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# The Effect of Myometrial Invasion Pattern to Stage in Endometrial Cancer

*Uslu E[1], Yalcin OT[1], Kabukcuoglu S[2]*, Ozalp SS[1] and Oge T[1]*

[1]Department of Obstetrics and Gynecology, Eskisehir Osmangazi University School of Medicine, Turkey

[2]Department of Pathology, Eskisehir Osmangazi University School of Medicine, Turkey

## Abstract

**Aim:** Myometrial invasion (MI) is one of the prognostic factors in endometrial cancer (EC). It has been argued that myometrial invasion pattern (MIP) is associated with prognosis. Our aim is to evaluate MIP in patients with EC.

**Materials and Methods:** The patient who had total abdominal hysterectomy, bilateral salpingo-oophorectomy, in fracolicomentectomy, pelvic-paraaortic lymphadenectomy, cytological sampling and also has a result of EC in postoperative pathology between May 2014- October 2015 in our clinic were included. Specimens were hystopathological classified as properly limited (pushing, PL), diffusely infiltrative (DI), adenomyozisinvolment by EC (A), microcystic, elongated and fragmented (MELF) groups by the same pathologist. The relationship between the MIP and stage and grade of endometrial cancer were evaluated.

**Results:** One hundred patients was operated and mean age was 57.4 ± 9.32 years. PL, DI, A, MELF patterns were observed in 41,14,17,28 patients respectively. Distribution of myometrial invasion patterns to stages, MELF pattern was observed mostly in Stage 3(n=12, 42.9%). Properly limited (n=30, 73.2%,), DI(n=5, 35.7%) and AL(n=9 , 52.9%) patterns are observed mostly in Stage 1A(P=0,001). Moreover, grade 1 was observed in most of the PL (n=6, 75%), andgrade 3 was observed in most MELF pattern in endometrial cancer (n=10, 52.6%)(P=<0,001).

**Conclusions:** MELF pattern was mostly observed in patients with high grades and stages of endometrial cancer. Properly limited pattern was mainly observed in low grade and stage of endometrial cancer. Further studies are needed to evaluate the clinical significance of this observation.

**Keywords: Endometrial cancer; Myometrial invasion pattern; Stage; Immunohistochemistry**

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***Correspondence:***
*Kabukcuoglu S, Department of Pathology, Eskisehir Osmangazi University School of Medicine, Eskisehir, Turkey;*
*E-mail: skabukcuoglu@hotmail.com*

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## Introduction

EC, with a lifetime risk of 2.5%, is the most common gynecologic cancer [1]. Despite good clinical outcome, a small but significant number of patients may experience recurrence, and it has not been possible to predict which patients are at increased risk. Prognostic factors for EC are patient age, tumor grade, histological subtype, depth (MI), extra uterine extension (EUE) and lymph node (LN) metastasis [2]. MI is one of the most important prognostic factor [3-5]. In recent years, the MI pattern has been proposed as a potential prognosis predictor. EC shows different MI patterns, PL, DI, A, MELF and adenoma malignum (AM) [6-8]. Murray et al. [7] first described MELF invasion pattern in 2003. Clinical significance of MELF pattern of invasion remains unclear, although it is reported to be associated with distinct changes in the invasive glandular tissues and a high frequency of lymphovascular space invasion (LVSI) [3,7,9,10]. In this study, we aimed to evaluate the relationship between the MIP and stage and grade of EC.

## Materials and Methods

The patient who had total abdominal hysterectomy, bilateral salpingo-oophorectomy, in fracolicomentectomy, pelvic-paraaortic lymphadenectomy, cytological sampling and also has a result of EC in postoperative pathology between May 2014- October 2015 in Eskişehir Osmangazi University Hospital were included. All cases were classified according to International Federation of Gynecology and Obstetrics (FIGO) staging system [11]. Fallopian tube sampling was made according to SEE-FIM protocol. Tissue specimens were formalin fixed, paraffin embedded and subsequently sectioned at 4µm thickness. The immunohistochemical studies were performed using

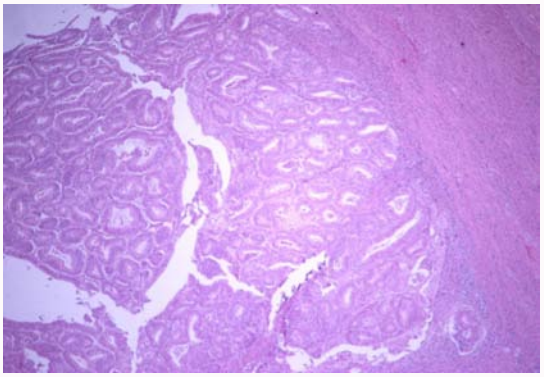

**Figure 1**: Low grade EC, PL pattern (H-E x200). Cases that seen PL, neoplastic glands were found to create pushing infiltration on myometrium.

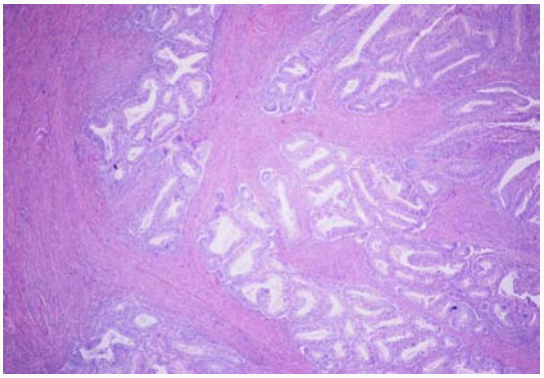

**Figure 2:** DI pattern (H-E x200).

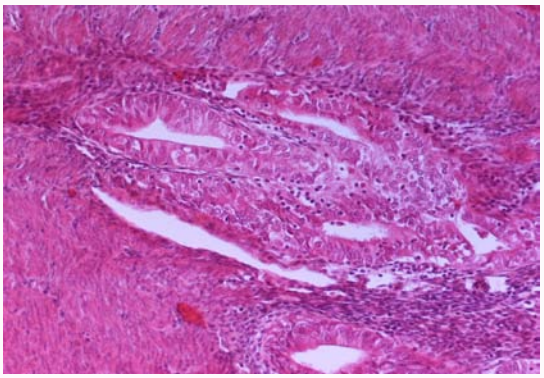

**Figure 3:** EC invasion in adenomyozis (H-E x 400).

a standart procedure on an automated immunostainer (Ventana ES, Ventana Medical Systems, Inc, AZ, U.S.A). Liquid rabbit monoclonal antigens were used as primary antigen. Immunohistochemical staining for estrogen receptor (ER), progesterone receptor (PR), Paired box 8 (PAX8), caudal type homeobox 2 (CDX2), CK19, E-cadherin, beta catenin (β-cat), TP53 was performed on selected sections. Appropriate positive control procedures were performed with satisfactory staining in the whole study. DAB chromogen was used. The sections counter stained with Mayer's hematoxyl in and the sections were dehydrated, cleared, mounted. Those specimens with histopathologic examination grade, myometrial invasion of myometrial invasion pattern (Pl, DI, A, MELF, AM), the presence of vascular invasion and extra uterin extension (EUE) were determined by the same pathologist.

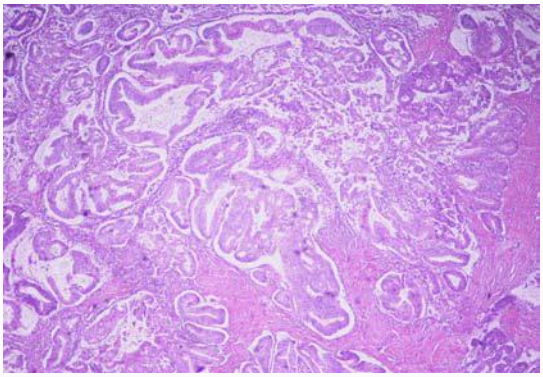

**Figure 4**: MELF pattern (H-E x200).

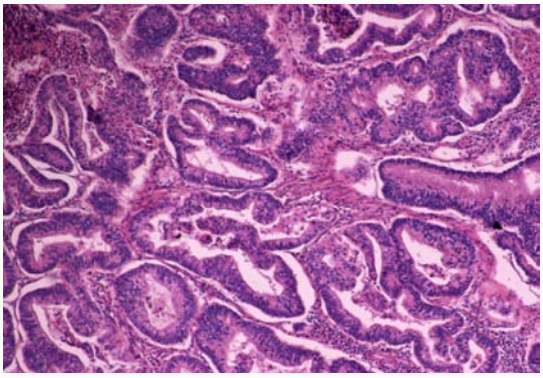

**Figure 5**: AM pattern (H-E x 400).

### Statistical analyses

All statistical analyses were performed using SPSS (Statistical Package of Social Services, Chicago, IL, USA) for Windows version 21. Data were analysed according to Pearson Chi – square, Shapiro Wilk normality test, ANOVA and Tamhane test. Probability values less than 0.05% were considered statistically significant.

## Results

In total, 102 consecutive cases of uterine ECwere identified. One hundred and two patients were operated and mean age was 57.4 ± 9.32 years. Stage 1A, 1B, 2, 3A, 3B, 3C were observed in 48 (47%), 29 (28%), 7 (7%), 11 (11%), 1(1%), 6(6%) patients respectively. As mentioned stage distribution of patients was statistically significant, though may be to stage 3A, 3B and 3C are taken together as stage 3(18 patients, 17%). Grade 1, 2, 3 were observed in 8 (8%), 75 (73%), 19 (%18) respectively. Properly limited, DI, A, MELF patterns were observed in 41 (40%), 14 (14%), 17 (17%), 28 (27%) patients respectively. Two patients' MIP are unidentified. Several cases displayed more than one pattern of invasion, and the predominant type of invasion was accepted in each case. Diagnostic criteria for the various patterns of myoinvasion were as follows: PL(Pushing): Infiltration that was marked by a large swath of neoplastic glands that appear to push into the underlying myometrium (Figure 1).

DI: Single to small groups (3 or less) of glands with irregular gland contours, with or without a desmoplastic stromal response (Figure 2). A: Adenomyosisinvolment by Endometroid cancer (Figure 3).

### MELF

Microcystic, elongated, and/or slit-like glands, with clusters or individual tumor cells, which often appeared squamoid or

**Table 1**: Comparison of MIP and stage.

| Stage | PL | DI | AL | MELF | |
|---|---|---|---|---|---|
| 1A Number % | 30 73,2 | 5 35,7 | 9 52,9 | 3 10,7 | Pearson χ2-test (p:0,0003) |
| 1B Number % | 7 17,1 | 4 28,6 | 7 41,2 | 11 39,3 | |
| 2 Number % | 3 7,3 | 1 7,1 | 0 0 | 2 7,1 | |
| 3 Number % | 1 2,4 | 4 28,6 | 1 5,9 | 12 42,9 | |
| Total Number % | 41 100 | 14 100 | 17 100 | 28 100 | |

**Table 2**: Comparison of MIP and grade.

| Patern | Grade 1 | Grade 2 | Grade 3 | |
|---|---|---|---|---|
| PL Number % | 6 75 | 32 43,8 | 3 15,8 | Pearson χ2-test (p:0,034) |
| DI Number % | 0 0 | 11 15,1 | 3 15,8 | |
| AL Number % | 2 25 | 12 16,4 | 3 15,8 | |
| MELF Number % | 0 0 | 18 24,7 | 10 52,6 | |
| Total Number % | 8 100 | 73 100 | 19 100 | |

eosinophilic. Frequently, there was an accompanying loose myxoid, mixed inflammatory reaction (Figure 4).

## AIM

Myometrial involvement of cervical minimal deviation adenocarcinoma (Figure 5). Stage and myometrial invasion patterns were compared and MELF pattern is mostly seen in stage 3, other patterns are mostly seen in stage 1A. This comparison found to be statistically significant (P=0,0003) (Table 1). A comparison of grade and myometrial invasion patterns is shown in (Table 2). Properly limited pattern is mostly seen in grade 1, MELF pattern is mostly seen in grade 3 (P=0,0034). There were 24 patients with focal squamous differentiation, 6 patients with focal mucinous differentiation, 1 patient with neuroendocrine differentiation and 71 patients had no diferentation.MIP and differentiations were compared and not found to be statistically significant (P=0,307). A comparison of MIP and LVSI is shown in (Table 3). Lymphovascular invasion was observed in all MELF pattern patients and most of them made lymphovascular invasion creating a group of cells. Properly limited, DI and A patterns made lymphovascular invasion without creating a group of cells (P=0,000).There was no significant difference in terms of the mean age and MIP (ANOVA, P=0,366). The mean age and stage were compared and found statistically significant (P=0,004). Stage 1A of average age 55, Stage 1B of average age 61. Stage and grade compared and found statistically significant (P=0,014) (Table 4). All of the Grade 1 was found in stage 1A. Grade 2 was observed most common in all stages. Immunohistochemical staining for ER, PR, PAX8, CDX2, CK19, E-cadherin, β-catenin, TP53 was performed. Tissue samples divided into the groups according to percentage of stained cells.

### Staining pattern of ER

Ninty seven samples stained by ER. Nuclear staining was observed in 3 samples at 1-10%, 13,4% 13 of samples at 11-50%, 81% 79 of samples at 51-100%. Two samples were negative.

**Table 3**: Comparison of MIP and lymphovascular invasion.

| MIP | Lymphovascularinvasion | | | Total | |
|---|---|---|---|---|---|
| | None | Without grup | Cell grup | | |
| PL N % | 20 48,8 | 21 51,2 | 0 0 | 41 100 | Pearson χ2-test (p:0,000) |
| DI N % | 2 14,3 | 7 50 | 5 35,7 | 14 100 | |
| A N % | 3 17,6 | 13 76,5 | 1 5,9 | 17 100 | |
| MELF N % | 0 0 | 4 14,3 | 24 85,7 | 28 100 | |
| Total N % | 25 25 | 45 45 | 30 30 | 100 100 | |

**Table 4**: Comparison of stage and grade.

| Stage | Grade 1 | Grade 2 | Grade 3 | Total | |
|---|---|---|---|---|---|
| 1A N % | 9 18,8 | 35 72,9 | 4 8,3 | 48 100 | Pearson χ2-test (p:0,014) |
| 1B N % | 0 0 | 23 79,3 | 6 20,7 | 29 100 | |
| 2 N % | 0 0 | 4 57,1 | 3 42,9 | 7 100 | |
| 3 N % | 0 0 | 11 61,1 | 7 38,9 | 18 100 | |

### Staining pattern of PR

Ninty seven samples stained by PR. Nuclear staining was observed in 5 samples at 1-10%, 22,6% 22 of samples at 11-50%, 67% 65 of samples at 51-100%. Five samples were negative.

### Staining pattern of PAX8

Of the 87 samples were stained by PAX8. Three samples were no staining. Three samples showed focal minimal nuclear staining, 33,7% 30 samples showed focal moderate staining, 51,7% 46 samples showed diffuse heterogen staining, 8,9% 8 samples showed diffuse nuclear staining.

### Staining pattern of CDX2

CDX2 showed focal staining in morular metaplasia and squamous differentiation areas and some cylindrical cells. CDX2 was positive in ER and PR negative areas. Of the 93 samples were stained by CDX2. Fourty two percent 39 of samples showed focal nuclear staining, 1 sample showed diffuse staining. Fifty seven percent 53 of samples were negative.

### Staining pattern of CK19

Of the 93 samples were stained by CK19. Two samples showed at 1-20%, 40% 37 samples showed at 21-50%, 29% 27 samples showed at 51-80% and 28% 26 samples showed at 81-100% staining. One sample was negative.

### Staining pattern of E-cadherin

Most of the cells are surrounded by E-cadherin staining. Of the 93 samples were stained by E-cadherin. Twenty eight percent 26 of samples showed heterogeneous membranous staining, 70% 66 samples diffuse membranous staining. One sample was negative.

### Staining pattern of β-cathenin

β-cathenin showed membranous and cytoplasmic staining. In squamous differentiation areas, nuclear staining was also observed. Of the 47 samples were stained by β-cathenin. Membranous staining observed in 85% 40 samples. Membranous, cytoplasmic and nuclear staining in 6 samples were observed. One sample was negative.

### Staining pattern of TP53

Of the 96 samples were stained by TP53. Fourty five percent 43 of samples showed at 1-10%, 11% 11 samples showed at 11-50%, 8% 8 samples showed at 51-100% staining. Thirty five percent of samples were negative.

There were no statistical significant differences among immunohistochemical staining patterns and MIP (Pearson χ2-test, P>0, 05).There was statistical significant difference between TP53 staining rate and stage. When staining percent more compared, negative staining was observed mostly stage 1A, 1-10% staing mostly observed in stage 1B. There were no statistical significant differences among immunohistochemical staining patterns of ER, PR, PAX8, CDX', CK19, E-cadherin,β-catheninand stage (Pearson χ2-test, P>0,05).

## Discussion

Endometroid cancer has good clinical outcome, on the other hand some cases have recurrence or methastasis. Prognostic factors for EC are patient age, tumor grade, histological subtype, depth of MI, EUE and LN metastasis [2]. In a study in which 513 patients participated Nofech-Moses et al. [12], showed that lymphovascular invasion an important predictor parameter for distant recurrence in early-stage EC. Guntupalli et al. [13] made a study with 628 patients who had systematic lymphadenectomy, 196 of patients had lymphovascular invasion and 66 of them had nodal metastases which was found statistically significant. Grading the LVSI is indicated in the study of Hachisug et al. [14] 303 patients were examined, grading of LVSI was found to be an important histologic prognostic variable. The severe degree of LVSI also was found to be a good indicator of lymph node metastasis. In our study 75% of cases had a LVSI and %30 of them made a cell groups (P=0,000). Properly limited group at least LVSI.

There are limited studies about MIP. Murray et al. [7] followed 115 EC cases with MI and investigated the MELF pattern exists or not. In cases of lymphovascular invasion, commonly MELF pattern associated with, including fibromyxoid reaction, death and recurrence was more followed. Stewart et al. [10] examined 133 cases of EC and in 27 of them were MELF positive. MELF-positive patients often focal mucinous differentiation and lymphovascular space invasion was observed. Pavlakiset al. [9] searched 351 patients. Lymph node-positive patients, positive for MELF 53.84% was observed. MELF negative of positive lymph nodes were seen in 6,97% and it was statistically significant. Quick et al. [8] examined 324 patients, 98 of them had MI. MIP were separated as infiltration of glands, MELF, impulsive and AM. MI that tumors with infiltration of the glands were high-grade, lymphovascular invasion and recurrence were found statistically more frequent. In 2013 they made a compilation, it was important to measure the depth of MI and MIP. They also suggested that there may be a prognostic factor in certain patterns. MELF pattern was seen in lymphovascular invasion were reported more frequently. It also supports the study of Hertel et al. [15] 80 well differentiated of EC with lymph node metastasis were investigated. Tumors with MELF pattern had more lymph node metastasis, which was statistically significant. Ismiil et al. [16] found that when the carcinoma invades to adenomyosis, it increases the MI depth. In addition, although rare, there are 2 studies about endometrial intraepithelial serous carcinoma develop from adenomyosis [17,18]. In Orejuell et al. [19] investigated of ER, PR, COX-2 immunohistochemical staining patterns of normal endometrium, endometrial hyperplasia and EC. COX-2 expression was more observed in hyperplasia and cancer but statistically significance not found. Staining insamples of EC and there was no significant difference in terms of grade and stage. Intensity of ER and PR staining was normal and hyperplastic endometrium much more than EC. Stewart et al. [20] showed in 21 patients with EC patients. Conventional pattern tumors showed intensemembranous staining by E-cadherin, hormone receptor activity and vimentin positivity. MELF type of MI characterized by strong CK7 expression, usually negative for hormone receptors and decreased expression of E-cadherin. Stewart et al. [21], observed basal and apical CK19 staining in proliferative endometrium; strong in the conventional type of large tumors cloth and around there is weak staining. In the study, also the strong staining pattern was observed in MELF. CK19 is useful determining of myometrial and lymphovascular invasion. CK19 is a selective estrogen receptor modulator and in our study, there was no correlation between the stage with CK19 staining. An actin-binding protein fascin, increases migratory capacity both in normal and neoplastic cells. Kabukcuoglu et al. [22] investigated the fascin staining patterns in28 proliferative and hyperplastic endometrium and 43 cases of EC. The study supported the dynamic role of actin bundling protein fascin in generating and maintaining endometrial neoplasms. It also showed that in the development of neoplasia, stromal fascin expression decreases but epithelial fascin expression up-regulates. Gun et al. [23] supported also this data. Stewart et al. [24], examined 28 EC cases by fascin and CK-7 staining. Focal fascin reactivity in classic glandular component, was observed. MELF pattern showed strong fascin immunoreactivity Observation of increased fascin expression in MELF pattern, is suggestive of active tumor invasion.

E-cadherin expression examined in 21 normal, 17 hyperplastic endometrium and 104 EC, methylation of E-cadherin promoter genes has been observed to be associated with the formation of tumor invasive capacity [25]. In our study there was no significant relationship between E-cadherin with MIP and stage. Yemelyanov et al. [26], showed PAX-8 expression in EC, endometrial hyperplasia and normal endometrium. PAX-8 expression has been observed also in adenocarcinoma. Faucegli et al. [27], 228 patients were compared according to the PAX-8 in high-grade, lymphovascular space invasion positive and type 2 tumors were showed significantly more intense PAX8 staining. Their 5-year disease-free survival rate was significantly decreased. In our study, we also observed down regulation and/or up regulation of PAX8 expression in EC patients. In our opinion intensity of PAX8 expression may be related differentiation and anaplasia. Dobrzyck et al. [28], 98 patients with EC have investigated the relationship between p53 and bcl-2 expression of immunochemical stage and survival.BCL-2 expression was observed more frequently in the early stages. In this study, expression of TP53 staining percent when compared with the stage, negative staining frequentlyassociated with stage 1A and 1-10% staining is observed frequently in stage 1B.

## Conclusion

As a result, there are some findings about MIP can affect the stage in EC. These findings should be investigated by examining the larger patient groups about the effect with pattern alone or multifunctional.

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