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ORIGINAL RESEARCH

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Correlation of prognostic factors and degree of myometrial invasion in endometrial carcinoma: prospective cohort study

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Abstract

The aim of this study is to assess the type and degree of correlation of prognostic factors with the degree of myometrial invasion (MI) in subjects with endometrial cancer (EC). The research included 60 female subjects hospitalized for a planned surgical procedure, due to histopathologically (PHD) proven EC in the period from 2019 to 2021. The following parameters were monitored and analyzed: histopathological parameters: histological type, MI in millimeters and percentages, distance of the tumor from the serosa, lymphovascular invasion, invasion of the stroma and mucosa of the cervix, invasion of the ovary or uterine tube, lymph node metastases, and the International Federation of Gynecology and Obstetrics (FIGO) stage. Patients were divided into two groups, after surgery and PHD assessment of MI degree, into those with less than and more than 50% MI. Statistical data processing was done in the SPSS 24.0 software package (Chicago, IL, USA). Out of the total number of patients (60), MI $<$50% was present in 34 (56.6%) patients, and $>$50% in 26 (43.4%). Our study showed that the anteroposterior (AP) diameter of the EC and the uterine wall is significantly larger with $>$50% myometrial invasion, while the AP diameter of the remaining myometrium is significantly smaller. A significant finding of our study is that the cut-off value of 11 mm for the distance of EC from the serosa correlates with the degree of MI. Based on the results of our study, we came to the conclusions that the degree of MI $>$50% correlates with the AP diameter of the EC, the distance of the tumor from the serosa, and that it is a significant predictor of the existence of lymphovascular invasion, invasion of the uterine cervix and adnexa.

Keywords

Endometrial cancer; Prognostic factors; Myometrial invasion

1. Introduction

Endometrial cancer (EC) is the most common malignancy of the female genital tract and its incidence is constantly increasing. If detected at an early stage, the prognosis is very good, and five-year survival is expected in 90% of cases [1]. The prognosis of EC depends on many factors; histological type, grade of histological differentiation, myometrial invasion (MI), tumor distance from the serosa, lymphovascular invasion, stroma and cervical mucosa invasion, ovarian or uterine tube invasion, lymph node metastases, tumor, lymph node and metastases classification (TNM) and FIGO stages [1].

The degree of MI in combination with the grade of EC is an important prognostic factor and correlates with the frequency of metastases in the pelvic and para-aortic lymph nodes [1, 2]. Patients with grade 1 EC and MI $<$50% rarely have metastases in pelvic and para-aortic lymph nodes, while 34% of patients with grade 3 and MI $>$50% have metastases in pelvic and 24% in para-aortic lymph nodes [2, 3].

Disease recurrence and lymph node involvement have been reported in less than 1% of EC patients who do not have MI [3]. The degree of MI should be recorded (in millimeters) along with the myometrial thickness at that level of invasion (recorded as a percentage of MI) in the final pathohistological report [2].

Tumor size is an independent predictive factor in patients with "low-risk" stage I disease [4]. Many studies have confirmed that tumor size less than or equal to 2 cm in low-risk patients is associated with a low possibility of metastasizing to lymph nodes [4, 5]. Tumor size greater than 2 cm is associated with involvement of lymph nodes in 7% to 10% of patients [2, 5]. Tumor size greater than 2 cm is significantly and independently associated with the presence of lymphovascular and MI among patients with early stage EC [4].

Routine lymphadenectomy can be safely omitted in patients with endometrioid EC, grade 1 or 2, with MI $<$50% and tumor size up to 2 cm [4, 5]. The pathohistological report should include the largest diameter of the primary tumor [2].

The presence of lymphovascular invasion is a strong negative predictive factor in EC, independent of the histological grade or degree of MI [2, 6]. Matsuo *et al.* [7] proved that present lymphovascular invasion is significantly associated with non-endometrioid type of EC, high grade, stage III disease, deep MI, invasion of uterine cervix and adnexa.

Lymphovascular invasion was found in 25% of FIGO stage IA patients and 67% of stage IB patients in the study by Laufer *et al.* [4]. Deep and extensive lymphovascular invasion is strongly associated with metastases to the pelvic lymph nodes and carries a high risk of disease recurrence [4, 7]. Invasion of lymphovascular spaces increases the risk of involvement of pelvic and para-aortic lymph nodes by 5–6 times, and increases the risk of disease recurrence by 2.5 times [8]. Chemotherapy in positive deep and extensive lymphovascular invasion reduces the risk of disease recurrence in lymph nodes and distant organs, while radiotherapy reduces the risk of disease recurrence only in the radiation field [7].

Clinical invasion of the uterine cervix is expected in 6–20% of patients with EC, usually as a result of implantation or lymphatic spread [9]. Invasion of the uterine cervix can be superficial spread into the glandular epithelium or invasion of the cervical stroma [2].

The 2009 revision of EC staging according to FIGO abolishes stage IIA, which implies superficial spread into the glandular epithelium, and only stage II remains, formerly IIB, which implies invasion of the stroma of the uterine cervix [9]. FIGO stage II (regardless of cervical gland or stroma invasion) does not have a significantly worse prognosis and survival compared to stage I EC [9]. Invasion of the uterine cervix reduces the chances of five-year survival compared to patients without invasion, 75% compared to 88% [9]. Invasion of the uterine cervix usually has additional negative prognostic factors, such as high grade, deep invasion into the myometrium and lymphovascular spaces, but it is not a significant and independent prognostic factor [2, 9].

Invasion of the serosa is associated with a worse prognosis and a high percentage of distant metastases [10]. The distance between the deepest invasion of the myometrium and the serosa can be an alternative measurement method and a better predictor of prognosis in cases where the degree of invasion is more difficult to determine due to the presence of leiomyoma or adenomyosis [10]. The distance between EC and serosa may be useful in predicting lymphovascular invasion, histological grade, lymph node metastasis, adnexal involvement, and cervical invasion. Some studies tried to determine the "cut off" value of the distance of EC from the serosa, which has the best predictive value, and concluded that a value of less than 10 mm is associated with lymph node metastases in all cases of EC [10].

Harbin *et al.* [11] proved that a distance of EC from the serosa of less than 5 mm is associated with an increased risk of disease recurrence. As an isolated finding, serosal invasion indicates a far worse prognosis than isolated positive peritoneal cytology or adnexal invasion [12].

Factors associated with a higher risk of adnexal invasion are non-endometrioid EC type, grade 3, positive lymphovascular invasion, lymph node invasion, and deep MI [13, 14]. Microscopic ovarian metastases occur in 0.8% of EC cases [15]. The five-year recurrence-free interval for isolated adnexal invasion ranges from 71% to 86% [15].

The spread of EC to the lymph nodes is one of the most common sites of extrauterine spread of the disease. Lymph node invasion is accompanied by serous, adnexal and vaginal metastases. The status of lymph nodes is one of the most significant prognostic factors for EC [3].

Although lymphadenectomy can help in assessing the extent of EC, thus predicting the prognosis, better survival, applying adequate adjuvant therapy, extensive lymphadenectomy also prolongs the operation time and increases intraoperative and postoperative complications. Unnecessary lymphadenectomy in patients with low-risk EC does not prolong survival [3]. Lee *et al.* [3] in their study showed that 20% of patients undergoing lymphadenectomy had metastases in lymph nodes, about 8% in pelvic, 11% pelvic and para-aortic, 2% isolated para-aortic, which coincides with other studies that 47% up to 56% of patients with metastases in pelvic lymph nodes also have metastases in para-aortic lymph nodes.

Numerous prospective studies have demonstrated that sentinel lymph node biopsy has similar diagnostic accuracy, and is an acceptable alternative to complete lymphadenectomy, however, further studies are needed to determine the value of sentinel lymph node mapping in the era of molecular classification of EC [16].

New FIGO 2023 staging of EC includes The Cancer Genome Atlas's (TCGA) molecular classification, various histological types and tumor patterns to better understanding of the complex nature of the several types of EC, their management and prognosis of EC [17].

The aim of this study is to assess the type and degree of correlation of prognostic factors with the degree of myometrial invasion in subjects with endometrial cancer.

2. Patients and methods

2.1 Patients

The prospective study was conducted in the Clinic for Gynecology and Obstetrics, University Clinical Center Tuzla in the period from 2019 to 2021. The research included 60 female subjects hospitalized in the Clinic for Gynecology and Obstetrics for a planned surgical procedure, due to histopathologically (PHD) proven endometrial cancer. Pathohistological diagnosis was established on the basis of dilatation and curettage of the cavum of the uterus.

The gold standard for assessing the degree of MI in EC was the definitive PHD finding of the surgical material.

The following histopathological parameters were monitored and analyzed: histological type, grade of histological differentiation, MI in millimeters and percentages, distance of the tumor from the serosa, lymphovascular invasion, invasion of the stroma and mucosa of the cervix, invasion of the ovary or uterine tube, lymph node metastases, TNM and FIGO stage.

The inclusion criteria are subjects with pathohistologically proven endometrial cancer.

The exclusion criteria for patients with PHD proven EC are those with a history of another malignant disease, who were previously operated on, treated with chemotherapy or

radiotherapy for EC or another malignant disease, and PHD proven EC incidentally after hysterectomy.

Patients were divided into two groups, after surgery and PHD assessment of MI degree, into those with less than and more than 50% myometrial invasion.

The prospective study was conducted with the approval of the Ethics Committee of the University Clinical Center Tuzla, and each patient signed an informed consent for inclusion in biomedical research before being included in this study.

2.2 Methods

The pathological-surgical material is transported to the laboratory fixed in 10% formalin. The uterus is opened immediately upon admission to the pathology laboratory, along the side/lateral walls up to 3 and 9 o'clock, and left in 10% formalin for 24 hours. The uterus with adnexa is macroscopically described and sampled according to the established protocol (Fig. 1). At least one slice of the full thickness of the uterine wall, including the serosa, is taken to assess the depth of the MI. The number of sections may be higher, when it is anticipated that the assessment of MI depth will be difficult due to the involvement of the adenomyosis field by the tumor [18].

Postsurgical macroscopic and microscopic pathological examination was performed according to the protocol of the College of American Pathologists [17, 18]. The 5-micrometer-thick sections from paraffin-embedded blocks were stained with hematoxylin-eosin. Immunohistochemical examination was performed when necessary to determine the histological type, invasion of the myometrium or cervix [17, 18].

Pathohistological analysis contains all prognostic factors: histological type, degree of histological differentiation, MI in millimeters and percentages, tumor distance from the serosa, lymphovascular invasion, invasion of the stroma of the cervix, parametria, vagina, invasion of the ovary or uterine tube, omentum, peritoneum, lymph node metastases, peritoneal cytology, TNM and FIGO stage [17, 18].

The process of microscopic assessment of the degree of MI consists of determining the endomyometrial zone and the deepest point of MI and measuring their distance (Fig. 2).

The measurement of MI is performed microscopically from the endomyometrial zone to the place of the deepest invasion into the myometrium (Fig. 3).

2.3 Statistical analysis

Statistical data processing was done in the SPSS 24.0 software package (IBM Corp., Chicago, IL, USA). Basic tests of descriptive statistics were performed, with the display of measures of central tendency and dispersion.

Each variable was tested for belonging to a normal distribution using the Kolmogorov-Smirnov test and a histogram display. Quantitative variables were compared by *t*-test with correction for unequal variances where they were normally distributed. Where they did not, the Mann-Whitney test was used. Categorical variables were analyzed using the χ^2-test, with Yates' continuity correction for 2×2 tables, or Fisher's test for analyzes in which the frequency in individual cells was less than 5.

All statistical tests were performed with a statistical probability level of 95% ($p < 0.05$).

3. Results

Out of the total number of patients (60), MI <50% was present in 34 (56.6%) patients, and >50% in 26 (43.4%). The distribution of patients according to FIGO stages of the disease was; FIGO IA stage 34 (56.6%) patients, IB stage 17 (28.3%), FIGO II stage 5 (8.3%) and FIGO III stage 3 (5%) patients.

The anteroposterior (AP) diameter of the uterine wall, endometrial cancer, as well as the rest of the myometrium expressed in millimeters, not affected by cancer according to the PHD findings, are shown in Table 1. The AP diameter of the uterine wall where the EC is located, as well as the EC diameter are smaller, while the AP diameter of the remaining myometrium not affected by EC is greater in the group of subjects with MI <50%. The differences between all the mentioned dimensions between the two investigated groups are statistically significant (Table 1).

AP diameter of EC is smaller on macroscopic PHD examination than on transvaginal ultrasonography (TVS), the difference of 10.76 millimeters is statistically significant ($t = 7.32$; $p < 0.00001$). There is a moderately strong positive significant correlation between AP diameter on TVS and PHD findings (Pearson $r = 0.595$; $p < 0.00001$).

The frequency of AP diameter of EC on pathohistological findings of less than 2 centimeters is statistically significantly higher in both examined groups, compared to diameter greater than 2 centimeters ($Z = 3.47$; $p = 0.00052$) (Table 2).

The distance of the EC from the serosa, assessed macroscopically and microscopically on PHD expressed in millimeters, is statistically significantly greater in the group of patients with MI <50%, and smaller in the group with MI >50% (Table 3). The distance of EC from the serosa was not statistically significantly different when it comes to macroscopic and microscopic evaluation within the same group of patients with MI <50% and >50% ($t = 1.68$; $p = 0.101$ and $t = -0.44$; $p = 0.659$) (Table 3). The distance of EC from the serosa assessed macroscopically and microscopically correlates strongly positively and significantly (Pearson $r = 0.846$; $p < 0.00001$).

The distance of EC from serosa assessed macroscopically and microscopically strongly negatively and significantly correlates with the degree of MI on PHD findings ($r_s = -0.517$; $r_s = -0.693$; $p < 0.00001$).

The distance of the EC from the serosa was not statistically significantly different when it comes to TVS and macroscopic, and TVS and microscopic assessment within the same group of subjects with MI <50% and >50% ($t = -0.656$; $p = 0.514$ and $t = -0.391$; $p = 0.697$) (Table 3). There is a significant medium-strong positive correlation between TVS and PHD macroscopic and microscopic assessment of EC distance from the serosa ($r_s = 0.525$; $p < 0.00001$ and $r_s = 0.546$; $p < 0.000006$).

The distance of the EC from the serosa, assessed macroscopically, is more often greater than 1.1 cm in the group of subjects with MI <50%, while it is less than 1.1 cm more often in the group of subjects with MI >50%, which is statistically significant (Table 4).

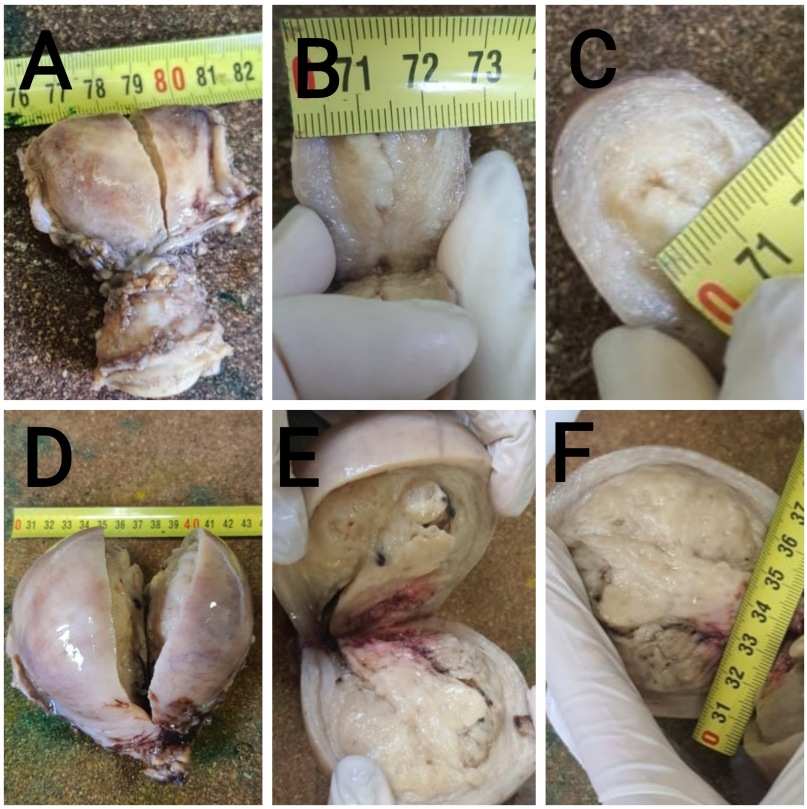

FIGURE 1. Macrodiagnosis on a specimen of the uterus with endometrial cancer (EC) myometrial invasion (MI) is 10%, in a postmenopausal 59-year-old patients. (A) external surface of the uterus, (B) view of the thickness of the sagittal section of the entire uterine wall and (C) measurement of the thickness of the tumor and (MI is 55%) in a premenopausal 28-year-old subject; (D) external surface of the uterus, (E) view of the sagittal section of the uterine wall and (F) measurement of the thickness of the entire wall and tumor.

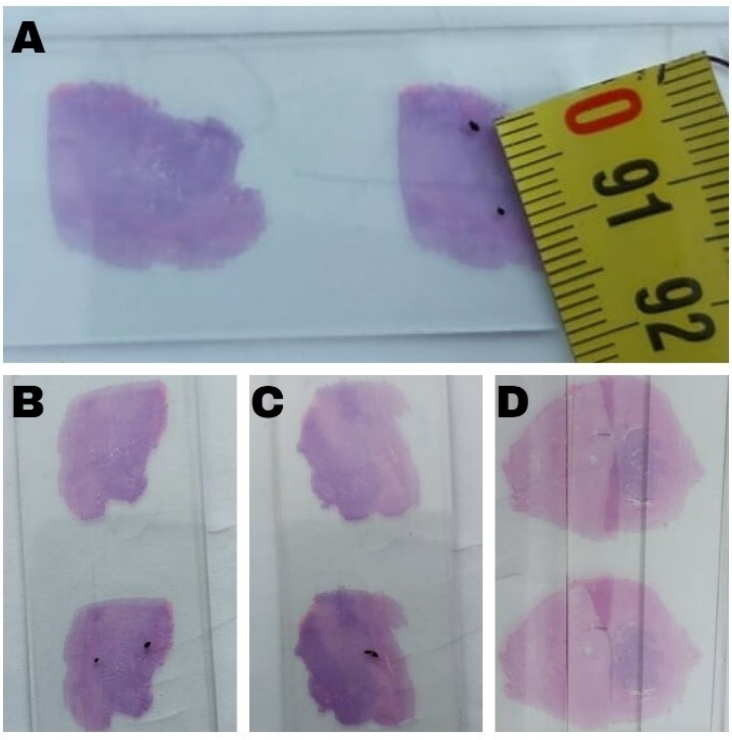

FIGURE 2. The process of microdiagnostic evaluation of the degree of myometrial invasion (MI), the degree of MI is 70%. (A,B) measurement of the degree of MI, (C) distance from the serosa, (D) complete transverse section of the uterus.

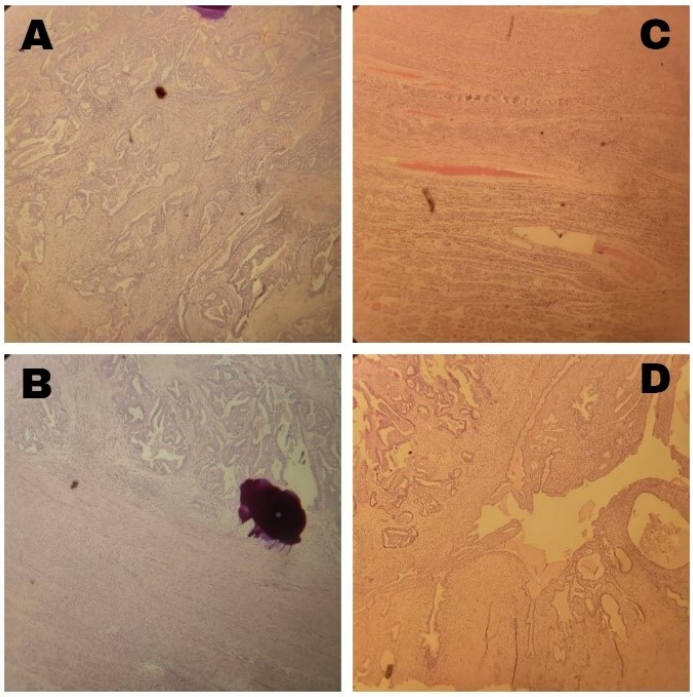

FIGURE 3. Microscopic evaluation of the degree of myometrial invasion (MI) in endometrial cancer (EC), the degree of MI is 70%. (A) upper, (B) lower border of EC, (C) distance of EC from serosa, (D) invasion of uterine cervix stroma.

TABLE 1. Anteroposterior diameter of the uterine wall, endometrial cancer and remaining myometrium according to pathohistological findings and the degree of myometrial invasion.

Anteroposterior diameter (mm)	PHD <50%	PHD >50%	Total	*p* (student *t* test)
Uterine wall, SD (±)	19.3 (6.8)	22.7 (8.3)	20.8 (7.6)	0.04212
Rank	8–32	3–40	3–40	
Endometrial cancer, SD (±)	6.5 (5.1)	15.7 (6.8)	10.5 (7.5)	0.00001
Rank	0.5–18	1.5–27	0.5–27	
Remaining myometrium, SD (±)	12.6 (6.0)	5.8 (3.7)	10.2 (6.5)	0.00019
Rank	2–30	2–14	2–30	

PHD: Histopathologically diagnosis; SD: standard deviation.

TABLE 2. The anteroposterior diameter of endometrial cancer on pathohistological findings is smaller and larger than 2 centimeters.

Anteroposterior diameter	PHD <50%	PHD >50%	Total %	*p* (*Z* test)
<2 cm N (%)	34 (100.0)	18 (69.23)	52 (86.66)	0.00052
>2 cm N (%)	0 (0.0)	8 (30.76)	8 (13.33)	0.00052
Total N (%)	34 (100)	26 (100)	60 (100)	-

Fisher test; p = 0.0006. PHD: Histopathologically diagnosis.

TABLE 3. Distance of endometrial cancer from serosa assessed macroscopically and microscopically on pathohistological analysis and degree of myometrial invasion.

Distance (mm)	PHD <50%	PHD >50%	Total	*p* (student *t* test)
Macroscopically, SD (±)	12.6 (6.0)	5.8 (3.7)	10.2 (6.5)	0.00019
Rank	2–30	2–14	2–30	
Microscopically, SD (±)	13.6 (5.2)	5.7 (3.3)	10.6 (6.1)	0.00001
Rank	5–29	1–10.5	1–29	
p (student *t* test)	0.101	0.659	0.383	-

PHD: Histopathologically diagnosis.

TABLE 4. The distance of endometrial cancer from the serosa assessed macroscopically on pathohistological analysis of less than and greater than 1.1 cm and the degree of myometrial invasion.

Macroscopically distance (cm)	PHD <50%	PHD >50%	Total %	*p* (*Z* test)
<1.1 N (%)	14 (41.2)	22 (84.6)	36 (60.0)	0.0006
>1.1 N (%)	20 (58.8)	4 (15.4)	24 (40.0)	0.0006
Total N (%)	34 (100)	26 (100)	60 (100)	-

$\chi^2 = 9.84$; $df = 1$; $p = 0.001$.

Lymphovascular invasion is statistically significantly more frequent in subjects with MI >50% ($p = 0.0006$). Invasion of the stroma and mucosa of the uterine cervix and invasion of the ovaries is statistically significantly more frequent in subjects with MI >50% (Table 5).

The presence of EC in the lumen of the uterine cervix without invasion of the stroma and mucosa of the uterine cervix is more common in subjects with MI <50%, but it is not statistically significant ($Z = 0.838$; $p = 0.4009$). Invasion of lymph nodes is not statistically significantly more frequent in subjects with MI >50% (Table 5).

4. Discussion

Our study showed that the AP diameter of the EC and the uterine wall is significantly larger with >50% myometrial invasion, while the AP diameter of the remaining myometrium is significantly smaller. There is also a significant negative correlation between the distance of the tumor from the serosa and the degree of MI. There is a significant medium-strong positive correlation between the PHD macroscopic and microscopic assessment of EC distance from the serosa. A significant finding of our study is that the cut-off value of 11 mm for the distance of EC from the serosa correlates with the degree of MI. The degree of MI >50% is a significant predictor of the presence of lymphovascular invasion, invasion of the uterine cervix and adnexa.

The AP diameter of the EC in our study is significantly larger with MI >50%. The average AP diameter for the entire sample was 10.54 mm, while in the analyzed studies it ranged from 25 mm to 40 mm [11, 19–23]. The AP diameter of the EC in our study corresponds more closely to the MI depth in the analyzed studies, which ranged from 5 mm to 14 mm [10, 11, 20, 21]. The differences in AP diameter between ours and the studies analyzed above can be explained by the higher proportion of subjects with MI >50%, and by different methods of measurement.

The AP diameter of the uterine wall in our study was significantly larger with MI >50%, and the average diameter was very similar to that in the analyzed studies (20.8 mm *vs.* 17–20 mm) [10, 11, 19–21].

The AP diameter of the remaining myometrium in our study was significantly smaller with MI >50%, and the average diameter was very similar to that in the analyzed studies (10.1 mm *vs.* 6–10.3 mm) [10, 20, 21].

The frequency of AP diameter of EC on pathohistological findings in our study of less than 2 centimeters is statistically significantly higher in both examined groups, compared to AP diameter greater than 2 centimeters, while in several analyzed studies there are significantly more patients with AP diameter of EC greater than of 2 cm, in which there is also a higher proportion of patients with MI >50% [22, 24–26].

In our study, there is a significant negative correlation between the distance of the EC from the serosa and the degree of MI. We also did not find a significant difference when it comes to macroscopically and microscopically measured distance of EC from the serosa on the PHD preparation. In our study, there is a significant medium strong positive correlation between TVS and PHD macroscopic and microscopic assessment of EC distance from serosa. Measuring the absolute depth of invasion is much more difficult for the gynecological pathologist than measuring the percentage of MI and the distance of EC from the serosa [27].

The average distance of EC from the serosa assessed macroscopically and microscopically on PHD was 10.16 mm and 10.56 mm, very similar to the study by Kondalsamy-Chennakesavan *et al.* [20], while in the study by Oge *et al.* [21] the average distance was slightly smaller, 6 mm, which can be explained by the fact that in the mentioned study, only patients with stage IB were analyzed, in which the distance between the tumor and the serosa is expected to be smaller.

The exact distance of the EC from the serosa or the cut-off value of 4 mm is a much more important prognostic factor than the percentage of MI [28]. The distance of EC from the serosa with a cut-off value of up to 11 mm correlates with the presence of lymph node invasion [10]. In our study, a cut-off value of 11 mm distance of the EC from the serosa correlates with the degree of MI. Many studies have shown that the best predictive significance of the distance of the EC from the serosa is at a cut-off value of 1.75 mm to 10 mm [10]. However, the distance of EC from the serosa is not an independent prognostic factor for stage IB endometrioid EC [21].

With every millimeter of reduction in the distance of the EC from the serosa, there is a 49% higher risk of death from cancer, as well as a 39% higher risk of disease recurrence [29]. However, some studies indicate a greater prognostic significance of the absolute depth of the MI in relation to the distance of the EC from the serosa [20, 30, 31].

The degree of MI is a better prognostic factor of lymph node invasion, while the distance of EC from the serosa is a better predictor of adnexal invasion [10].

In our study, lymphovascular invasion was significantly more frequent in subjects with MI >50%. Lymphovascular invasion was present in 13.3% of patients, while in the study by O'Toole *et al.* [24], it was present in 26%, and in the study by Espiau Romer *et al.* [25], 9.5%. Numerous studies have shown

TABLE 5. Prognostic factors and degree of myometrial invasion in endometrial carcinoma (EC).

Prognostic factors	PHD <50%	PHD >50%	Total %	*p* (*Z* test)	*p* (Fisher test)
Lymphovascular invasion					
Yes N (%)	0 (0.0)	8 (30.8)	8 (13.3)	0.00052	0.0006
No N (%)	34 (100.0)	18 (69.2)	52 (86.7)	0.00052	
Invasion of stroma of uterine cervix					
Yes N (%)	0 (0.0)	4 (15.3)	4 (6.66)	0.0177	0.0307
No N (%)	34 (100.0)	22 (84.6)	56 (93.33)	0.0177	
Invasion of mucosa of uterine cervix					
Yes N (%)	3 (8.8)	11 (42.3)	14 (23.33)	0.002	0.0045
No N (%)	31 (91.1)	15 (57.7)	46 (76.66)	0.002	
EC in lumen of uterine cervix					
Yes N (%)	5 (14.7)	2 (7.7)	7 (11.66)	0.4009	0.6871
No N (%)	29 (85.3)	24 (92.3)	53 (88.33)	0.4009	
Lymph node invasion					
Yes N (%)	0 (0.0)	2 (7.7)	2 (3.33)	0.101	0.1912
No N (%)	34 (100.0)	24 (92.3)	58 (96.66)	0.101	
Ovarian invasion					
Yes N (%)	0 (0.0)	3 (11.5)	3 (5.0)	0.04	0.0934
No N (%)	34 (100.0)	23 (88.5)	57 (95.0)	0.04	
Total N (%)	34 (100)	26 (100)	60 (100)	-	

PHD: Histopathologically diagnosis.

that the degree of MI >50% is a significant predictor of the existence of lymphovascular invasion, this was also confirmed by our study [10, 30, 31].

AP tumor diameter greater than 2 cm and involvement of the lower uterine segment are independent predictors of lymphovascular invasion. Lymphovascular invasion is more common in type I EC with MI grade >50%, high histological grade and invasion of the uterine cervix [23]. Kim *et al.* [19] developed a risk index of lymphovascular invasion to predict the presence of lymphovascular invasion that could help in clinical practice when deciding on the extent and type of surgery. The risk index consists of the product of points assigned for the AP diameter of the tumor, percentage of MI, histological grade, invasion of the stroma of the uterine cervix [19, 31].

Invasion of the stroma of the uterine cervix in our study was present in 6.6% of subjects, mucosal invasion in 23.3%, significantly more often in MI >50%. The presence of a tumor in the lumen of the cervix without invasion of the mucosa or stroma was present in 11.6% of the subjects. A very similar percentage of cervical invasion was in the study by Espiau Romero *et al.* [25] (6.3%). Numerous studies have shown that the degree of MI >50% is a significant predictor of the existence of invasion of the uterine cervix, this was also confirmed by our study [10, 30, 31].

Invasion of lymph nodes is not significantly more frequent in subjects with MI >50%, which can be explained by the small number of cases with invasion of lymph nodes in our study (3.3%). In the study by Espiau Romero *et al.* [25], lymph node invasion was in a similar percentage (5.6%). In the study by O'Toole *et al.* [24], lymph node invasion was present in 9.5% of patients, and a significant association of lymph node invasion with lymphovascular and MI >50% was verified. MI >50% did not correlate with lymph node invasion in the study by Doghri *et al.* [30], as well as in our study, in both studies the number of subjects was the same.

Adnexal invasion in our study was present in 5% of subjects, very similar to the study by Espiau Romero *et al.* [25] (4%). The degree of MI >50% is a significant predictor of adnexal invasion, which was also confirmed by our study [12–14]. However, in the two analyzed studies, the degree of MI does not correlate with adnexal invasion [10, 30].

Advances in understanding the pathologic and molecular features of EC have resulted in the new FIGO 2023 classification. The most changes are seen in the first and second stages of the disease, where the histological types of EC (non-aggressive and aggressive forms of EC), the presence of lymphovascular invasion, myometrial invasion are taken into account [32]. The molecular classification was also taken into account, in the case when the molecular subtype is known, it is entered in the subscript. The novelties in FIGO 2023 are considered to contribute to a better understanding of the complex nature of different types of EC, but to have a role in the selection of adequate treatment as well as in the assessment of the prognosis

of the disease [32, 33].

There is already performed study with evaluating the clinical impact of the new 2023 FIGO staging system by comparing it to the previous 2009 system. Authors concluded that the new 2023 FIGO stating system led to a stage shift in about one quarter of patients leading to a higher prognostic precision [33].

Our study has limitations, primarily a small sample of study participants and short period of sample collection. Also we did not used sentinel lymph node mapping and biopsy, and molecular classification of EC, because of limited availability of necessary equipment and financial resources needed for implementation. The limitation of our study is represented by the new FIGO 2023 staging of EC, which is published in the period when we finalised our study and the writing of our article. The advantage of the study refers to the prospective, single tertiary center and to the fact that one person performed data collection and analysis of all study participants.

5. Conclusions

Based on the results of our study, we came to the conclusions that the degree of myometrial invasion >50% correlates with the anteroposterior diameter of the EC, the distance of the tumor from the serosa, and that it is a significant predictor of the existence of lymphovascular invasion, invasion of the uterine cervix and adnexa. However, future prospective randomized and controlled studies are necessary that will indicate new biomolecular prognostic and predictive factors before the treatment itself, as well as during and after the EC treatment.

AVAILABILITY OF DATA AND MATERIALS

The data are contained within this article.

AUTHOR CONTRIBUTIONS

AC—designed the research study; performed the research and analyzed the data; contributed to editorial changes in the manuscript; read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All subjects gave informed consent to be included before participating in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the University Clinical Center Tuzla (approval number: No. 02-09/2-2/20).

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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