaginal ultrasound with intraoperative frozen section analysis and final pathology results. The subjective assessment of transvaginal ultrasound can guide surgeons as a useful preoperative tool for preparing surgery.

## Keywords

Endometrial cancer; Myometrial invasion; Ultrasound

## 1. Introduction

Endometrial cancer (EC) is the most common gynecological tumor in industrialized countries and its incidence is rising [1]. Most of the cases are diagnosed when the tumor is confined to the uterus. Nevertheless, it is the fourth leading cause of death due to gynecological cancer among women worldwide [1]. EC is staged surgically, standard treatment is hysterectomy and bilateral salpingo-oophorectomy, with or without lymph node dissection, which is mostly decided in accordance to risk stratification usually made intraoperatively with frozen section analysis.

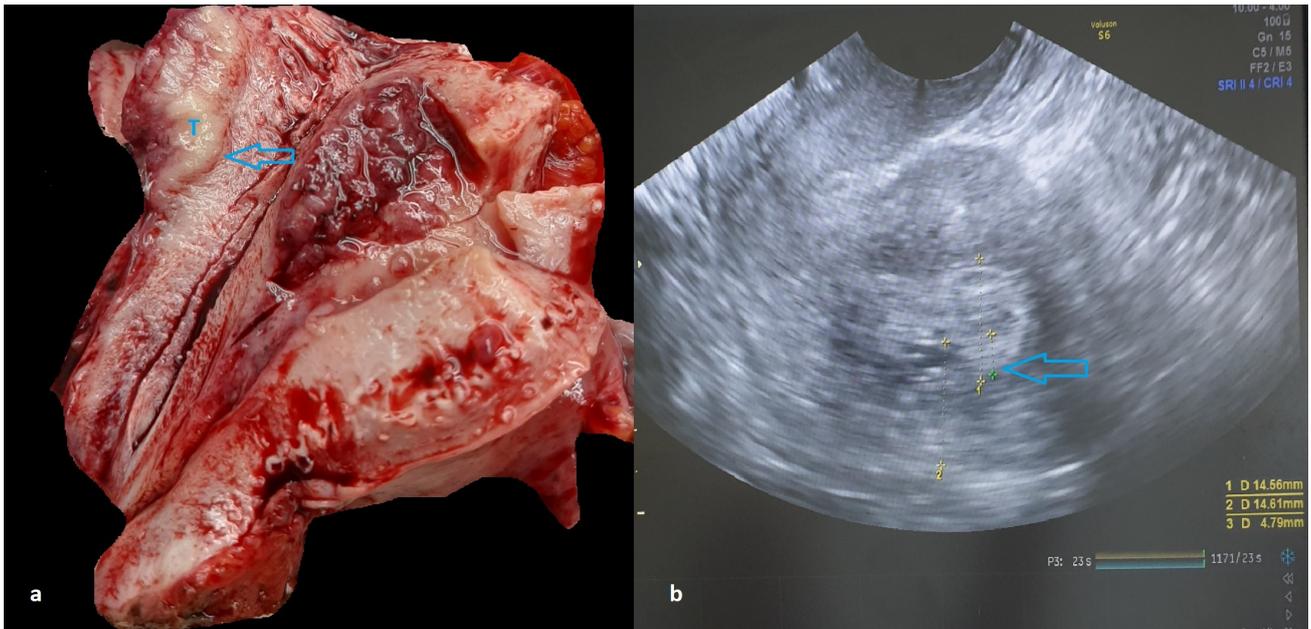
Lymph node involvement in endometrial cancer is an independent and one of the most important prognostic factors,

and guides adjuvant therapy [2]. Routine pelvic and para-aortic lymphadenectomy up to the level of the renal veins is controversial in endometrial cancer, as the complication rate is considerable (hemorrhage, nerve injury, lymphedema, lymphocyst formation, longer operating time) and the benefit is questionable. In stage I endometrioid, grade 1 or 2 tumors, with myometrial invasion less than 50%, lymph node metastasis is about 5%. Metastasis occurs in less than 1% of cases with tumors smaller than 2 cm in diameter and lymphadenectomy does not seem to prolong the survival of these patients [3, 4]. On the other hand, for intermediate and high-risk patients, systematic pelvic and para-aortic lymphadenectomy seems to improve overall survival [5].

There are studies utilizing magnetic resonance imaging (MRI) or ultrasonography with or without doppler for predicting myometrial invasion in EC to determine which patients require a systematic lymph node dissection (LND) [6–9]. In a meta-analysis, no significant difference is observed between MRI and transvaginal ultrasonography (TVUS) preoperatively [10]. These non-invasive tools may aid clinicians in counseling patients and discussing the risks thoroughly, as well as getting prepared for a longer surgery with higher complication rates in comparison with hysterectomy alone [11].

Subjective assessment of myometrial invasion with TVUS is found to be as good as or better than objective measurement with TVUS [8, 12]. Several other studies also confirm that subjective evaluation is useful and reliable for the assessment of myometrial invasion [13–15]. In a meta-analysis, of TVUS in the preoperative detection of deep myometrial infiltration in patients with endometrial cancer, comparing subjective and objective methods found no difference among methods in terms of diagnostic performance [16].

In this study, we evaluated the predictive accuracy of preoperative TVUS in predicting the degree of myometrial invasion, its correlation with frozen section analysis and factors that are associated with false negative and false-positive results.



**Fig. 1. (a) Specimen cut for intraoperative frozen section analysis to determine myometrial invasion.** (Blue arrow shows deepest part of the tumor (T) in myometrium. (b) Preoperative TVUS in sagittal plane for assessing myometrial invasion. 1. Tumor thickness (14.56 mm). 2. Maximum diameter of normal-looking myometrium (14.61 mm). 3. Maximum invasion of the tumor in myometrium (4.79 mm) which is less than half of the myometrium.

## 2. Materials and methods

### 2.1 Methods

Eighty consecutive patients operated by a single surgeon between August 2017 and December 2019 with a histologically confirmed diagnosis of endometrial carcinoma at a tertiary referral center, Health Sciences University Samsun Research and Training Hospital, Gynecologic Oncology Unit are the subjects of this study. They were evaluated within two weeks before surgery by TVUS (Voluson S6, GE Healthcare Ultrasound, Milwaukee, WI, USA) by the same surgeon. Preoperative diagnosis was made by a gynecologist in Samsun or surrounding cities by dilatation and curettage in all cases and then referred to our institution. Tumor invasion into the myometrium (as  $< 50\%$  or  $\geq 50\%$  of myometrium) and cervical stroma was evaluated subjectively with preoperative TVUS and recorded. The depth of myometrial invasion was measured from the deepest tumoral area in myometrium to normal-looking endo-myometrial junction evaluated in relation to the width of the normal myometrium next to the tumor in mid-sagittal plane. Any fluid in the uterine cavity was excluded. The ratio of myometrial infiltration to the normal-looking myometrium in antero-posterior (AP) diameter was recorded as  $< 50\%$  or  $\geq 50\%$  of myometrium (Fig. 1). In cases with no myometrial infiltration observed, the depth of invasion was also recorded as  $< 50\%$ . At surgical staging, all patients underwent total abdominal or laparoscopic hysterectomy with bilateral salpingo-oophorectomy and a frozen section analysis was required from all subjects. Intraoperative macroscopic examination for frozen section analysis was performed by a pathologist unaware of the preoperative ultrasound findings (Fig. 1). In patients with myometrial invasion

$\geq 50\%$  of myometrium, grade 3 tumors, non-endometrioid tumors or cervical stromal involvement, systematic pelvic and para-aortic lymphadenectomy up to the level of the left renal vein was performed. In two patients operated laparoscopically, due to morbid obesity and co-morbidities para-aortic dissection was limited to the origin of the inferior mesenteric artery. For patients, who had a tumor  $\geq 2$  cm but had  $< 50\%$  myometrial invasion, the LND was limited to the pelvis only. According to the final pathology results, the stage was recorded according to the FIGO (International Federation of Gynecology and Obstetrics) 2009 staging criteria.

### 2.2 Statistical analysis

The correlation between ultrasound prediction, frozen section analysis and final pathology results was made by using Statistical Package for Social Sciences (SPSS) 21 software (SPSS Inc, IL., Chicago, USA). Correlation analysis was performed by using Pearson correlation analysis and Fisher's exact test. Degree of agreement between preoperative ultrasound and frozen section analysis was calculated with Cohen's kappa index.

## 3. Results

Patient demographics, stage, cell type and grade are shown on Table 1. Definitive histological diagnosis revealed that myometrial infiltration was  $< 50\%$  in 46 women and  $\geq 50\%$  in 34 women. The mean pelvic lymph node count was 27 (6 to 82) and the mean para-aortic lymph node count was 18 (4 to 49). Preoperative TVUS had 76.5% sensitivity, 91.3% specificity, whereas frozen section analysis had 85.3% sensitivity and 93.5% specificity and they correlate well with each other (Pearson's test  $P < 0.01$ ) (Table 2). TVUS and frozen

**Table 1. Patient demographics and tumor histological characteristics.**

Characteristics	Mean $\pm$ SD or n (%)
Age (years)	59 ( $\pm$ 9.2)
FIGO stage*	
IA	41 (51)
IB	19 (24)
II	8 (10)
IIIA–IIIC2	10 (12.5)
IVA–IVB	2 (2.5)
Tumor diameter	3.5 (1.9)
Histological Subtype	
Low grade (endometrioid adenocarcinoma, Grade 1 or 2)	67 (84)
High grade (endometrioid adenocarcinoma Grade 3 or serous adenocarcinoma or clear cell adenocarcinoma or carcinosarcoma)	13 (16.3)
Lymphovascular space involvement	18 (22.5)
Pelvic lymph node metastasis	8 (10)
Para-aortic lymph node metastasis	7 (8.8)

\*FIGO (International Federation of Gynecology and Obstetrics) 2009 staging criteria.

**Table 2. Frozen section, preoperative transvaginal ultrasound and final pathology diagnosis for invasion  $> 1/2$  or  $< 1/2$  of the myometrium.**

	Invasion $> 1/2$ (%)	Invasion $< 1/2$ (%)	Total (n) (%)
Ultrasound Prediction	30 (37.5)	50 (62.5)	80 (100)
Frozen Section	32 (40)	48 (60)	80 (100)
Final Pathology	34 (42.5)	46 (57.5)	80 (100)

**Table 3. Frozen section analysis and preoperative transvaginal ultrasound examination results for detecting myometrial invasion.**

		Ultrasound prediction		Total
		Invasion $> 1/2$	Invasion $< 1/2$	
Frozen section	Invasion $> 1/2$	44	4	48
	Invasion $< 1/2$	6	26	32
Total		50	30	80

section analysis were in concordance for 44 tumors with  $> 1/2$  myometrial invasion and 26 tumors  $< 1/2$  myometrial invasion. In 10 tumors, there was discordance between two methods (Table 3). Agreement between these two methods was substantial according to Cohen's kappa index ( $\kappa$ ) = 0.74 ( $P < 0.01$ ) and percentage of agreement was 88%. Mean tumor diameter was 3.47 cm (maximum 9 cm, minimum 1 cm, standard deviation 1.9). Larger tumor size seems to affect the accuracy of ultrasound prediction of myometrial invasion. For greater than 3 cm maximum tumor diameter, preoperative ultrasound accurately predicted 27 of 38 cases. For tumors equal to or smaller than 3 cm preoperative ultrasound accurately predicted the invasion of 41 of 42 tumors and that difference is statistically significant ( $P < 0.01$ ) (Table 4).

There is one isolated paraaortic metastasis without pelvic lymph node involvement in a Grade 3 tumor that both preoperative ultrasound and frozen section analysis defined myometrial invasion accurately. There are 2 patients with only pelvic lymph node metastasis without para aortic involve-

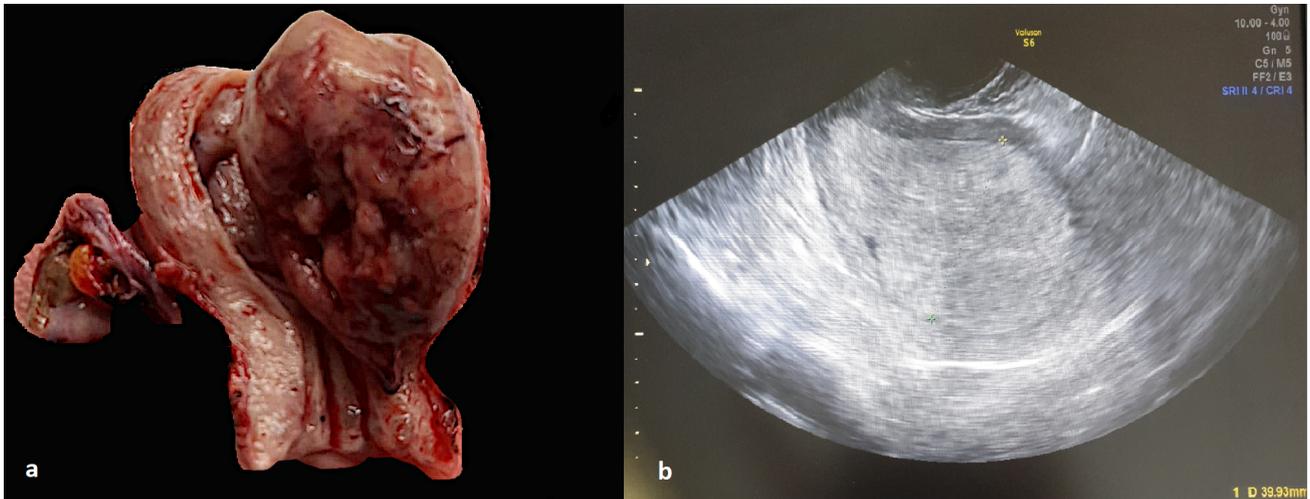
ment, and 6 with both pelvic and paraaortic lymph node metastasis. One patient with pelvic and paraaortic lymph node metastasis, lymphadenectomy was done for a grade 3 tumor without myometrial invasion and one for having a bulky tumor and suspicious bulky lymph nodes with myometrial invasion to less than half of the myometrium. For all the 9 patients with lymph node involvement, myometrial invasion was accurately defined by frozen section analysis whereas preoperative ultrasound was accurate in 7 of these patients.

#### 4. Discussion

There is neither a standard nor a consensus on the utilization of imaging techniques for preoperative assessment of endometrial cancer. Despite studies demonstrating subjective preoperative ultrasound as a robust tool for the assessment of myometrial invasion [8, 13, 15, 17–19], intraoperative frozen section analysis is still the standard for evaluating myometrial invasion to help decide whether or not to proceed with lymphadenectomy.

**Table 4. Accuracy of preoperative transvaginal ultrasound examination to predict tumor invasion in comparison to tumor diameter.**

		Preoperative Ultrasound Prediction		Total
		Inaccurate	Accurate	
Tumor diameter	≤ 3 cm	1	41	42
	> 3 cm	11	27	38
Total		12	68	80



**Fig. 2. (a) Specimen cut for intraoperative frozen section analysis to determine myometrial invasion for a bulky tumor without apparent myometrial invasion, rather than stretching normal myometrium. (b) Preoperative TVUS in sagittal plane. Bulky tumor with antero-posterior 4 cm diameter, has stretched normal myometrium making hard to assess the invasion.**

Three-dimensional transvaginal ultrasonography (3D-TVS) may have the advantage of showing a coronal view, especially for possible invasion to uterine horns [19]. This technique requires more experience and is more time consuming in comparison to 2D TVUS and does not seem to have a better diagnostic performance [20].

A strength of our study is that all the patients were evaluated by the same physician, an experienced gynecologic oncologist and all pathologic examination was done at the same center. This may eliminate inter-observer variance.

In bulky tumors more than 3 cm, the preoperative ultrasound sensitivity decreases in our study. This may be explained as due to the stretch of the normal myometrium rather than invasion in many areas and making it more difficult to assess the tumoral and myometrial borders (Fig. 2a,b).

Despite its high specificity, preoperative assessment for cervical invasion was excluded, due to low sensitivity of preoperative TVUS for detecting cervical stromal invasion as mentioned in previous studies [8, 9, 19]. This may seem as a limitation, but in our study; 8 (10%) of patients had stage II tumors, and 5 of them had > 50% myometrial invasion and underwent a staging lymphadenectomy. Thus, three patients (3.7%) would have been missed for a staging lymphadenectomy if managed only with preoperative ultrasound for myometrial invasion assessment. These three patients were found to have cervical stromal invasion on frozen section and

underwent lymphadenectomy. None had lymph node metastasis.

Besides good correlation with intraoperative frozen section analysis, preoperative TVUS has 76.5% sensitivity, 91.3% specificity in our study and this may aid clinicians preoperatively, especially for decision making in complicated cases with co-morbidities. This may result in proceeding with vaginal hysterectomy only in a morbid obese patient without evidence of myometrial invasion or taking extra preoperative precautions and patient counselling for lymphadenectomy for a patient with co-morbidities who seems to require a systematic lymphadenectomy.

## 5. Conclusions

In conclusion, we found good correlation of TVUS with intraoperative frozen section analysis and final pathology result. The subjective assessment of TVUS can guide surgeons as a useful preoperative tool for preparing for surgery especially for non-bulky tumors, which TVUS has high sensitivity for detecting or excluding invasion.

## Author contributions

B.T. designed the study, performed preoperative ultrasound examinations, surgeries, analyzed the data and wrote the paper.

## Ethics approval and consent to participate

The data is analyzed in retrospective fashion and the study protocol was approved by Ethical Committee and Institutional Review Board at Health Sciences University Samsun Research and Training Hospital. Approval number is: TUEK 67-2019BADK/13-100.

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## Conflict of interest

As the sole author, I disclose that I do not have any financial and personal relationships with other people or organizations that could inappropriately influence this work.

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