

PATTERNS OF MYOINVASION IN ENDOMETRIOID ADENOCARCINOMA OF ENDOMETRIUM

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ABSTRACT

Objective: To assess the patterns of myoinvasion of endometrial endometrioid adenocarcinoma, their frequencies in our hospital and to correlate these patterns with survival.

Study Design: Retrospective observational study.

Place and Duration of Study: Department of Pathology, Shaukat Khanum Memorial Cancer Hospital & Research Centre, Lahore, from Aug 2019 to Apr 2020.

Methodology: All cases of endometrial endometrioid adenocarcinoma between 2015 and 2017 were retrieved from the archives, independently reviewed by two researchers, all key reporting parameters recorded in addition to the pattern of myoinvasion as per their operational definitions described by Cole and Quick. The follow-up of 3-5 years was obtained from archives and through telephonic contact for outside hospital patients. Disease free survival and relapse-associated mortality were represented through Kaplan-Meier curves.

Results: Eighty cases of myoinvasive endometrial endometrioid adenocarcinoma were reviewed. We found that infiltrating irregular gland pattern was the most frequent in all the age groups. Thirty-five (43.75%) cases showed this type of invasion, followed by broad front pattern 23 (28.75%), Microcystic Elongated and Fragmented (MELF) pattern 15 (18.75%) and adenomyotic pattern 6 (7.5%). One case showed a combination of the last two patterns, whereas adenoma malignum pattern was not seen. Follow-up of these patients showed 8 (10%) patients with relapse related mortality including 5 (62.5%) infiltrating irregular glands, 2 (25%) adenomyosis-like and 1 (12.5%) broad front pattern of myoinvasion. Seventy-two (90%) patients had recurrence free survival.

Conclusion: Frequency of infiltrating irregular pattern of myoinvasion in endometrial endometrioid adenocarcinoma is high and associated with recurrence related mortality. Recognition of these patterns is important as their impact on overall management and prognosis is, however, unknown, and further studies are required to determine the importance of these patterns.

Keywords: Endometrial carcinoma, Lymphovascular invasion, MELF, Myoinvasive pattern.

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INTRODUCTION

Endometrial cancer is the most common cancer of female genital tract, with endometrioid adenocarcinoma of the endometrium the most common type.¹

Approximately 75% of women with endometrial cancer are postmenopausal. Decisions regarding surgical treatment, adjuvant therapy and follow-up of the patient depend on accurate tumor staging and grading.² Traditionally, for this purpose, College of American Pathologists and Royal College of Pathologists have been using tumor type, grade, extent of invasion and lymphovascular invasion in their datasets for reporting cancers.³ Extent of invasion is of critical importance in determining the stage and further treatment. Recently many studies have been conducted on the significance of various invasive morphologies within

the spectrum of endometrioid adenocarcinoma, identifying few of these as adverse prognostic factors.^{4,5} Five different patterns of myoinvasion have been described such as infiltrating irregular glands, broad front, adenoma malignum, adenomyosis like and Microcystic Elongated and Fragmented (MELF) glands. In broad front pattern, potential pitfall is that it may be misinterpreted as non-myoinvasive. Invasion across a broad front may be difficult to distinguish from an irregular endomyometrial interface unless it can be compared to the adjacent uninvolved endomyometrium. MELF merits attention because it is easy to overlook at low magnification yet it may be the only pattern of myoinvasion. It is also associated with lymphovascular invasion and higher probability of nodal metastasis. Awareness of adenoma malignum pattern of myoinvasion is essential from a diagnostic standpoint, because it may be difficult to distinguish from non-invasive cancer in the setting of an undulating endomyometrial

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junction, involvement of stroma-poor adenomyosis or to measure true extent of invasion. These patterns should be recognized to improve staging accuracy, treatment and follow up.⁶⁻⁸

The objective of this study was to assess these patterns of myoinvasion and their frequencies in our hospital and to correlate these patterns with survival.

METHODOLOGY

This retrospective observational study was conducted at the Department of Pathology, Shaukat Khanum Memorial Cancer Hospital & Research Centre, Lahore, from August 2019 to April 2020. With permission from Institutional Review Board (Letter Number EX-04-10-19-01), 80 females were selected through purposive non-probability sampling.

Inclusion Criteria: Patients, who fulfilled the criteria i.e. primary endometrial endometrioid adenocarcinoma, any FIGO grade, any pT stage, hysterectomy and bilateral salpingo-oophorectomy performed between January 2015 to December 2017 were included in the study.

Exclusion Criteria: Patients with diagnosed serous carcinomas, history of metastasis and pre-surgery therapy were excluded from the study.

The follow-up of 3-5 years was obtained from archives and through telephonic contact for outside hospital patients. All cases were retrieved from the archives and independently reviewed by two researchers. Prognostic factors including FIGO grade, myoinvasion, lymphovascular invasion and tumor stage were assessed from pathological reports and reassessed during evaluation for patterns of myoinvasion. Presence of different morphologic patterns of invasion were noted as per their operational definitions described by Cole and Quick.⁸ Infiltrating, irregular glands are individually dispersed glands or groups of 3 or less, have irregular gland contours, widely scattered throughout the endometrium. Broad front or pushing defined as infiltration marked by large swath of neoplastic glands that appear to push into the underlying myometrium with or without desmoplasia. They may appear noninvasive if not carefully assessed. MELF are neoplastic cells and glands that appear MELF admixed with inflammation and represent deepest extent of invasion. Adenomyotic-like Invasion shows groups of invasive endometrioid adenocarcinoma glands (usually 3 or more) that infiltrate the myometrium in irregular islands. Adenoma malignum is composed of regular and round glands, often widely spaced, invade the my-

ometrium with no surrounding desmoplasia response; exceedingly rare and it is deceptively bland and maybe overlooked.

Finally, all the above-mentioned parameters were recorded. pT staging was done according to AJCC guidelines.⁹ Data was entered and analyzed through SPSS version 20. All the qualitative variables like myoinvasion and patterns of myoinvasion were described by using frequency and percentage. Data were stratified for age, FIGO grade and pT stage and Lymphovascular Invasion (LVI). Disease Free Survival (DFS) and relapse-associated mortality were defined and plotted in Kaplan-Meier curves.

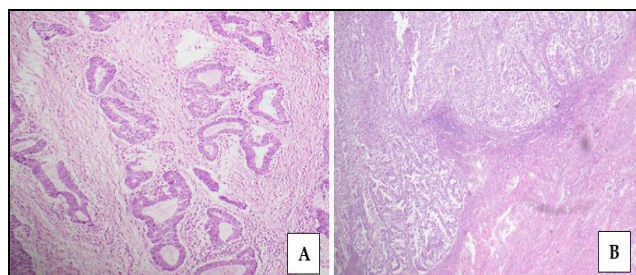
RESULTS

Eighty myoinvasive endometrial endometrioid adenocarcinoma were reviewed. The mean age of the patients was 58.57 ± 9.83 years. Patients in their sixth decade constituted just over half of the study population (n=41) whereas only one patient was younger than 40 years. The frequencies of the patterns of invasion in our cases were as follows (Table-I): infiltrating

Table-I: Distribution of patients by patterns of myoinvasion (n=80).

Patterns of Myoinvasion	n (%)
Infiltrating, Irregular Glands	35 (43.75)
Broad Front/ Pushing	23 (28.75)
Microcystic elongated and fragmented pattern	15 (18.75)
Adenomyotic-like Invasion	6 (7.55)
Adenoma Malignum	-
Adenomyotic-like & Microcystic elongated and fragmented pattern	1 (1.25)

irregular glands pattern 35 (43.75%) (Figure-1A), broad front pattern 23 (28.75%) (Figure-1B), MELF pattern 15 (18.75%) (Figure-1C) and adenomyosis-like pattern 6 (7.5%) (Figure-1D). One case showed a combination of the last two patterns in equal proportion (Figure-1E & 1F), whereas adenoma malignum pattern was not seen in any case. Infiltrating irregular glands pattern was the most frequent in all age groups, histological grades and pT stages except in cases of FIGO grade I and pT1a cancers.



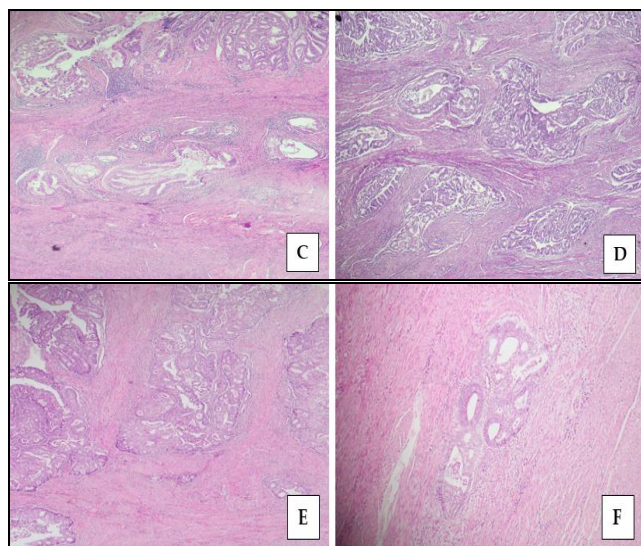


Figure-1(A): Irregular infiltrating irregular glands with no stromal response (B): Broad front myoinvasion (C): Myoinvasion by microcystic elongated glands (MELF) (D): Adenomyosis-like & MELF.

Notably, FIGO grade I and pT1a cancers predominantly showed broad front invasion being 10 (43.4%) and 20 (86.95%) respectively. Lymphovascular invasion was noted in 13 cases (16%) and were mostly limited to cases exhibiting infiltrating irregular glands pattern and MELF pattern (Table-II).

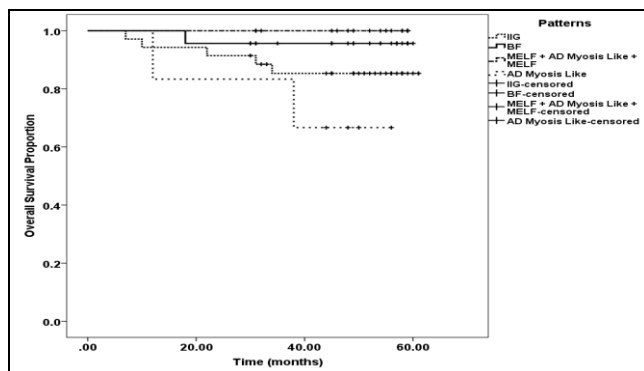
During the follow-up period (35 years), all patients underwent standard hysterectomy with or without bilateral salpingo-oophorectomy. None of them had lymphadenectomy. Thirty four patients (42.5%) received radiotherapy and 19 (33.8%) patients (23.75%) had only surgery. We could not get data of adjuvant therapy in 27 patients. There were 8 (10%) patients who showed relapse related mortality. Among these patients, 5 (62.5%) had infiltrating irregular glands, 2 (25%) had adenomyosis-like and 1 (12.5%) had broad front pattern of myoinvasion. One patient died of an unknown cause. Seventy two (90%) patients had recurrence free survival (Table-III). The disease free-survival rate is shown in Kaplan-Meier curves (Figure-2).

Table-III: Disease free survival based on pattern of myoinvasion.

Patterns of Myoinvasion	No. of Deaths (Relapse Related Mortality)	Disease Free Survival n (%)
Infiltrating irregular glands	5 (14.3)	30 (85.7)
Broad Front	1 (4.3)	22 (95.7)
Microcystic elongated and fragmented pattern + Adenomyosis-like & Microcystic elongated and fragmented pattern	-	16 (100)
Adenomyosis-like	2 (33.3)	4 (66.7)
Overall	8 (10.0)	72 (90)

Table-II: Pathological characteristic of study population.

Variable	Infiltrating Irregular Glands, n=35 (%)	Broad Front n=23 (%)	Microcystic Elongated and Fragmented Pattern (MELF), n=15 (%)	Adenomyosis-Like n=6 (%)	Adenomyosis-like and Microcystic Elongated and Fragmented Pattern, n=1 (%)	p-value
Age (years)						
31-40	1 (2.85)	-	-	-	-	0.001
41-50	6 (17.14)	5 (21.73)	1 (6.67)	2 (33.34)	-	
51-60	18 (51.42)	12 (52.1)	7 (46.67)	3 (50)	1 (100)	
61-70	7 (20)	4 (17.39)	5 (33.34)	-	-	
71-80	3 (8.57)	2 (8.69)	2 (13.34)	1 (16.67)	-	
International Federation of Gynecology and Obstetrics (FIGO) Grade						
Grade-I	8 (22.85)	10 (43.47)	4 (26.66)	4 (66.66)	-	0.030
Grade-II	19 (54.28)	9 (39.13)	11 (73.33)	2 (33.33)	-	
Grade-III	8 (22.85)	4 (17.39)	-	-	1 (100)	
Primary Tumor(pT) Stage						
pT1	28 (80)	20 (86.95)	15 (100)	6 (100)	-	0.303
pT2	3 (8.57)	3 (13.04)	-	-	1 (100)	
pT3	4 (11.2)	-	-	-	-	
pT4	-	-	-	-	-	
Lymphovascular Invasion (LVI)						
Present	5 (14.24)	-	7	-	1 (100)	0.002
Lymphovascular Invasion (LVI)						
Absent	30 (85.71)	23 (100)	8 (22.85)	6 (100)	-	



Log Rank Test *p*-value (0.09)

IIG=Infiltrating irregular glands, BF=Broad front, MELF=Microcystic elongated and fragmented pattern, AD myosis= Adenomyosis-like

Figure-2: Kaplan-Meier curves showing disease free survival of our pattern of myoinvasion.

DISCUSSION

Cole and Quick first described patterns of myoinvasion in endometrial endometrioid adenocarcinoma in 2013.⁸ Recognition of these patterns is linked with adverse prognostic features. In broad front pattern, potential pitfall is that it may be misinterpreted as non-myoinvasive. Moreover, there is a study by Caracuel *et al.* which showed an independent association of broad front pattern with tumor relapse in early stage, low grade EEC.¹⁰ MELF merits attention because it is easy to overlook at low magnification yet it may be the only pattern of myoinvasion present and it is easy to misinterpret as lymphovascular invasion or adenomyosis. It is commonly associated with lympho-vascular invasion and high nodal metastasis.¹¹ Adenoma malignum pattern of myoinvasion merits awareness from a diagnostic standpoint because it may be difficult to distinguish may lead to more accurate staging, but perhaps more importantly, some patterns may be associated from non-invasive cancer in the setting of an undulating endomyometrial junction, to distinguish from involvement of stroma-poor adenomyosis or to measure true depth of invasion.^{12,13}

In our study, the most common pattern was of infiltrative irregular glands pattern of myoinvasion i.e. 43.75%. In a study by Price *et al.*, observed infiltrative invasion pattern in 47.8%, MELF in 12.9%, pushing borders of invasion in 2.8%, adenomyosis-like invasion in 1.1% and adenoma malignum-like invasion in 0.2% patients with endometrioid adenocarcinomas.¹⁴ We found this pattern in all age groups, FIGO grade I/II cancers and pT stages except pT1a. Lymphovascular invasion (LVI) was found in 5/35 cases. On follow-up, this pattern showed 85.7% overall survival rate and 5 (62.5%) disease related deaths. Similarly, Park *et al.*, and

his colleagues also showed an association between this pattern and disease recurrence, however, their series included grade III high-staged tumors.¹⁵

The second common pattern of invasion in our study was broad front pattern, seen in 28.75% cases (Table-I), common in the age group of 51-60 years. In a study conducted by Quick *et al.*, broad front pattern was seen in 21% of the tumors.¹⁶ This pattern was more commonly observed in low-grade low-stage tumors (43.47% in FIGO grade I & 86.95% in pT1 stage) and no LVI observed. Our 3-5 year follow up study depicted a very good disease free survival rate of 95.7% and only 1 (12.5%) had disease related death. On the contrary, Caracuel and his colleagues found significant tumor relapse associated with this pattern of myoinvasion in early stage.¹⁰

MELF pattern of invasion was seen in 15 patients (18.75%) and 1 case showed mixed adenomyosis-like and MELF patterns in equal proportions, whereas, larger cases are also reported in many other studies including a study by Espinosa *et al.*, (43% MELF pattern) 17 and a study by Hertel *et al.*, (36% MELF cases).¹⁸ This pattern commonly shows lymphovascular invasion and lymph node metastasis.¹⁹ Not only this, MELF pattern has also been reported with extrauterine disease.²⁰ We observed LVI in 7 out of 15 of our MELF cases. Despite its association with LVI that is considered bad prognostic factor, interestingly, we found 100% survival rate in this pattern as well as the combined pattern with adenomyosis-like. No disease-relapse was identified (Figure-6). Similarly, Kihara *et al.* also demonstrated no significant worsening of prognosis with MELF pattern.²¹

In our study, we described that apart from MELF association with LVI, it has no worse impact on outcome. Likewise, broadfront pattern of invasion also showed good disease-free survival rate. As a result, the on the other side, our strength included strict morphological criteria used to determine frequencies of patterns of myoinvasion and positive impact of some patterns in our setup. Hence, further studies should be done to work on the importance of myoinvasion patterns and its outcome.

LIMITATION OF STUDY

There were, however, many limitations acknowledged in this study including relative low number of tumor relapses, different surgical protocols used by different surgeons, non-availability of adjuvant therapy and patients lost on follow-ups.

CONCLUSION

This study concluded that frequency of infiltrating irregular pattern of myoinvasion in endometrial endometrioid adenocarci-

noma is high among patients in our study group and has association with recurrence related mortality. Some of the patterns of myoinvasion are associated with good outcome despite the lymphovascular invasion. Identification of each pattern promotes understanding of the unique challenges associated with each, especially with regard to assessing for depth of invasion, extent of tumor spread, lymphovascular invasion and nodal involvement.

Conflict of Interest: None.

Authors' Contribution

MS: Acquisition of data, interpretation of results and writing, SM: Concept, design, review of the case and proof reading, NA: Review of the cases, interpretation and proof reading, UH: Proof reading, IAR: Proof reading, RM: Proof reading, concept and writing.

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