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ORIGINAL ARTICLE/ORİJİNAL MAKALE

The relationship of MELF (microcystic, elongated and fragmented) invasion pattern with prognostic factors in endometrial endometrioid adenocarcinoma

Endometrial endometrioid adenokarsinomda mikrokistik, elonge ve fragmente (MELF) invazyon paterninin prognostik faktörlerle ilişkisi

Metehan Uzundal[1], Taylan Şenol[2], Enis Özkaya[3]

[1] Keşan Hospital , Department of Obstetrics and Gynecology, Edirne, Türkiye
[2] Istanbul Atlas University, Faculty of Medicine, Department of Obstetrics and Gynecology, Istanbul, Türkiye
[3] Kirklareli University, Faculty Of Medicine, Department of Obstetrics and Gynecology, Istanbul, Türkiye

ABSTRACT

Introduction: The aim of the present study was to investigate whether the Microcystic, Elongated And Fragmented (MELF) pattern of myometrial invasion is related to an increased occurrence of lymph node metastasis and could be considered as an additional risk factor for advanced stage disease.

Methods: One hundred and five patients who were operated for endometrial cancer between March 2015 and October 2020 in the Department of Obstetrics and Gynecology, Health Sciences University Bağcılar Training and Research Hospital, were included in this study. Survival and recurrence rates were evaluated between MELF positive and negative groups.

Results: Disease-free survival (DFS) curves were compared between the MELF(+) and MELF(-) groups. No statistically significant difference was found between groups in terms of disease-free survival. (P=0.310). The 5-year DFS was 88.1% in the MELF(+) group, while the 5-year DFS was 93.2% in the MELF(-) group. There was no significant difference between the overall survival (OS) curves (P=0.894). While the 5-year OS was 90.8% in the MELF(+) group, the 5-year OS was 93.1% in the MELF(-) group.

Conclusion: No significant effect of MELF invasion pattern was observed on disease-free survival and overall survival in endometrioid type endometrial cancer. We found a significantly higher incidence of lymphovascular space invasion (LVSI) in the MELF positive group. The presence of MELF pattern may indirectly affect the prognosis negatively with the increase in LVSI.

Keywords: Endometrial carcinoma, MELF, Lenfovascular invasion

ÖZET

Amaç: Mikrokistik, Elonge ve Fragmente(MELF) myoinvazyon paterninin diğer histopatolojik faktörlerle ilişkili olup olmadığını ve böylece lenf nodu metastazının artmış bir görülme sıklığı ile ilişkili olup olmadığını araştırmaktı, dolayısıyla ileri evre hastalık için ek bir risk faktörü olarak değerlendirilebilir mi?

Yöntem: Mart 2015 ile Ekim 2020 tarihleri arasında Sağlık Bilimleri Üniversitesi Bağcılar Eğitim ve Araştırma Hastanesi Kadın Hastalıkları ve Doğum Kliniği'nde endometrial kanser için ameliyat edilen 105 hasta bu çalışmaya dahil edildi. MELF pozitif ve negatif gruplar arasında sağkalım ve nüks oranları değerlendirildi.

Bulgular: Hastalıksız sağkalım eğrileri MELF(+) ve MELF(-) gruplar arasında karşılaştırıldı. Gruplar arasında hastalıksız sağkalım açısından istatistiksel olarak anlamlı bir fark bulunamadı (P=0,310). 5 yıllık hastalıksız sağkalım MELF(+) grubunda %88,1 iken, MELF(-) grubunda %93,2 idi. Genel sağkalım eğrileri arasında anlamlı bir fark bulunmadı (P=0,894). 5 yıllık genel sağkalım MELF(+) grubunda %90,8 iken, MELF(-) grubunda %93,1 idi.

Sonuç: Endometrioid tip endometrial kanserde MELF invazyon paterninin hastalıksız sağkalım ve genel sağkalım üzerinde anlamlı bir etkisi gözlenmedi. MELF pozitif grupta anlamlı derecede daha yüksek bir LVSI insidansı bulduk. MELF paterninin varlığı, LVSI'da artışla dolaylı olarak prognozu olumsuz etkileyebilir.

Anahtar Kelimeler: Endometrium karsinomu, MELF, Lenfovasküler invazyon

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Correspondence: Metehan Uzundal, Keşan Hospital , Department of Obstetrics and Gynecology, Edirne, Türkiye.
E-mail: metehan_uzndl@hotmail.com

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INTRODUCTION

There has been an increasing trend in the incidence of endometrial carcinoma. The most commonly encountered histological subtype is endometrioid carcinoma (1). Although the histopathological grade of the tumor is a good indicator for outcome prediction, a better histologic indicator is still required to predict outcomes, ensure careful follow-up, enable early detection of a recurrence, and improve prognosis in patients with low-grade endometrioid carcinoma. Several types of myometrial invasion have been proposed such as infiltrating type, broad front type, adenoma malignum type, adenomyosis-like type, and "microcystic, elongated, and fragmented (MELF)" type (2,3). Depth of invasion has been the most frequently used parameter for predicting outcomes (4). While the standard surgical treatment for endometrioid endometrial adenocarcinoma remains total abdominal hysterectomy with bilateral salpingo-oophorectomy, there is controversy regarding the indications for and type of lymphadenectomy that should be performed (5,6). Few studies have focused on the benefits of lymphadenectomy in patients with stage IA [former International Federation of Gynecology and Obstetrics (FIGO 1B)], grade 1 or 2 endometrial carcinoma. The results of these studies revealed that women in the lymphadenectomy group did not provide any survival benefit (7-9).

In addition, the risk of pelvic recurrence was found to vary between 0% and 2% (10). Lymphadenectomy prolongs operative time and is associated with potential short- and long-term side effects (11). Additional pelvic radiotherapy is recommended for patients with additional risk factors such as deep myometrial invasion or lymphovascular tumor embolism in the hysterectomy material (12). Recently, a distinct pattern of myometrial invasion has been described, referred to as 'MELF' (4). This pattern is characterized by neoplastic glands that separate by sacculating outward, forming microcysts covered with flat epithelium due to a fibromyxoid stromal reaction (Figure 1). The glands often contain dense neutrophilic infiltrates within their lumens, with an accompanying fibromyxoid stroma observed around them. This microcystic, elongated and fragmented (MELF) myometrial invasion pattern was initially reported in a small series of three cases and was associated with a histiocyte-like lymph node metastasis pattern (13).

The aim of this study was to investigate whether the MELF pattern of myometrial invasion is associated with increased lymph node metastasis formation and, therefore, can be considered an additional risk factor for advanced disease.

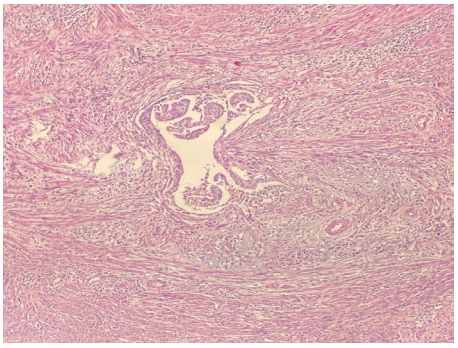

Figure 1. Typical MELF myoinvasion pattern: Microcystic, elongated and fragmented tumor cells associated with extensive fibromyxoid and inflammatory stromal reaction. Hematoxylin and eosin stained preparation

MATERIALS AND METHODS

Patients who underwent surgery for endometrial cancer between March 2015 and October 2020 in the Department of Obstetrics and Gynecology, Health Sciences University Bağcılar Training and

Research Hospital, were included in this study. Ethics committee approval was obtained from the Ethics Committee of T.C. Ministry of Health Istanbul Prof. Dr. Cemil Taşçıoğlu City Hospital with protocol code 214, dated 2021.

All patients underwent at least total hysterectomy and bilateral salpingo-oophorectomy, and in some cases, additional procedures such as pelvic lymphadenectomy, paraaortic lymphadenectomy, or infracolic omentectomy were performed. The decision for systematic lymphadenectomy was based on preoperative findings and intraoperative frozen section results. Systematic lymphadenectomy was performed for patients with grade 3 tumors, grade 2 tumors larger than 2 cm, myometrial invasion greater than 50%, or cervical involvement. The FIGO 2009 criteria were used to establish the final pathology diagnosis of endometrial cancer. Patients (n=105) whose final pathology results showed endometrioid carcinoma with myometrial invasion were included in the study, while non-endometrioid endometrial carcinomas and tumors confined to the endometrium were excluded. Patient information, surgical procedures, and pathology results were obtained from the hospital's patient information system. Prognostic information, such as survival and disease recurrence, was gathered from patient files, computer records, and telephone interviews. Informed consent was obtained from the patients at the time of admission. Postoperative adjuvant treatments were determined according to the decisions of the hospital's oncology council. Low-risk patients with grade 1 or 2 tumors smaller than 2 cm in diameter and with myometrial invasion less than 50% did not receive postoperative radiotherapy or chemotherapy. The existing hematoxylin-eosin-stained pathology slides of the patients were re-examined by a pathology specialist for the MELF myoinvasion pattern. Cases were divided into two groups based on the presence or absence of the MELF myoinvasion pattern under microscopy. Among these groups, pathological features such as tumor grade, myometrial invasion, lymphovascular space invasion (LVSI), tumor size, and stage, as well as demographic and clinical features such as age, diabetes, hypertension, and BMI, were compared.

Survival and recurrence rates were evaluated between the MELF positive and negative groups. In addition, DFS and OS were evaluated separately according to stage, grade, LVSI, tumor size, and myometrial invasion using Kaplan-Meier analysis.

Statistical Analysis

SPSS 20.0 (SPPS Inc, Chicago, IL, USA) statistical package program was used for the statistical evaluation of the study data. Normality and homogeneity analyses were performed using the Kolmogorov-Smirnov and Levene's tests. The Student's t-test and Mann-Whitney U test were used to compare numerical data as descriptive statistics tests, while the Chi-square test was used to compare categorical data. Disease-free survival and overall survival times were evaluated using Kaplan-Meier analysis. Cox regression analysis was performed to examine the effects of different prognostic factors on disease-free survival and overall survival. A 95% confidence interval (P=0.05) was used for the evaluation of all data.

RESULTS

Among the 105 women, 4 (3.8%) were of normal weight, 28 (26.6%) were overweight, and 73 (69.5%) were obese. Considering the surgical FIGO staging of the patients, 83 (79%) were stage 1, 7 (6.66%) were stage 2, and 15

(14.3%) were stage 3. There were no stage 4 patients included in the study.

After examining the pathology slides of the patients, the MELF (microcystic-elongated-fragmented) pattern was found to be positive in 29 (27.62%) patients and negative in 76 (72.38%) patients. The MELF-positive and MELF-negative groups were compared in terms of pathological features and prognostic findings, such as recurrence and survival. Accordingly, while the mean age was 61.66 ± 7.18 years in the MELF(+) group and 60.95 ± 9.48 years in the MELF(-) group, with no significant difference between the groups (P=0.646).

In terms of tumor size, the mean size was 5.17 cm in the MELF(+) group compared to 4.27 cm in the MELF(-) group (P=0.207). In addition, 13 patients had tumors smaller than 2 cm, while 92 patients had tumors 2 cm or larger.

Recurrence was observed in 7 of 105 patients during follow-up. The recurrence rate in patients is 6.6%. MELF(+) in 3(10.34%) of 29 patients; Recurrence was observed in 7 of the 105 patients during follow-up, corresponding to a recurrence rate of 6.6%. Recurrence occurred in 3 (10.34%) of the 29 MELF(+) patients and in 4 (5.26%) of the 76 MELF(-) patients. Although the difference was not statistically significant, the recurrence rate was approximately twice as high in the MELF(+) group (P=0.351). The mean disease-free survival (DFS) was 29.97 months in the MELF(+) group compared to 36 months in the MELF(-) group. While not statistically significant, DFS was lower in the MELF(+) group (P=0.092). During the follow-up period, 7 (6.66%) deaths were observed among the 105 patients, all due to primary tumors. Two deaths occurred in the MELF(+) group, while five occurred in the MELF(-) group, with no significant difference found between the groups (P=0.092).

When the patients were evaluated in terms of grade, it was found that 37 (35.23%) were in grade 1, 49 (46.66%) were in grade 2, and 19 (18.09%) were in grade 3. Among the MELF(+) patients, there were 6 grade 1, 19 grade 2, and 4 grade 3 patients, while the MELF(-) group consisted of 31 grade 1, 30 grade 2, and 15 grade 3 patients. Although the p-value approached 0.05, the relationship between grade and MELF was not statistically significant (P=0.053). Of the included patients, 74 (70.48%) had less than 50% myometrial invasion, while 31 (29.52%) had 50% or more. Among the MELF(+) patients, 13 had ≥ 50% myometrial invasion, compared to 18 in the MELF(-) group. There was no significant difference between the groups (P=0.942). Cervical stromal involvement was present in 4 (13.8%) of the 29 MELF(+) patients and in 10 (13.16%) of the 76 MELF(-) patients, which was not statistically significant (P=0.932).

Adnexal/ovarian metastases were present in 8 (7.6%) of the 105 patients. Among the MELF(+) group, 4 (13.8%) had adnexal/ovarian metastasis, while 4 (5.26%) of the MELF(-) group had metastases (P=0.141).

Considering the surgical staging, there were 83 (79%) stage 1, 7 (6.66%) stage 2, and 15 (14.3%) stage 3 patients. No stage 4 patients were included. Among the 29 MELF(+) patients, 21 (72.4%) were stage 1, 2 (6.9%) were stage 2, and 6 (20.7%) were stage 3. Among the 76 MELF(-) patients, 62 (81.6%) were stage 1, 5 (6.6%) were stage 2, and 9 (11.8%) were stage 3. No significant statistical relationship was found between the groups in terms of stage (P=0.502). Regarding lymphovascular space invasion (LVSI), LVSI was present in 50 (47.6%) of the 105 patients. Among the MELF(+) patients, 19 (65.5%) had LVSI, while 31 (40.8%) of the MELF(-

) patients had LVSI. The relationship between MELF and LVSI was statistically significant (P=0.023). Disease-free survival (DFS) curves were compared between the MELF(+) and MELF(-) groups, but no statistically significant difference was found (P=0.310). The 5-year DFS was 88.1% in the MELF(+) group and 93.2% in the MELF(-) group. No significant difference was found between the overall survival (OS) curves (P=0.894). The 5-year OS was 90.8% in the MELF(+) group and 93.1% in the MELF(-) group.

When the patients were grouped according to stage, a significant difference was found in the DFS curves (P=0.001). Similarly, a significant difference was found between the groups in terms of OS (P=0.001).

When the patients were divided into three groups based on grade, grades did not have a significant effect on DFS.

When the patients were compared in terms of overall survival (OS) across the three grade groups, no significant relationship was found (P=0.066).

No significant disparities emerged between tumor sizes (<2 cm vs. ≥2 cm) regarding disease-free survival (DFS) or overall survival (OS). Among patients with tumors smaller than 2 cm, the 5-year DFS rate was 100%, while it was 90.3% for those with tumors of 2 cm or larger (P=0.316). Similarly, the 5-year OS was 100% for the <2 cm tumor group and 91.6% for the ≥2 cm tumor group, with no significant difference (P=0.329).

Analysis of factors influencing DFS revealed no significant impact of myometrial invasion. The 5-year DFS rates were 94.3% for patients with less than 50% myometrial invasion and 84.3% for those with 50% or more (P=0.460). Likewise, there was no significant difference in OS between these groups, with 5-year OS rates of 89.9% for <50% myometrial invasion and 100% for ≥50% myometrial invasion (P=0.081).

Cox regression analysis identified stage (P=0.021) and diabetes (P=0.016) as significantly associated with disease-free survival. However, no parameter had a statistically significant effect on overall survival in the Cox regression analysis.

DISCUSSION

Determining prognostic factors for risk calculations remains an ongoing area of research. Studies have focused on factors such as lymphovascular space invasion (LVSI), deep myometrial invasion, lymph node involvement, lower uterine segment involvement, and molecular markers. Myometrial invasion can manifest in various forms, including well-circumscribed (pusher), diffuse stromal inflammation, adenomyosis-like, adenoma malignum, and the MELF pattern. The subject of our research is the MELF myoinvasion pattern.

MELF(+) was detected in 29 (27.6%) of 105 endometrioid endometrial cancer cases in our study. The MELF myoinvasion pattern, first described by Murray et al. in 2003, has an incidence ranging from 7% to 48% in various studies. In Murray et al.'s study, MELF(+) was found in 44.3% of 115 cases with myometrial invasion out of 175 endometrial cancer cases examined. In Naki et al.'s study of 83 cases, the rate of MELF(+) was 42.2%, while Altunpulluk et al. reported a 23.1% incidence in a series of 121 cases. The incidence of MELF in our study is consistent with the literature (14,15).

Most of the patients, about 75%, were diagnosed at an early stage, and their final prognosis was relatively favorable. In our study, 79% of the

patients were stage 1, a rate consistent with the literature.

Stage is the foremost prognostic factor in endometrial cancer, with survival rates decreasing as the stage advances. In Choi et al.'s study, 5-year survival rates were 81.8% for stage 1, 62.9% for stage 2, and 37% for stage 3 (16). Similarly, Buldanlı et al. reported survival rates of 91.2%, 75.2%, and 17.4% for stages 1, 2, and 3-4, respectively. Our study revealed significant differences in disease-free survival (DFS) and overall survival (OS) by stage (P=0.001). Specifically, 5-year OS rates were 95.5% for stage 1, 100% for stage 2, and 73.3% for stage 3. Additionally, Cox regression analysis identified stage as an independent prognostic factor for DFS (P=0.021).

In our study, the incidence of MELF increased with stage progression: 25.3% in stage 1, 28.5% in stage 2, and 40% in stage 3. While the relationship between stage and MELF lacked statistical significance, further research is needed. Altunpulluk et al. found MELF to be associated with advanced stages, with 10 stage 3 patients in the MELF(+) group compared to 4 in the MELF(-) group. Similarly, Kihara et al. reported a significant correlation between MELF positivity and advanced disease, with rates of 29% for stage 3+ in the MELF(+) group compared to 9% in the MELF(-) group (17).

Endometrial cancer typically affects postmenopausal women, with an average onset age of 60, and only 5% of cases occur in women under 40. The mean age of patients in our study was 61 ± 8.9 years, which aligns with this demographic trend. In terms of metabolic and chronic diseases, hypertension, diabetes mellitus (DM), and obesity are known to increase the risk of endometrial cancer. The higher rates of DM (47.6%) and hypertension (56.2%) in our study population support this association. However, there was no significant difference between the MELF-positive and MELF-negative groups regarding DM, hypertension, and obesity (P=0.429, P=0.897, P=0.452, respectively). Chia et al.'s study also highlights the increased risk of death associated with obesity and diabetes following an endometrial cancer diagnosis (18). In our Cox regression analysis, diabetes was significantly associated with disease-free survival (P=0.016).

Limited studies have explored the myometrial invasion pattern in endometrial cancer. Murray et al. investigated the presence and outcomes of the MELF pattern in 115 cases of endometrial cancer with myometrial invasion (4). They found that recurrence and death were more common in cases with a fibromyxoid stromal response involving lymphovascular space invasion (LVSI), often associated with the MELF pattern. However, they concluded that the MELF pattern alone was not an independent prognostic factor. Similarly, our study did not find a significant effect of MELF positivity on disease-free survival or overall survival in the univariate analysis. Although not statistically significant, the recurrence rate was approximately twice as high in MELF(+) patients, and disease-free survival rates were lower. Additionally, the relationship between MELF and LVSI was statistically significant (P=0.023), suggesting that MELF positivity may negatively impact prognosis by increasing the rate of LVSI.

Stewart et al. identified 133 out of 170 patients with endometrioid endometrial cancer, among whom 27 were MELF(+) patients (19). They reported a MELF incidence of 20.3% in their study, compared to 27.6% in ours. They argued that the MELF pattern is exclusive to endometrioid endometrial and low-grade cancers. Additionally, they found focal mucinous

differentiation and LVSI more frequently in MELF-positive patients. The LVSI positivity rate in MELF(+) patients was 63%, which is comparable to the 65.5% rate observed in our study and consistent with the literature.

Cole et al. suggested in their review that the type of myometrial invasion pattern is crucial in assessing the depth of myometrial invasion and can impact prognosis (2). They noted a higher frequency of lymphovascular space invasion in the MELF pattern. Many studies have associated the MELF invasion pattern with the presence of LVSI (3, 4, 14). A recent study of 979 cases reported that the MELF pattern was associated with LVSI (20).

Altunpulluk et al. compared clinicopathological features between MELF-positive and MELF-negative groups (15). They found that low grade, deep myometrial invasion, cervical stromal involvement, lymphovascular space invasion, lymph node metastasis, and advanced clinical stage were more common in the MELF-positive group. However, in our study, apart from LVSI, no significant differences were observed between the MELF-positive and MELF-negative groups. Due to an insufficient number of lymph node-positive patients in our cohort, we did not compare the groups based on lymph node involvement.

In a study by Özgül et al. (2020), the impact of myometrial invasion patterns on prognosis in patients with low-grade endometrioid endometrial cancer was investigated. They found the MELF pattern in 69 (25%) of 276 cases. Although the presence of the MELF pattern in myometrial invasion was an independent risk factor for lymphatic spread, the rate of lymph node metastasis was higher in patients with this pattern (P<0.001).

In addition, according to the results of the study, a significant decrease in the rate of disease-free survival (DFS) was observed in the presence of the MELF pattern in myometrial invasion (P=0.015). The authors concluded that the MELF myoinvasion pattern is associated with a more aggressive clinical course. However, in our study, no significant difference was found between the DFS curves of the MELF-positive and MELF-negative groups (P=0.310). Although not statistically significant, the recurrence rate in MELF(+) patients was approximately twice as high. While the 5-year DFS was found to be 88.1% in the MELF(+) group, it was 93.2% in the MELF(-) group. Although these rates were not statistically significant, DFS rates were lower in MELF(+) patients, indicating the need for studies with higher patient numbers.

In the study by Pavlakis et al., endometrioid endometrial carcinomas were divided into two groups: patients who underwent only hysterectomy and bilateral salpingo-oophorectomy, and patients who had additional lymph node sampling (21). Of the 99 patients who underwent lymph node sampling, MELF was positive in 13 and negative in 86. Lymph node involvement was observed in 7 (53.8%) of the MELF-positive patients, while lymph node involvement was observed in 6 (7%) of the MELF-negative patients. MELF positivity was found to be significantly associated with lymph node involvement (P=0.00014). However, no recurrence or death was observed in any of the patients with MELF invasion in this study. This finding agrees with Murray et al., who reported that the MELF invasion pattern alone was not associated with a negative outcome. In our study, there was no statistically significant effect of MELF positivity on disease-free survival or overall survival. However, the presence of lymphovascular space invasion (LVSI) is an important pathological finding that

affects recurrence and survival in endometrial cancer. Studies have shown that LVSI positivity in endometrial cancer is an independent prognostic factor for lymph node involvement. In the study conducted by De Gois et al., patients with and without recurrence were divided into two groups over a 5-year period to compare the prognostic values of histological grade, myometrial invasion, and LVSI. They reported that LVSI was more frequent in the recurrence-positive group and that it was a reliable parameter for worse prognosis. In the same study, they found that LVSI was always accompanied by myometrial invasion (22). Similarly, Gemer et al. reported that patients with positive LVSI had more advanced disease, a higher recurrence rate, and worse 5-year survival (23). In our study, LVSI was observed in 65.5% of MELF(+) patients. The relationship between MELF and LVSI was statistically significant (P=0.023), suggesting that MELF positivity may indirectly increase lymph node involvement by increasing LVSI.

In Kihara et al.'s study, the MELF pattern was present in 11% of low-grade endometrioid carcinoma cases but absent in high-grade cases. It was associated with larger tumor size, >50% myometrial invasion, advanced stage, LVSI, and lymph node metastasis (17). Similarly, Naki et al. found the MELF pattern significantly linked to lymphovascular invasion in 83 cases of endometrioid endometrial carcinoma (14). However, unlike our study, they found MELF positivity associated with high-grade tumors and deep myometrial invasion.

Sancı et al. examined 27 endometrioid endometrial carcinoma patients with grade 1-2 and lymph node involvement, compared to 28 grade 1-2 patients without lymph node involvement (24). They identified MELF invasion and LVSI as predictors for lymph node involvement. However, similar to our findings, they found no statistically significant effect of MELF invasion on disease-free survival.

Quick et al., in their study of 98 patients with low-grade myoinvasive endometrioid endometrial carcinoma, showed that lymphovascular invasion was more common in MELF-positive patients, but lymph node involvement was not frequent (25).

To further elucidate the role of MELF invasion in prognosis and survival, a systematic review was published, including articles written until May 2018. This review consisted of 14 studies and 588 patients. All included patients were evaluated for the presence of the MELF myometrial invasion pattern. Accordingly, MELF-positive patients were found to have a higher probability of larger tumor size, high-grade tumors, lymph node metastasis, lymphovascular invasion, and >50% myometrial invasion. However, no difference was reported in disease-free survival, overall survival, or vaginal recurrence rates (26).

CONCLUSION

Studies since Murray et al.'s 2013 research have explored the relationship between the MELF myometrial invasion pattern and clinicopathological features in endometrioid endometrial cancer, but a definitive consensus remains elusive. Our study similarly found no significant impact of the MELF invasion pattern on disease-free or overall survival in this cancer type. However, we observed a notably higher incidence of lymphovascular space invasion (LVSI) in the MELF-positive group (P=0.023). This suggests that the presence of the MELF pattern may indirectly worsen prognosis through increased LVSI. Further research with larger cohorts and longer follow-up periods is needed to clarify these findings.

In addition, our study identified stage and diabetes as independent risk factors for disease-free survival in endometrioid endometrial cancer (EEC). With this study, we aim to contribute to the existing literature.

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REFERENCES

1. Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. Lancet. 2016 Mar 12;387(10023):1094-1108. doi: 10.1016/S0140-6736(15)00130-0. Epub 2015 Sep 6. PMID: 26354523.

2. Cole AJ, Quick CM. Patterns of myoinvasion in endometrial adenocarcinoma: recognition and implications. Adv Anat Pathol. 2013 May;20(3):141-7. doi: 10.1097/PAP.0b013e31828d17cc. PMID: 23574770.

3. Quick CM, May T, Horowitz NS, Nucci MR. Low-grade, low-stage endometrioid endometrial adenocarcinoma: a clinicopathologic analysis of 324 cases focusing on frequency and pattern of myoinvasion. Int J Gynecol Pathol. 2012 Jul;31(4):337-43. doi: 10.1097/PGP.0b013e31823ff422. PMID: 22653347.

4. Murray SK, Young RH, Scully RE. Unusual epithelial and stromal changes in myoinvasive endometrioid adenocarcinoma: a study of their frequency, associated diagnostic problems, and prognostic significance. Int J Gynecol Pathol. 2003 Oct;22(4):324-33. doi: 10.1097/01.pgp.0000092161.33490.a9. PMID: 14501811.

5. Papanikolaou A, Kalogiannidis I, Goutzioulis M, Misailidou D, Makedos A, Vergote I, Makedos G. Pelvic lymphadenectomy as alternative to postoperative radiotherapy in high risk early stage endometrial cancer. Arch Gynecol Obstet. 2006 May;274(2):91-6. doi: 10.1007/s00404-006-0138-y. Epub 2006 Mar 4. PMID: 16518607.

6. Mohan DS, Samuels MA, Selim MA, Shalodi AD, Ellis RJ, Samuels JR, Yun HJ. Long-term outcomes of therapeutic pelvic lymphadenectomy for stage I endometrial adenocarcinoma. Gynecol Oncol. 1998 Aug;70(2):165-71. doi: 10.1006/gyno.1998.5098. PMID: 9740684.

7. Benedetti Panici P, Basile S, Maneschi F et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J. Natl Cancer Inst. 2008; 100; 1707–1716.

8. Kilgore LC, Partridge EE, Alvarez RD et al. Adenocarcinoma of the endometrium: survival comparisons of patients with and without pelvic node sampling. Gynecol. Oncol. 1995; 56; 29–33.

9. Cragun JM, Havrilesky LJ, Calingaert B et al. Retrospective analysis of selective lymphadenectomy in apparent early-stage endometrial cancer. J. Clin. Oncol. 2005; 23; 3668–3675.

10. Alektiar KM, McKee A, Lin O et al. The significance of the amount of myometrial invasion in patients with Stage IB endometrial carcinoma. Cancer 2002; 95; 316–321.

11. Bottke D, Wiegel T, Kreienberg R, Kurzeder C, Sauer G. Stage IB endometrial cancer. Does lymphadenectomy replace adjuvant radiotherapy? Strahlenther. Onkol. 2007; 183; 600–604.

12. Keys HM, Roberts JA, Brunetto VL 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; 744–751.

13. McKenney JK, Kong CS, Longacre TA. Endometri adenocarcinoma associated with subtle lymph-vascular space invasion and lymph node metastasis: a histologic pattern mimicking intravascular and sinusoidal histiocytes. Int. J. Gynecol. Pathol. 2005; 24; 73–78.

14. Naki MM, Oran G, Tetikkurt S, et al. Microcystic, elongated, and fragmented pattern of invasion in relation to histopathologic and clinical prognostic factors in endometrioid endometrial adenocarcinoma. Journal of the Turkish German Gynecological Association, 2017;18(3), 139.

15. Dogan Altunpulluk M, Kir G, Topal CS, et al. The association of the microcystic, elongated and fragmented (MELF) invasion pattern in endometrial carcinomas with deep myometrial invasion, lymphovascular space invasion and lymph node metastasis. Journal of Obstetrics and Gynaecology, 2015;35(4), 397-402.).

16. Choi, E. C., Kim, J. H., Kim, O. B., Byun, S. J., Park, S. G., & Kwon, S. H. (2012). Postoperative radiotherapy for endometrial cancer. Radiation oncology journal, 30(3), 108.

17. Kihara, A., Yoshida, H., Watanabe, R., Takahashi, K., Kato, T., Ino, Y., ... & Hiraoka, N. (2017). Clinicopathologic association and prognostic value of microcystic, elongated, and fragmented (MELF) pattern in endometrial endometrioid carcinoma. The American journal of surgical pathology, 41(7), 896-905.

18. Chia VM, Newcomb PA, Trentham-Dietz A, et al. Obesity, diabetes, and other factors in relation to survival after endometrial cancer diagnosis. International Journal of Gynecologic Cancer, 2007;17(2).

19. Stewart CJR, Brennan BA, Leung YC, et al. MELF pattern invasion in endometrial carcinoma: association with low grade, myoinvasive endometrioid tumours, focal mucinous differentiation and vascular invasion. Pathology, 2009;41(5), 454-459.

20. Van den Heerik ASVM, Aiyer KTS, Stelloo E, et al. Microcystic elongated and fragmented (MELF) pattern of invasion: Molecular features and prognostic significance in the PORTEC-1 and -2 trials. Gynecol Oncol. 2022;166(3):530-537. doi:10.1016/j.ygyno.2022.06.027

21. Pavlakis K, Messini I, Vrekoussis T, et al. MELF invasion in endometrial cancer as a risk factor for lymph node metastasis. Histopathology, 2011,58(6), 966-973.

22. De Góis N, Martins NV, Abrão F, et al. Peritumorous lymph-vascular invasion, grade of histologic differentiation, and myometrial infiltration as prognostic factors of endometrial carcinoma. Revista paulista de medicina. 1993;111(3):385-90.

23. Gemer O, Arie AB, Levy T, et al. Lymphvascular space involvement compromises the survival of patients with stage I endometrial cancer: results of a multicenter study. European Journal of Surgical Oncology (EJSO). 2007;33(5):644-7.

24. Sanci M, Güngördük K, Gülseren V, et al. MELF pattern for predicting lymph node involvement and survival in grade I-II endometrioid-type endometrial cancer. International Journal of Gynecological Pathology, 2018;37(1), 17-21.

25. Quick CM, May T, Horowitz N S, et al. Low-grade, low-stage endometrioid endometrial adenocarcinoma: a clinicopathologic analysis of 324 cases focusing on frequency and pattern of myoinvasion. International journal of gynecological pathology, 2012;31(4), 337-343.

26. Prodromidou A, Vorgias G, Bakogiannis K, et al. MELF pattern of myometrial invasion and role in possible endometrial cancer diagnostic pathway: A systematic review of the literature. European Journal of Obstetrics & Gynecology and Reproductive Biology, 2018;230, 147-152.