DOI: 10.4274/MMJ.galenos.2022.40336
Medeni Med J 2022;37:212-219

Original Article

Prognositc Significance of Microcystic Elongated and Fragmanted (MELF) Myometrial Invaison Pattern: A Retrospective Study

Mikrokistik Elonge Fragmante (MELF) Myomterial İnvazyon Paterninin Prognostik Önemi: Retrospektif Bir Çalışma

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ABSTRACT

Objective: Endometrioid endometrial carcinomas (EEC) are the most commonly diagnosed malignancies of the female genital tract. Myometrial invasion depth is one of the most significant pathological prognostic parameters. Different morphological invasion patterns have been characterized. This study aimed to investigate the prognostic significance of the microcystic elongated and fragmented (MELF) myometrium invasion pattern in patients with EEC and its relationship with other clinicopathological parameters.

Methods: This study included 101 patients with EEC in our institution between 2011 and 2020. The MELF pattern was evaluated in hematoxylin-eosin-stained sections. Pan-cytokeratin staining was performed on paraffin-embedded blocks of lymph nodes for cases without lymph node metastasis.

Results: The MELF pattern was observed in 29 (29.8%) patients. It was significantly associated with lymphovascular invasion (p<0.001), pathologic stage (p=0.048), infiltrative pattern (p<0.001), and necrosis (p=0.005). No significant correlation was observed between the MELF pattern and overall and disease-free survival rates.

Conclusions: The MELF pattern is associated with other prognostic parameters, but its prognostic significance for survival has not been found. If the MELF pattern is observed in the hysterectomy material for cases without lymph node dissection during the first surgery, these patients may need additional surgery or adjuvant therapy due to the high risk of lymphovascular invasion and lymph node metastasis.

Keywords: Microcystic elongated and fragmented (MELF), endometrioid endometrial carcinomas, survival

ÖZ

Amaç: Endometrioid endometriyal karsinomlar (EEK) kadın genital sistemin en sık karşılaşılan maligniteleridir. Myometrium invazyon derinliği en önemli patolojik prognostik parametrelerden birisidir. Farklı morfolojik invazyon paternleri tanımlanmıştır. Biz çalışmamızda EEk olgularında mikrokistik elonge fragmante (MELF) myometirum invazyon paterninin prognostik önemini ve klinikopatolojik parametrelerle ilişkisini araştırmayı amaçladık.

Yöntemler: 2011-2020 yılları arasında kurumumuzda EEK tanısı alan 101 hasta çalışmaya dahil edildi. Hematoksilen eozin kesitlerde MELF paterni değerlendirildi. Lenf nodu metastazı izlenmeyen olgularda lenf nodu bloklarına pan-sitokeratin uygulandı.

Bulgular: Yirmi dokuz hastada (%29,8) MELF paterni izlendi. MELF paterni lenfovasküler invazyon (p<0,001), patolojik evre (p=0,048), infiltratif patern (p<0,001), ve nekroz (p=0,005) ile anlamlı ilişkili izlendi. Genel ve hastalıksız sağkalımda MELF paterni istatistiksel olarak anlamlı ilişkili izlenmedi.

Sonuçlar: MELF paterni diğer prognostik parametrelerle ilişkili olup tek başına prognostik önemi saptanmamıştır. Ancak ilk cerrahi sırasında lenf nodu diseksiyonu yapılmayan EEK hastalarında histerektomi materyalinde MELF paterni saptanması durumunda yüksek lenfovasküler invazyon ve lenf nodu metastaz riski nedeniyle ek cerrahi işlem ya da adjuvan terapi kararında MELF paterni varlığının dikkate alınması gerektiğine inanıyoruz.

Anahtar kelimeler: Mikrokistik elonge fragmante (MELF), endometrioid endometrial kanser, sağkalım

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Received: 30 May 2022
Accepted: 06 July 2022
Online First: 26 July 2022

Cite as: Okcu O, Askan G, Sen B, Ozturk C, Duman Ozturk S, Findik Guvendi G. Prognositc Significance of Microcystic Elongated and Fragmanted (MELF) Myometrial Invaison Pattern: A Retrospective Study. Medeni Med J 2022;37:212-219

INTRODUCTION

Endometrioid endometrial carcinoma (EEC) is classified as type 1 endometrial carcinoma and is the most commonly diagnosed malignancy of the female genital tract[1]. Hysterectomy and bilateral salpingo-oophorectomy is the first choice of treatment, whereas pelvic or paraaortic lymph node dissection is additionally performed in moderate- to high-risk cases due to extrauterine extension risk assessment. Adjuvant therapy is added depending on disease grade and stage[2,3]. Cases with early-stage EEC that are confined to the uterus have a good prognosis with a 5-year survival rate of 90%-96%, whereas this ratio is reduced to 49%-57% in advanced-stage EEC[4,5]. The most substantial prognostic parameters are being considered as the stage, International Federation of Gynaecology and Obstetrics (FIGO) grade, depth of myometrial invasion, lymphovascular invasion, and lymph node metastasis[6,7].

The depth of myometrial invasion is a considerable prognostic parameter in determining the need for adjuvant chemoradiotherapy and lymph node dissection. Different morphological invasion patterns have been described, with the infiltrative pattern as the most common. Other patterns such as pushing border, adenomyosis-like, and microcystic elongated and fragmented (MELF) are also detected at a lower rate[8,9]. The MELF pattern, first described by Murray et al.[10], was associated with lymphovascular invasion and lymph node metastasis.

Despite the lack of a direct relationship between MELF pattern and survival rate, it may be overlooked at low magnification as having an ordinary appearance and concomitant fibromyxoid stroma and inflammatory cells. This can lead to understaging and misclassification as low risk[11,12]. Since it is associated with lymphovascular invasion and lymph node metastasis, it may play a role in the decision for additional surgery or demand for adjuvant therapy where lymph node dissection is not performed during the first surgical procedure.

This study aimed to explore the prognostic value of the MELF pattern by evaluating the relationship between MELF pattern and clinicopathological parameters such as FIGO grade, lymphovascular invasion, lymph node metastasis, depth of myometrium invasion, distant metastasis, survival, etc., in EEC.

MATERIALS and METHODS

Patient Selection

In this retrospectively planned study, the list of patients who had undergone surgery for EEC in our institution between 2010 and 2020 was obtained from the hospital's electronic database. Hematoxylin and eosin (H&E)-stained sections were retrieved from the pathology archive. All H&E-stained sections were reevaluated, and cases with myometrial invasion were determined. Cases in which paraffin-embedded blocks, H&E slides, and clinical data could not be obtained were excluded. As a result, 101 patients were finally included in the study. Pan-cytokeratin (PanCK, AE1/AE3) immunohistochemical staining was performed on lymph node blocks of patients without lymph node metastasis.

Patient Data

The age, history of adjuvant chemotherapy treatment, distant-organ metastasis, and survival information of the cases were obtained from the hospital's electronic database. Tumor size was obtained from the pathology reports. FIGO grade, nuclear grade, pathological stage, myometrial invasion pattern, lymphovascular invasion, cervical invasion, lymph node metastasis, squamous metaplasia, necrosis, and adenomyosis data were reevaluated from H&E-stained slides for each case. The cases were classified as endometrioid type endometrial adenocarcinoma according to the World Health Organization classification of gynecological cancers[13], and grading was made according to FIGO[14].

Outcomes

Disease-free survival (DFS) was defined as the time to clinical, radiological, or pathological metastasis or recurrence after major surgery or to the last follow-up. Overall survival (OS) is the time from surgery to the last control date or date of death.

Histopathological Examination and MELF Invasion Pattern

The MELF pattern, first described by Murray et al.[10], is localized in the myometrium invasion area, frequently in the deepest area. It comprises blind-like squamoid-looking cells with eosinophilic cytoplasm that forms a microcystic and elongated architecture, with retraction artifact and inflammatory cells within a background of a specific fibromyxoid stroma (Figure 1a-d). Around these structures, there are single cells or groups of fragmented cells forming clusters[10]. Although the retraction artifact and flattened tumor cells observed in the MELF pattern are morphologically similar to lymphovascular invasion, fibromyxoid stroma, and tumoral cells with squamoid features and CD31, CD34, and D2-40 immunohistochemical stains help distinguish these two entities.

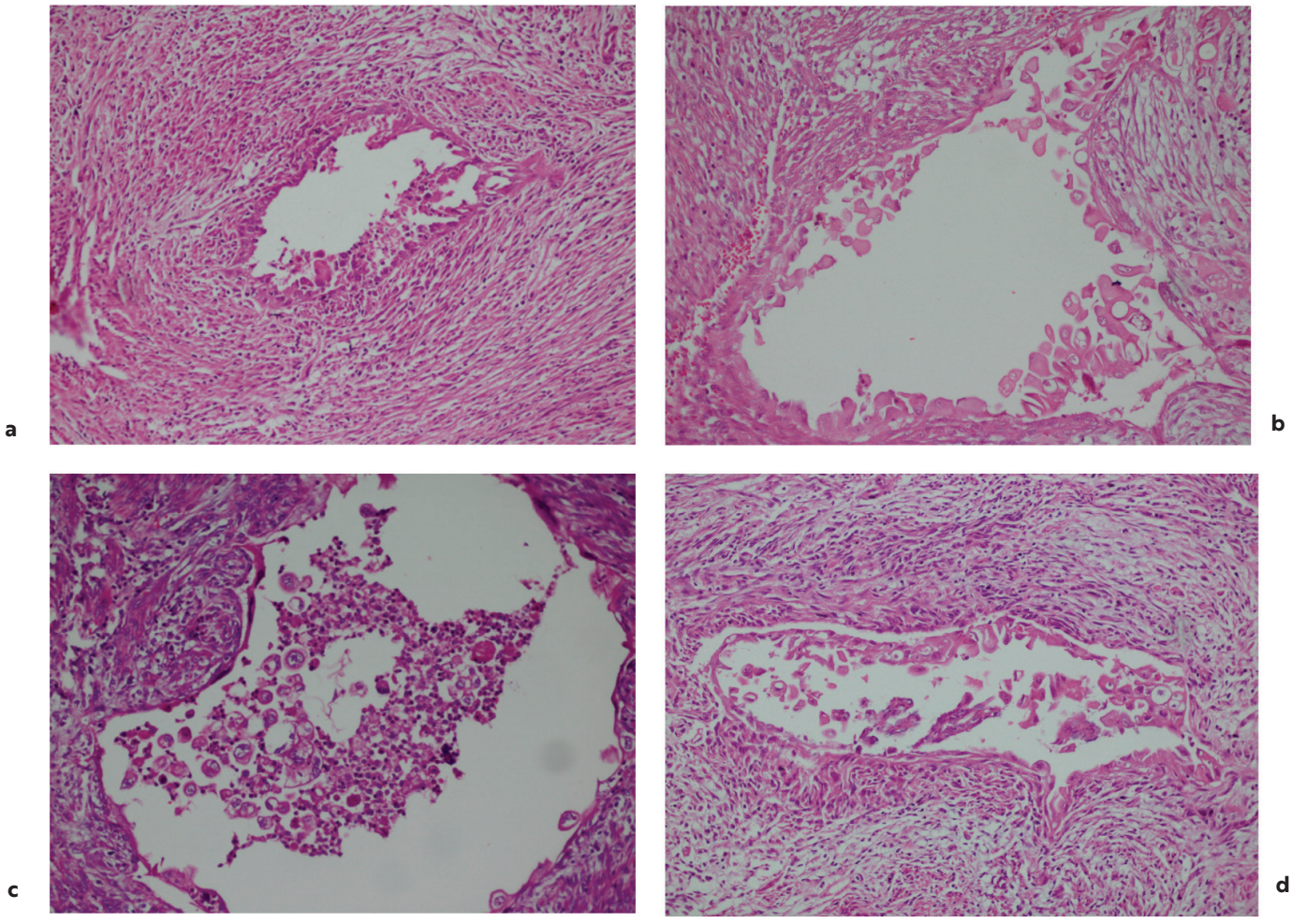

Figure 1. Microcystic elongated and fragmented myometrium invasion pattern: **(a, b)** Hematoxylin and eosin ×200, **(c, d)** Hematoxylin and eosin ×400.

Ethical Approval

Ethics committee confirmation for our study was obtained from the Ethics Committee of Recep Tayyip Erdogan University Faculty of Medicine, Non-Interventional Clinical Research (decision no: 2022/107, date: 28.04.2022). The study was conducted following the Reporting Recommendations for Tumor Marker Prognostic Studies guidelines[15].

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Categorical variables were evaluated with chi-square (Pearson chi-square) and Fisher's Exact test. To assess DFS and OS, Cox regression analysis was performed and a hazard ratio (HR) of 95% confidence interval (CI) was presented. The p-value was accepted as $p<0.05$ for statistical significance.

RESULTS

In this study, 97 (96%) patients had undergone hysterectomy and bilateral salpingo-oophorectomy, 2 (2%) had undergone hysterectomy and unilateral salpingo-oophorectomy, and another 2 (2%) had undergone hysterectomy and bilateral salpingectomy. Pelvic and/or paraaortic lymph node dissection was performed in 81 (80%) patients. The mean age of the patients was 59 years, ranging from 41 to 87 years. The FIGO grade was 1 in 62 (61%) cases, 2 in 33 (33%), and 3 in 6 (6%). Moreover, 76 (75%) cases were at pT1a, 15 (15%) at pT1b, and 10 (10%) at pT2. Lymphovascular invasion was observed in 22 (22%) cases, and cervical invasion and lymph node metastasis were observed in 10 (10%) and 6 (6%) cases, respectively. PanCK staining was performed to lymph nodes without metastasis according to H&E sections. The clinicopathological features of the cases are summarized in Table 1.

Relationship Between MELF Pattern and Clinicopathological Parameters

The MELF pattern was observed in 29 (2%) patients. This pattern was significantly related to lymphovascular invasion (p<0.001), pathologic stage (p=0.048), infiltrative pattern (p<0.001), and necrosis (p=0.005). No significant relationship was found between the MELF pattern and FIGO grade (p=0.086), squamous metaplasia (p=0.292), adenomyosis (p=0.469), lymph node metastasis (p=1.000), distant metastasis (p=1.000), and survival (p=1.000). Detailed clinicopathological features of the cases are summarized in Table 1.

Table 1. MELF invasion pattern and clinicopathological features.

		MELF				
		No		Yes		
		n	%	n	%	p
FIGO grade	1	49	68.1	13	44.8	0.086
	2	19	26.4	14	48.3	
	3	4	5.6	2	6.9	
Nuclear grade	1	23	31.9	2	6.9	0.028
	2	44	61.1	25	86.2	
	3	5	6.9	2	6.9	
Pathologic stage	1a	59	81.9	17	58.6	0.048
	1b	8	11.1	7	24.1	
	2	5	6.9	5	17.2	
Tumor size	<3 cm	39	54.2	11	37.9	0.14
	≥3 cm	33	45.8	18	62.1	
Lymphovascular invasion	Negative	64	88.9	15	51.7	<0.001
	Positive	8	11.1	14	48.3	
Myometrial invasion ratio	<50%	61	84.7	20	69.0	0.072
	>50%	11	15.3	9	31.0	
Necrosis	Negative	64	88.9	19	65.5	0.005
	Positive	8	11.1	10	34.5	
Squamous metaplasia	Negative	61	84.7	22	75.9	0.292
	Positive	11	15.3	7	24.1	
Adenomyosis	Negative	39	54.2	18	62.1	0.469
	Positive	33	45.8	11	37.9	
Cervical invasion	Negative	67	93.1	24	82.8	0.145
	Positive	5	6.9	5	17.2	
Paracentesis cytology	Benign	42	93.3	17	89.5	0.629
	Malign	3	6.7	2	10.5	
Lymph node status	Negative	68	94.4	27	93.1	1.000
	Positive	4	5.6	2	6.9	
Distant metastasis	Negative	65	90.3	26	89.7	1.000
	Positive	7	9.7	3	10.3	
Follow-up	Negative	65	90.3	26	89.7	1.000
	Positive	7	9.7	3	10.3	
Infiltration pattern	Infiltrative	28	38.9	24	82.8	<0.001
	Pushing	38	52.8	4	13.8	
	Adenomyosis-like	6	8.3	1	3.4	

MELF: Microcystic elongated and fragmented invasion pattern

The proportion of lymphovascular invasion was 48% and lymph node metastasis was 7% in 29 cases with the MELF pattern, whereas the ratio of lymphovascular invasion was 11% and lymph node metastasis was 5.5% in 72 patients without the MELF pattern. Although lymphovascular invasion and lymph node metastasis were observed at a higher ratio in patients with MELF patterns, only lymphovascular invasion was found to be significantly related.

Survival Analysis

No significant relationship was found between OS and DFS and the MELF pattern (Tables 2 and 3). The age (p=0.002), FIGO grade (2 vs. 1; p=0.014, 3 vs. 1; p=0.007), lymphovascular invasion (p=0.034), and distant metastasis (p=0.002) were associated with OS in the univariate analysis. In the multivariate analysis, the age [HR 1.097, 95% CI (1.030-1.169)], FIGO grade [2 vs. 1; HR 0.416, 95% CI (1.235-87.828)], FIGO grade [3 vs. 1; HR 47,088, 95% CI (4,063-545,762)] was determined as independent prognostic factors for OS (Table 2).

In the univariate analysis, FIGO grade (2 vs. 1) (p=0.016), lymphovascular invasion (p=0.032), myometrial invasion rate (p=0.023), and lymph node metastasis (p=0.002) were associated with DFS. In the multivariate analysis, FIGO grade [2 vs. 1; HR 5,533, 95% CI (1,113-27,505)] and lymph node metastasis [HR 5,643, 95% CI (1,373-23,187)] were identified as an independent prognostic factor for DFS (Table 3).

DISCUSSION

EECs are the most common and mostly low-grade and low-stage tumors of the female genital tract. The depth of myometrial invasion is one of the most crucial prognostic parameters and morphological findings that determine the treatment. Although an infiltrative pattern is easy to recognize morphologically, the evaluation of other patterns such as pushing border, adenomyosis-like, adenoma malignum, and MELF is difficult because they are uncommon and more complex[8,9]. Although morphological patterns have been described in relation to various prognostic parameters, no precise consensus has been reached on their prognostic importance alone.

In our study, the MELF pattern was detected in 29.8% of EEC cases. In the literature, this rate varies between 9% and 44%[16-21]. This broad variation may be due to the inclusion of patient groups with different FIGO grades and stages in the studies or differences in the assessment among observers. Moreover, the MELF pattern was associated with deep myometrial invasion, lymphovascular invasion, tumor necrosis, and infiltrative-type myometrium invasion pattern, compatible with the literature.

Table 2. Overall survival in endometrioid endometrial carcinoma cases. Cox regression analysis.

	Univariate		Multivariate	
	p	**HR (95% CI)**	**p**	**HR (95% CI)**
Age	0.002	1.103 (1.035-1.175)	0.004	1.097 (1.030-1.169)
MELF	0.940	0.95 (0.246-3.674)	-	-
FIGO grade (2 vs. 1)	0.014	13.706 (1.681-111.734)	0.031	10.416 (1.235-87.828)
FIGO grade (3 vs. 1)	0.007	27.203 (2.457-301.246)	0.002	47.088 (4.063-545.762)
Nuclear grade	0.818	-	-	-
Pathologic stage (1)	0.866	0.833 (0.1-6.955)	-	-
Pathologic stage (2)	0.126	2.971 (0.737-11.97)	-	-
Tumor size	0.692	1.293 (0.363-4.603)	-	-
Lymphovascular invasion	0.034	3.829 (1.108-13.235)	-	-
Myometrial invasion ratio	0.138	2.621 (0.735-9.352)	-	-
Necrosis	0.541	0.525 (0.066-4.148)	-	-
Squamous metaplasia	0.931	0.934 (0.198-4.416)	-	-
Cervical invasion	0.108	3.054 (0.782-11.921)	-	-
Lymph node status	0.104	3.64 (0.766-17.293)	-	-
Distant metastasis	0.002	7.362 (2.07-26.188)	-	-

FIGO, lymphovascular invasion, distant metastasis, and age were selected as covariates.

FIGO: International Federation of Gynaecology and Obstetrics, MELF: Microcystic elongated and fragmented invasion pattern, HR: Hazard ratio, CI: Confidence interval

Table 3. Disease-free survival in endometrioid endometrial carcinoma cases. Cox regression analysis.				
	Univariate		Multivariate	
	p	HR (95% CI)	p	HR (95% CI)
Age	0.799	1.009 (0.945-1.076)	-	-
MELF	0.924	1.068 (0.276-4.13)	-	-
FIGO grade (2 vs. 1)	0.016	6.91 (1.435-33.28)	0.037	5.533 (1.113-27.505)
FIGO grade (3 vs. 1)	0.171	5.357 (0.484-59.308)	0.380	3.054 (0.252-36.948)
Nuclear grade	0.988	-	-	-
Pathologic stage (1)	0.123	3.087 (0.737-12.933)	-	-
Pathologic stage (2)	0.195	2.967 (0.573-15.363)	-	-
Tumor size	0.242	2.246 (0.58-8.706)	-	-
Lymphovascular invasion	0.032	3.887 (1.124-13.436)	-	-
Myometrial invasion ratio	0.023	4.221 (1.22-14.601)	-	-
Necrosis	0.834	1.181 (0.251-5.56)	-	-
Squamous metaplasia	0.070	3.228 (0.91-11.449)	-	-
Cervical invasion	0.318	2.207 (0.467-10.443)	-	-
Lymph node status	0.002	8.685 (2.237-33.722)	0.016	5.643 (1.373-23.187)
FIGO, lymphovascular invasion, myometrial invasion ratio, and lymph node status were selected as covariates. FIGO: International Federation of Gynaecology and Obstetrics, MELF: Microcystic elongated and fragmented invasion pattern, HR: Hazard ratio, CI: Confidence interval				

Although MELF pattern is observed in low-grade EECs in different studies[17,18,21], Naki et al.[22] revealed an association between the MELF pattern and a high FIGO grade. Unlike these results, in our study, similar to the study of Espinosa et al.[23], the MELF pattern was not associated with the FIGO grade. Although the cases with the MELF pattern were mostly FIGO grade 2, no significant relationship was found between the FIGO grade and the MELF pattern. Pavlakis et al.[19] and Sanci et al.[24] highlighted that the MELF pattern is an independent predictor of lymph node metastasis. In our study, while the MELF pattern was found to be associated with lymphovascular invasion, no significant relationship was observed between lymph node metastasis and MELF pattern. This may be due to the small number of patients with lymph node metastasis.

Sanci et al.[24] and Zinovkin et al.[25] found a relationship between the MELF pattern and OS, while some studies did not find a relationship between the MELF pattern and survival[19,21,23]. In the study of Kihara et al.[21], no relationship was found between the MELF pattern and survival; similarly, no significant relationship was found between the number of glands forming the MELF pattern and survival. In another study, although a higher MELF gland was detected in cases with lymph node metastasis, this situation was not significant[16].

Although the MELF pattern was related with deep myometrial invasion and lymphovascular invasion in our study, it was not an independent prognostic factor for survival compatible with other studies.

Initially, the MELF pattern was first reported to occur because of degenerative changes[10]. Subsequently, the MELF pattern was defined as an active process resulting from the relationship between tumor and stroma rather than degenerative changes and may be associated with epithelial-mesenchymal transition (EMT), especially with cells that are located around the glands that tend to decompose[16,17]. Stewart and Little[26] identified CK7 and vimentin expression, whereas estrogen and progesterone hormone receptors and E-cadherin expression were lost in MELF glands, supporting the EMT-MELF theory, and defined MELF as EMT-associated endometrial neoplasia. In another study, the Ki-67 proliferation index was low in MELF cells, whereas p16 and p21 immunohistochemical markers were found to be positively stained, and this was interpreted as MELF cells being senescent whose growth phase stopped[21]. Although the MELF pattern was associated with lymphovascular invasion and lymph node metastasis in some studies, it was not an independent parameter related with OS.

Determining the MELF pattern is important because of two reasons. Primarily, as a separate focus from the main tumor and because of its microabscess-like degenerative appearance mixed with inflammatory cells, it may be overlooked, particularly in the low-magnification area, which causes low-grade staging.

Similar to the depth of myometrium invasion, lymph node metastases may be overlooked in cases with the MELF pattern, since lymph node metastases may be histiocyte-like and isolated single cell. Thus, we performed PanCK immunohistochemical staining to the paraffin-embedded blocks of cases which were previously reported to have no lymph node metastasis. However, we did not detect metastasis, even as a single cell. This may have been caused by the low-grade and low-staged nature of the majority of our cases. Even so, theoretically, each lymph node should be examined with multiple repeated serial sections and ancillary studies to exclude a single cell or micrometastases. Since such an application cannot be performed due to excessive labor and financial requirements, single cell or micrometastasis cannot be definitively excluded. Lymph node metastasis was detected after performing PanCK in some patients whose initial diagnosis were negative for lymph node metastasis[20]. Consequently, lymph node examination, additional sectioning, and immunohistochemical staining will increase the chance of success in detecting single cell and micrometastases in patients with the MELF pattern.

Lymph node dissection is crucial in surgical staging, prognosis prediction, and adjuvant treatment decisions. However, it may cause various short- and long-term complications, such as bleeding, lymphedema, and vascular or nerve damage[27]. Lymph node dissection is not recommended for FIGO grades 1 and 2, endometrioid histology, small tumor size (≤2 cm), and <50% invasion in the myometrium, which is considered as a low risk in terms of extrauterine spread[2]. Additionally, lymph node dissection increases survival in moderate- and high-risk cases, but does not affect survival in low-risk cases[28,29]. Although the number of patients in our study was relatively small, our findings could shed light on regular follow-up and performing the standard treatment method. If the MELF pattern is observed in the hysterectomy material for cases without lymph node dissection during the first surgery, these patients may need additional surgery or adjuvant therapy due to the high risk of lymphovascular invasion and lymph node metastasis. The prognostic significance of the MELF pattern has not been clearly defined yet; thus, new studies with a large number of patients from different centers are needed.

CONCLUSION

MELF is associated with lymphovascular invasion and lymph node metastasis. Given its discrete morphological appearance, it should be cautiously examined by both the depth of myometrium invasion and lymph node metastasis. Additional sectioning and immunohistochemical studies should be performed to lymph nodes to detect micrometastasis or a single cluster of cells. The MELF pattern is associated with other prognostic variables, and its prognostic significance alone has not been emphasized. However, it should be considered in the decision for additional therapy such as surgery or adjuvant chemotherapy or radiotherapy due to the increased risk of lymph node metastasis, especially in patients with EEC without lymph node dissection during the initial operation.

Ethics

Ethics Committee Approval: Our study was obtained from the Ethics Committee of Recep Tayyip Erdogan University Faculty of Medicine, Non-Interventional Clinical Research (decision no: 2022/107, date: 28.04.2022).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Author Contributions

Surgical and Medical Practices: O.O., G.A., B.S., C.O., S.D.O., G.F.G., Concept: O.O., G.A., B.S., C.O., S.D.O., G.F.G., Design: O.O., G.A., B.S., C.O., S.D.O., G.F.G., Data Collection and/or Processing: O.O., G.A., B.S., C.O., S.D.O., G.F.G., Analysis and/or Interpretation: O.O., G.A., B.S., C.O., S.D.O., G.F.G., Literature Search: O.O., G.A., B.S., C.O., S.D.O., G.F.G., Writing: O.O., G.A., B.S., C.O., S.D.O., G.F.G.

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

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71:209-49.
2. Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. Ann Oncol. 2016;27:16-41. Erratum in: Ann Oncol. 2017;28(suppl_4):iv167-8.
3. Lu M, Zheng J, Xu N, Lin H, Wan S. Postoperative chemotherapy as adjuvant treatment for endometrioid adenocarcinoma: early stage vs late stage. Cancer Chemother Pharmacol. 2019;84:299-305.
4. Lewin SN, Herzog TJ, Barrena Medel NI, et al. Comparative performance of the 2009 international Federation of gynecology and obstetrics' staging system for uterine corpus cancer. Obstet Gynecol. 2010;116:1141-9.

5. Kilgore JE, Jackson AL, Ko EM, et al. Recurrence-free and 5-year survival following robotic-assisted surgical staging for endometrial carcinoma. Gynecol Oncol. 2013;129:49-53.
6. Roma AA, Rybicki LA, Barbuto D, et al. Risk factor analysis of recurrence in low-grade endometrial adenocarcinoma. Hum Pathol. 2015;46:1529-39.
7. Widschwendter P, Bauer E, De Gregorio N, et al. Influence of Prognostic Factors on Lymph Node Involvement in Endometrial Cancer: A Single-Center Experience. Int J Gynecol Cancer. 2018;28:1145-52.
8. Amălinei C, Aignătoaei AM, Balan RA, et al. Clinicopathological significance and prognostic value of myoinvasive patterns in endometrial endometrioid carcinoma. Rom J Morphol Embryol. 2018;59:13-22.
9. Cole AJ, Quick CM. Patterns of myoinvasion in endometrial adenocarcinoma: recognition and implications. Adv Anat Pathol. 2013;20:141-7.
10. 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;22:324-33.
11. Euscher E, Fox P, Bassett R, et al. The pattern of myometrial invasion as a predictor of lymph node metastasis or extrauterine disease in low-grade endometrial carcinoma. Am J Surg Pathol. 2013;37:1728-36.
12. Prodromidou A, Vorgias G, Bakogiannis K, Kalinoglou N, Iavazzo C. MELF pattern of myometrial invasion and role in possible endometrial cancer diagnostic pathway: A systematic review of the literature. Eur J Obstet Gynecol Reprod Biol. 2018;230:147-52.
13. Siegel RL, Miller KD, Jemal A. World Health Organization Classification of Tumours Editorial Board. WHO Classification of Tumours. Female Genital Tumours, 5th ed., volume 4, 2020.
14. Soslow RA, Tornos C, Park KJ, et al. Endometrial Carcinoma Diagnosis: Use of FIGO Grading and Genomic Subcategories in Clinical Practice: Recommendations of the International Society of Gynecological Pathologists. Int J Gynecol Pathol. 2019;38 Suppl 1(Iss 1 Suppl 1):S64-S74.
15. Sauerbrei W, Taube SE, McShane LM, Cavenagh MM, Altman DG. Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK): An Abridged Explanation and Elaboration. J Natl Cancer Inst. 2018;110:803-11.
16. Joehlin-Price AS, McHugh KE, Stephens JA, et al. The Microcystic, Elongated, and Fragmented (MELF) Pattern of Invasion: A Single Institution Report of 464 Consecutive FIGO Grade 1 Endometrial Endometrioid Adenocarcinomas. Am J Surg Pathol. 2017;41:49-55.
17. Stewart CJ, Brennan BA, Leung YC, Little L. MELF pattern invasion in endometrial carcinoma: association with low grade, myoinvasive endometrioid tumours, focal mucinous differentiation and vascular invasion. Pathology. 2009;41:454-9.
18. Dogan Altunpulluk M, Kir G, Topal CS, Cetiner H, Gocmen A. 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. J Obstet Gynaecol. 2015;35:397-402.
19. Pavlakis K, Messini I, Vrekoussis T, et al. MELF invasion in endometrial cancer as a risk factor for lymph node metastasis. Histopathology. 2011;58:966-73.
20. Hertel JD, Huettner PC, Pfeifer JD. Lymphovascular space invasion in microcystic elongated and fragmented (MELF)-pattern well-differentiated endometrioid adenocarcinoma is associated with a higher rate of lymph node metastasis. Int J Gynecol Pathol. 2014;33:127-34.
21. Kihara A, Yoshida H, Watanabe R, et al. Clinicopathologic Association and Prognostic Value of Microcystic, Elongated, and Fragmented (MELF) Pattern in Endometrial Endometrioid Carcinoma. Am J Surg Pathol. 2017;41:896-905.
22. Naki MM, Oran G, Tetikkurt SÜ, Sönmez CF, Türkmen İ, Köse F. Microcystic, elongated, and fragmented pattern of invasion in relation to histopathologic and clinical prognostic factors in endometrioid endometrial adenocarcinoma. J Turk Ger Gynecol Assoc. 2017;18:139-42.
23. Espinosa I, Serrat N, Zannoni GF, Rovira R, D'Angelo E, Prat J. Endometrioid endometrial carcinomas with microcystic, elongated, and fragmented (MELF) type of myoinvasion: role of immunohistochemistry in the detection of occult lymph node metastases and their clinical significance. Hum Pathol. 2017;70:6-13.
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. Int J Gynecol Pathol. 2018;37:17-21.
25. Zinovkin DA, Pranjol MZI, Petrenyov DR, Nadyrov EA, Savchenko OG. The Potential Roles of MELF-Pattern, Microvessel Density, and VEGF Expression in Survival of Patients with Endometrioid Endometrial Carcinoma: A Morphometrical and Immunohistochemical Analysis of 100 Cases. J Pathol Transl Med. 2017;51:456-62.
26. Stewart CJ, Little L. Immunophenotypic features of MELF pattern invasion in endometrial adenocarcinoma: evidence for epithelial-mesenchymal transition. Histopathology. 2009;55:91-101.
27. How J, Gotlieb WH, Press JZ, et al. Comparing indocyanine green, technetium, and blue dye for sentinel lymph node mapping in endometrial cancer. Gynecol Oncol. 2015;137:436-42.
28. Vargas R, Rauh-Hain JA, Clemmer J, et al. Tumor size, depth of invasion, and histologic grade as prognostic factors of lymph node involvement in endometrial cancer: a SEER analysis. Gynecol Oncol. 2014;133:216-20.
29. Todo Y, Kato H, Kaneuchi M, Watari H, Takeda M, Sakuragi N. Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. Lancet. 2010;375:1165-72. Erratum in: Lancet. 2010;376:594.