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► **To cite this version:**

Kitty Pavlakis, Irimi Messini, Theodoros Panoskaltsis, Thomas Vrekoussis, Dimitris Chrysanthakis, et al.. MELF invasion in endometrial cancer as a risk factor for lymph node metastasis.. *Histopathology*, 2011, 58 (5), pp.739. 10.1111/j.1365-2559.2011.03801.x . hal-00626293

HAL Id: hal-00626293

<https://hal.science/hal-00626293>

Submitted on 25 Sep 2011

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MELF invasion in endometrial cancer as a risk factor for lymph node metastasis.

Journal:	<i>Histopathology</i>
Manuscript ID:	HISTOP-03-10-0175.R2
Wiley - Manuscript type:	Original Article
Date Submitted by the Author:	09-Jul-2010
Complete List of Authors:	Pavlakis, Kitty; "IASO" Women's Hospital, Pathology MESSINI, IRINI; "IASO" Women's Hospital, Pathology Panoskaltzis, Theodoros; "IASO" Women's Hospital, Gynecological Oncology Vrekoussis, Thomas; University of Crete, Pathology Chrysanthakis, Dimitris; "IASO" Women's Hospital, Pathology Yiannou, Petros; "IASO" Women's Hospital, Pathology Voulgaris, Zannis; Alexandra Hospital, National and Kapodistrian University, Gynecological Oncology
Keywords:	endometrioid endometrial carcinoma,, MELF pattern invasion, lymph node metastasis



1 **MELF invasion in endometrial cancer as a risk factor for**
2 **lymph node metastasis.**

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21 **Abstract**

22 **Aim:** To investigate whether the microcystic, elongated and fragmented (MELF) pattern
23 of myometrial invasion encountered in certain endometrioid endometrial carcinomas can
24 be considered as a risk factor for lymph node metastasis.

25 **Materials and Methods:** 351 cases of total abdominal hysterectomy and bilateral
26 salpingo-oophorectomy with/without lymphadenectomy or lymph node sampling,
27 performed for endometrioid endometrial adenocarcinoma were enrolled in the study. The
28 existence of MELF invasion, vascular invasion, fibromyxoid stromal reaction and lymph
29 node metastasis were recorded. Immunohistochemistry for endothelial and epithelial
30 markers was performed on selected cases.

31 **Results:** MELF invasion was identified in 20 (10.81%) and 13 cases (13.13%) treated
32 without and with lymphadenectomy respectively. All of these cases were either well or
33 moderately differentiated carcinomas, stage IA to II (without considering lymph node
34 status). Positive lymph nodes were detected in 7/13 MELF positive (53.84%) and in 6/86
35 MELF negative cases (6.97%) This observation was statistically significant. Out of the 7
36 MELF positive tumours with lymph node metastasis, 3 cases exhibited intravascular
37 tumour emboli while 4 showed a fibromyxoid stromal reaction.

38 **Conclusion:** MELF pattern invasion was found to be statistically related to lymph node
39 metastasis. Nevertheless, further studies are needed in order to evaluate the clinical
40 significance of this observation.

41 **Key words:** endometrioid endometrial carcinoma, MELF pattern invasion, lymph node
42 metastasis.

43 **Introduction**

44 The standard surgical treatment for endometrioid endometrial adenocarcinoma remains
45 the total abdominal hysterectomy with bilateral salpingo-oophorectomy, whereas there is
46 controversy concerning the indications for and the type of lymphadenectomy that should
47 be performed (pelvic and/or para-aortic, systematic or selective)^(1, 2). Several studies have
48 focused on the benefit of lymphadenectomy for patients with Stage IA (former FIGO
49 1B), grade 1 or 2 endometrial carcinomas. The results of these studies revealed no
50 survival benefit for the women enrolled in the lymphadenectomy group as opposed to
51 those without lymphadenectomy^(3, 4, 5). Moreover, this group of patients is considered at
52 low risk for having positive lymph-nodes, since the risk of pelvic recurrences has been
53 found to range from 0-2%⁽⁶⁾.

54 Since lymphadenectomy prolongs the operation time with potential short-term and long-
55 term side effects, several authors conclude that lymphadenectomy in Stage IA
56 endometrial carcinoma should only be performed in patients with adenosquamous, serous
57 or clear cell carcinoma and grade 3 tumours of any histological type⁽⁷⁾. For those patients
58 in whom additional risk factors are revealed in the hysterectomy material, such as deep
59 myometrial invasion or presence of lymph-vascular tumour emboli, an additional pelvic
60 radiotherapy is recommended⁽⁸⁾.

61 Recently, a distinctive pattern of myometrial invasion has been described under the
62 “MELF” acronym⁽⁹⁾. This microcystic, elongated and fragmented (MELF), pattern of
63 myometrial invasion has been reported in a small series of three cases to be associated
64 with a histiocyte-like pattern of lymph node metastasis⁽¹⁰⁾.

65 The aim of the present study was to investigate in a large retrospective analysis of
66 endometrioid endometrial carcinomas treated with total abdominal hysterectomy,

67 bilateral salpingo-oophorectomy and sampling or systematic pelvic, with or without para-
68 aortic lymph-node dissection, whether the MELF pattern of myometrial invasion is
69 related to an increased occurrence of lymph node metastasis and as such, could be
70 considered as an additional risk factor for advanced stage disease.

71 **Materials and Methods**

72 Three hundred and fifty one (351) consecutive unselected cases of endometrioid
73 endometrial adenocarcinoma operated between Jan. 1998, and Dec. 2009 were retrieved
74 from the files of the Pathology Department of “IASO” Women’s Hospital. Out of these
75 cases, only 238 (Group A) had been treated by total abdominal hysterectomy (TAH) and
76 bilateral salpingo-oophorectomy (BSO), while in 113 cases (Group B) lymph node
77 sampling or systematic pelvic lymphadenectomy with or without para-aortic lymph node
78 sampling had also been performed. In 53 Group A cases and 14 Group B cases the
79 carcinoma was confined to the endometrium, thereafter they were not enrolled in the
80 study. All cases were classified according to FIGO 2009 staging system ⁽¹¹⁾. **The last**
81 **three cases, operated in November 2009 were not included in the study, since they**
82 **represented intraendometrial carcinomas. Thereafter, survival and recurrence status were**
83 checked on October 2009.

84 The haematoxylin and eosin stained slides of each hysterectomy and lymphadenectomy
85 specimen were reviewed by two different pathologists of the team (I.M and D.C). The
86 presence or absence of MELF pattern invasion, vascular space (either lymphatic or blood
87 vessel) invasion and fibromyxoid stromal reaction was recorded. Moreover, the
88 morphology of lymph node metastasis, if present, either as a typical gland-forming
89 adenocarcinoma or as individual intranodal neoplastic cells was evaluated.

90 Immunohistochemical staining with the endothelial marker CD31 for the identification of
91 tumour emboli was performed on all sections from the myoinvasive tumour in all MELF
92 cases, while only selected sections exhibiting morphologic features suggestive of vascular
93 space invasion were immunostained in some MELF negative tumours.
94 Immunohistochemistry with cytokeratin AE1/AE3 for the search of metastatic neoplastic
95 cells was performed in all negative lymph nodes.

96 *Immunohistochemistry*

97 Immunohistochemistry was performed using the avidin-biotin complex method. Briefly,
98 after dehydration in xylol and graded alcohol, sections were exposed to 3% H₂O₂ for 15
99 min. After retreatment in a microwave for 15 min, the tissue sections were incubated with
100 the primary antibodies against CD31 (clone JC/70A, Dako Corp) and AE1/AE3 (Dako)
101 with 1:40 and 1:100 dilution respectively, at 4⁰C. After overnight incubation, the slides
102 were treated with biotinylated antimouse IgG as secondary antibody. Reaction was
103 visualized using an avidin-biotin-peroxidase complex with 3,3' Diaminobenzidine (DAB,
104 Sigma Chemical Comp.) as a chromogen. Counterstaining was performed with Harris
105 Haematoxylin. The vascular endothelium and sections from the uterine tumour were used
106 as positive controls. Negative controls were obtained by omitting the primary antibody.

107 *Statistical analysis*

108 To discriminate significant differences between categorical variables the Fisher exact test
109 was used. To examine whether the presence of MELF pattern invasion, of tumour emboli
110 or of a fibromyxoid stromal reaction could act as a predictive factor for lymph node
111 metastasis, the logistic regression analysis was applied. Any observation when $p < 0.05$

112 was considered as statistically significant. Statistical analysis was applied on the results
113 of group B.

114 **Results**

115 Out of the two hundred and eighty four (284)) cases of endometrioid endometrial
116 carcinomas (185 group A cases and 99 group B cases) that were finally enrolled in the
117 study, MELF pattern invasion was identified in 20/185 group A (10.81%) and in 13/99
118 group B cases (13.13%). All of these cases were either well or moderately differentiated
119 carcinomas, stage IA to II (without considering lymph node status). The myoinvasive
120 MELF glands were typically forming microcysts or elongated structures lined by cells
121 with conspicuous eosinophilic cytoplasm, while clusters of detached cells were also
122 identified (Fig 1).

123 In group B, positive lymph nodes were detected in 7/13 MELF positive cases (53.84%)
124 and in 6/86 MELF negative cases (6.97%). This observation was statistically significant
125 (Fisher exact test, $p = 0.00014$). The pattern of metastasis was either in the form of
126 isolated, discohesive cells or in the form of small pseudopapillary cell clusters that were
127 identified mostly within the subcapsular and interfollicular sinuses (Fig 2).

128 Additionally, positive lymph nodes were detected in 8/20 cases (40%) and in 5/79 cases
129 (6.32%) with and without tumour emboli respectively, as well as in 6/29 cases (20.68%)
130 and in 7/70 cases (10%) with or without fibromyxoid stromal reaction. The former of
131 these observations was statistically significant (Fisher exact test, $p = 0.0005$) while the
132 latter was not (Fisher exact test, $p=0.1352$). The clinicopathological features of all cases
133 are summarized in Table 1.

134 In 7 out of the 20 MELF positive cases belonging to group A, lymph vascular space
135 invasion was identified, while 8 cases presented a fibromyxoid stromal reaction. Out of
136 the 7 MELF positive tumours with lymph node metastasis (group B), 3 cases exhibited
137 intravascular tumour emboli while 4 showed a fibromyxoid stromal reaction.

138 In both groups, all but one of the MELF positive patients with final stage 1A disease
139 received no further therapy. The remaining patient had a concurrent ovarian carcinoma.
140 She was treated with radio and chemotherapy but died five years later from her ovarian
141 cancer. All other patients had been treated either with radiotherapy alone or with radio
142 and chemotherapy. Five of the patients were lost from follow up (Table 2).

143 Logistic regression analysis, performed on group B, revealed that there is a significantly
144 increased possibility for an endometrial cancer to be lymph node positive when MELF
145 pattern invasion [OR=15.55 / $p < 0.001$, 95% C.I. (3.88-62.29)] is present, compared to
146 cases where MELF is absent. Additionally, there is an increased possibility for lymph
147 node metastasis when tumour emboli are present [OR=9.86 / $p < 0.001$, 95% C.I. (2.71-
148 35.81)], as opposed to cases without tumour emboli. On the other hand, the presence of a
149 fibromyxoid stromal reaction was not found to be a predictor of lymph node metastasis
150 [OR=2.34/ $p=0.1662$,95% C.I.(0.43-12.64)].

151 Discussion

152 The acronym "MELF" (microcystic, elongated, fragmented) has been recently attributed
153 to an unusual glandular change of myoinvasive endometrioid carcinoma glands,
154 characterized by the formation of microcysts lined by cells with conspicuous eosinophilic
155 cytoplasm, elongated structures and clusters of detached cells occasionally associated
156 with retraction artifact⁽⁹⁾. Although it was initially thought that these changes represented

157 a degenerative process, several studies have suggested that MELF changes might
158 represent a specific tumour-stromal reaction similar to epithelial-mesenchymal
159 interactions observed in other tumours^(12, 13, 14). In that context, MELF pattern of invasion
160 could be considered as an active rather than a degenerative cellular process.

161 The distinct glandular changes that characterize MELF are often associated with a
162 fibromyxoid stromal reaction. In a univariate analysis, the presence of a fibromyxoid
163 stromal reaction has been found to be associated with an adverse effect on the prognosis
164 of endometrioid carcinomas⁽⁹⁾. One could speculate that this particular stroma represents
165 a “milieu” of decreased resistance favoring the dissemination of neoplastic cells. A
166 similar explanation has been attributed to vulvar squamous cell carcinomas featuring a
167 prominent fibromyxoid stromal response and an aggressive clinical behavior⁽¹⁵⁾.

168 In the present study, MELF pattern invasion was found only in well or moderately
169 differentiated endometrioid endometrial adenocarcinomas, as already mentioned in
170 previous reports^(9,13), and was usually but not always associated with a fibromyxoid
171 stroma or with vascular space invasion. Nevertheless, to our knowledge, the relation of
172 MELF pattern invasion and the probability of lymph node metastasis have never been
173 studied before.

174 Our results indicate that, when MELF pattern invasion is encountered in an endometrioid
175 endometrial carcinoma, there is a statistically significant chance of concurrent lymph
176 node metastasis. Most probably, as seen in the present study, this occurrence is at least in
177 part related to the great frequency of concurrent lymph vascular space invasion or, to a
178 lesser extent to the observed fibromyxoid stromal reaction. The above finding is
179 consistent with the results of other investigators who reported an adverse effect on

180 prognosis and a high risk of recurrence in cases of endometrioid endometrial carcinomas
181 characterized by a fibromyxoid stroma or by vascular space invasion respectively ^(9, 16, 17).
182 The morphological and molecular characteristics of the neoplastic cells in areas of MELF
183 pattern of invasion, characterized by discohesiveness and by a loss, on
184 immunohistochemistry, of the cell adhesion molecule e-cadherin, as reported by other
185 investigators ⁽¹⁴⁾, could probably be considered as factors leading to an increased
186 infiltrative ability of these cells and to an enhancement of their metastatic potential.
187 Of most importance was the constantly observed pattern of lymph node metastasis. It was
188 either in the form of isolated, discohesive cells or in the form of small pseudopapillary
189 cell clusters that were identified mostly within the subcapsular and interfollicular sinuses.
190 In both conditions the cells were of large size, with abundant eosinophilic cytoplasm and
191 large nuclei while occasionally some intracytoplasmic vacuoles were identified. These
192 morphological features are the same as the ones encountered in the myoinvasive MELF
193 pattern. The above neoplastic cells might be confused with sinusoidal histiocytes or with
194 serous epithelial non-invasive lymph node “implants” respectively. Characteristically, in
195 one of our cases, the scattered neoplastic cells were identified only after the performance
196 of immunohistochemistry with the antibody AE1/AE3. The respective lymph node was
197 initially considered as being free of metastasis.
198 Our results are in agreement with those of McKenney et al ⁽¹⁰⁾ who first reported this
199 subtle pattern of lymph node metastasis. They stated that although the main tumour was a
200 gland-forming adenocarcinoma, the metastatic cells had similar morphological features
201 with the cells observed in areas of MELF pattern invasion. Nevertheless, it seems that on
202 rare occasions, this pattern of lymph node metastasis can also be encountered in

203 conventionally myoinvasive endometrial adenocarcinomas. In one of our cases, both
204 gland forming and scattered or small pseudopapillary metastatic foci were identified in
205 some pelvic and one paraaortic lymph node.

206 In conclusion, MELF pattern invasion was found to be statistically related to lymph node
207 metastasis. Such a distinct myoinvasive pattern should prompt the pathologist to search
208 for vascular space invasion by performing more sections from the myoinvasive tumour
209 and/or immunohistochemistry for endothelial markers. Nevertheless, the clinical
210 significance of this observation is not elucidated. As shown in the present study, MELF
211 invasion did not worsen the prognosis of the patients since none recurred or died from the
212 disease. This result is in agreement with Murray et al ⁽⁹⁾ who reported that MELF pattern
213 invasion alone did not correlate with an adverse outcome. Yet, in our study, most MELF
214 cases belonging to group A and all MELF cases with positive lymph nodes (group B) had
215 received adjuvant treatment since they were intermediate and high stage/risk tumours
216 (>1A). The therapeutic procedure might have obscured the natural history of the disease.
217 For all stage 1A MELF cases belonging to group A who did well without further therapy,
218 no solid conclusion can be drawn. These patients might have been lymph node negative.
219 On the other hand, the pattern of lymph node metastasis in several MELF cases is in the
220 form of isolated tumour cells/micrometastasis, whose prognostic significance, to our
221 knowledge, has not been thoroughly studied in endometrial carcinomas.

222 Further studies with larger series of cases are needed in order to decide whether MELF
223 pattern invasion should be considered as a risk factor for higher stage disease.
224 Endometrioid endometrial carcinomas treated with TAH and BSO with
225 lymphadenectomy/lymph node sampling, when featuring MELF pattern invasion should

226 be very carefully examined in order to exclude the presence of lymph node metastasis in
227 the form of isolated tumour cells. In that context, performing immunohistochemistry with
228 cytokeratin AE1/AE3 should be considered as a routine diagnostic procedure. However,
229 as already stated, clinical studies are required in order to determine the significance of
230 such isolated tumour cells/micrometastasis in MELF cases.

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285 Figures legends

286 Figure 1: A, C and E. Morphology of MELF pattern invasion (H&E, CD31 and AE1/AE3
287 respectively, X 100). B, D and F. Lymph vascular space invasion (H&E, CD31 and
288 AE1/AE3 respectively, X 200).

289 Figure 2:A. Isolated tumor cells of large size and eosinophilic cytoplasm are infiltrating a
290 lymph node (H&E X 100). B. The neoplastic cells are highlighted with keratin
291 AE1/AE3 (X100).

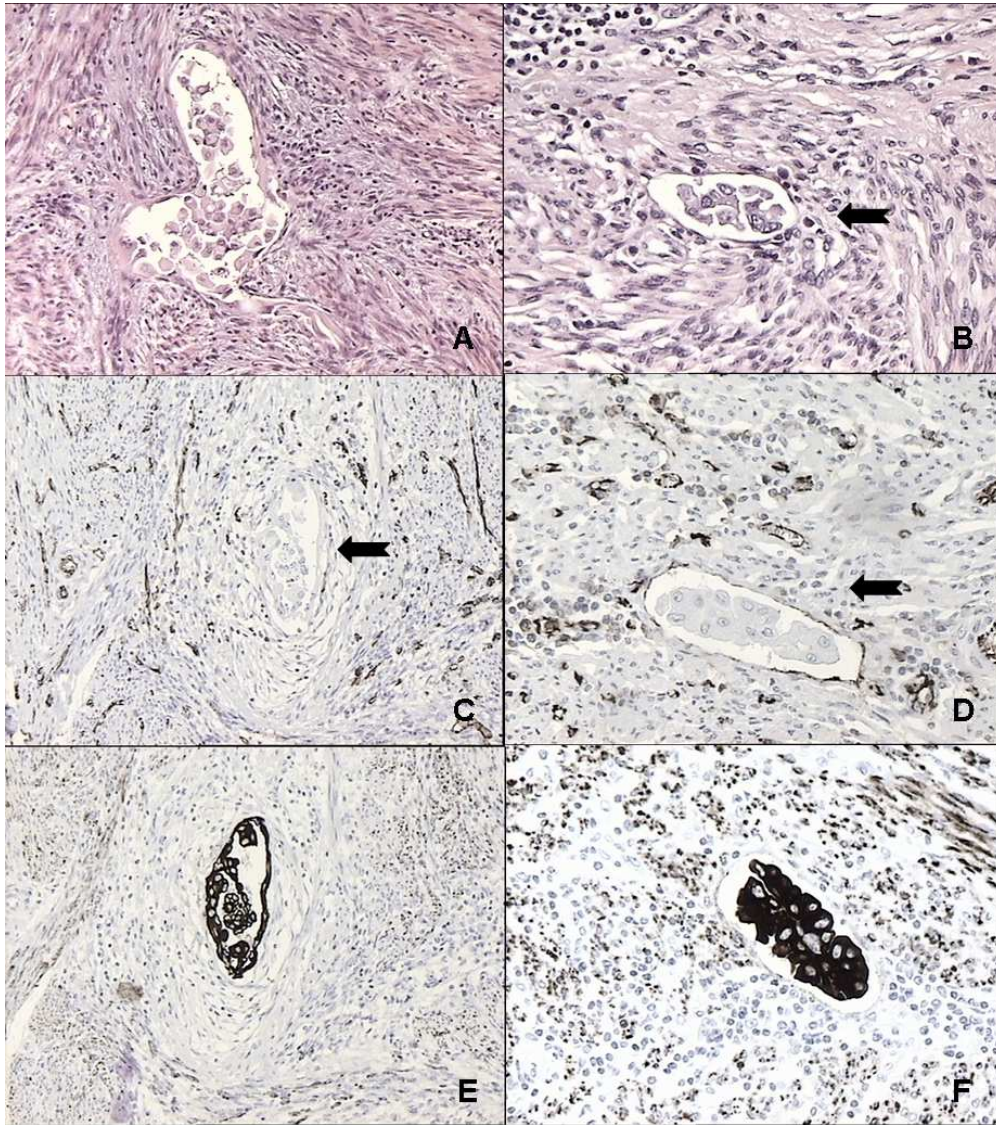
Table 1 Clinicopathological feature of the cases that were enrolled in the study.

Clinicopathological features	Group A (%) n=185	Group B (%) n=99		
		LN (-)	LN (+)	Total
Grade				
1	80 (43,2)	43	2	45 (45.5)
2	74 (40)	28	7	35 (35.3)
3	31 (16,8)	15	4	19 (19.2)
Stage				
IA	113 (61,1)	55	-	55 (55,6)
IB	57 (30,8)	14	-	14 (14,1)
II	9 (4,9)	14	-	14 (14,1)
IIIA	6 (3,2)	3	-	3 (3,0)
IIIC1	N/A	-	11	11 (11,1)
IIIC2	N/A	-	2	2 (2,0)
M.E.L.F				
Yes	20 (10,8)	6	7	13 (13,1)
No	165 (89,2)	80	6	86 (86,9)
Vascular space invasion				
Yes	18 (9,7)	12	8	20 (20,2)
No	167 (90,3)	74	5	79 (79,8)
Fibromyxoid stromal reaction				
Yes	11 (5,9)	23	6	29 (29,3)
No	174 (94,1)	63	7	70 (70,7)

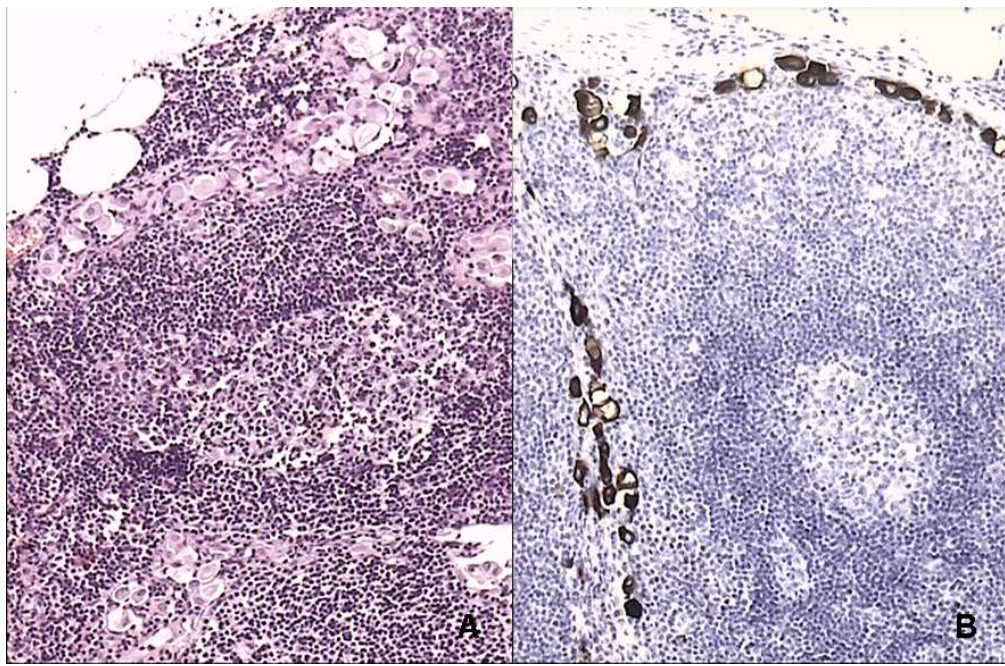
Table 2. Clinicopathologic features of all MELF positive cases

<i>Case No</i>	<i>Grade</i>	<i>Stage</i>	<i>Lymph node metastasis</i>	<i>Vascular space invasion</i>	<i>Fibromyxoid Stromal reaction</i>	<i>Adjuvant treatment</i>	<i>Outcome</i>
Group A							
1	1	IB	N / A	+	+	R	Alive
2	2	IA	N / A	-	-	R & C	Dead ¹
3	1	IA	N / A	-	+	No	Alive
4	2	IB	N / A	+	-	R	Lost from FU
5	1	IB	N / A	-	-	R	Alive
6	1	IA	N / A	-	+	No	Alive
7	1	IB	N / A	+	+	R	Alive
8	2	IA	N / A	-	-	No	Alive
9	2	IA	N / A	-	-	No	Alive
10	2	IA	N / A	-	-	No	Alive
11	2	IB	N / A	+	+	R	Alive
12	2	IB	N / A	+	-	R	Lost from FU
13	1	IA	N / A	-	+	No	Alive
14	2	IB	N / A	+	-	R	Alive
15	1	IB	N / A	-	-	R	Alive
16	1	IB	N / A	-	+	R	Lost from FU
17	1	IA	N / A	-	-	No	Alive
18	2	IA	N / A	-	-	No	Alive
19	2	IA	N / A	-	-	No	Alive
20	2	IB	N / A	+	+	R	Alive
Group B							
1	2	IA ² /IIIC2	+	-	+	R & C	alive
2	2	IA ² /IIIC1	+	-	-	R & C	alive
3	2	IB	-	-	+	R	alive
4	1	IA	-	-	+	No	alive
5	1	II	-	-	+	R	Lost from FU
6	1	IA	-	-	-	No	alive
7	1	IA ² /IIIC1	+	-	-	R	alive
8	2	II ² /IIIC1	+	+	+	R & C	alive
9	2	II ² /IIIC1	+	+	+	R & C	alive
10	2	IA ² /IIIC1	+	-	-	R	Lost from FU
11	1	IB	-	-	+	R	alive
12	1	IA	-	-	-	No	alive
13	1	IA ² /IIIC1	+	+	+	R	alive

¹ died but not from the disease, ² stage without considering lymph node status, R: Radiotherapy, C: Chemotherapy



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Review

To: Histopathology,
Editorial-Production Office
Maura MacDonald

Dear Sirs

I am sending you our manuscript entitled "MELF invasion in endometrial cancer as a risk factor for lymph node metastasis", by Kitty Pavlakis, MD, Iriini Messini, Thomas Vrekoussis, Theodoros Panoskaltsis, Dimitris Chrysanthakis, Petros Yiannou, and Zannis Voulgaris.

We would like it to be considered for publication in Histopathology. The work is original and has not been and will not be published, in part or in whole, in any other journal. All authors have agreed to the contents of the manuscript in its submitted form and declare that they have no conflicts of interest for it.

Thank you in advance for considering our work,

Sincerely
Iriini Messini, MD.