

1 Preoperative risk stratification of endometrial carcinoma: L1 cell  
2 adhesion molecule as a biomarker

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5 **Objective:** Pre- or intraoperative risk assessment models are used to stratify patients with  
6 endometrial carcinoma to lymphadenectomy. Our aim was to determine whether  
7 preoperative analysis of L1 cell adhesion molecule (L1CAM) can improve risk assessment.

8 **Methods:** Immunohistochemical L1CAM staining was performed on endometrial biopsies of  
9 241 patients and paired hysterectomy samples of 75 patients. Risk assessment models based  
10 on preoperative histological type and grade, myometrial invasion and/or tumor diameter and  
11 alternative models incorporating preoperative L1CAM were compared with regard to their  
12 capability of predicting lymph nodal or distant metastasis. Soluble L1 levels were measured  
13 by ELISA in serum samples of 40 patients with endometrial carcinoma.

14 **Results:** The concordance rate between L1CAM staining results of preoperative and  
15 hysterectomy samples was moderate (kappa 0.586,  $P < 0.0001$ ). Preoperative L1CAM  
16 expression was associated with non-endometrioid histology, lymph node involvement,  
17 advanced stage and positive peritoneal cytology. Receiver operating characteristic (ROC)  
18 analyses showed that L1CAM did not significantly improve risk stratification algorithms  
19 based on traditional risk factors. Intraoperative tumor diameter was an effective surrogate  
20 for myometrial invasion. There was no statistical difference between L1 serum levels of  
21 patients with a L1CAM-positive or L1CAM-negative endometrial carcinoma ( $P = 0.786$ ).

22 **Conclusions:** L1CAM expression in endometrial biopsy correlates with high risk features of  
23 endometrial carcinoma but does not significantly improve risk stratification algorithms based  
24 on traditional factors. Soluble L1 detected in the serum of patients with endometrial  
25 carcinoma does not correlate with tumoral L1CAM expression.

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29 **Keywords** endometrial cancer, risk stratification, lymphadenectomy, L1CAM, soluble L1CAM

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## 31 **Introduction**

32 The standard primary treatment of endometrial carcinoma consists of surgery with total  
33 hysterectomy and bilateral salpingo-oophorectomy, complemented with pelvic and para-aortic  
34 lymphadenectomy in selected cases [1]. There is no compelling evidence that lymphadenectomy as  
35 such is therapeutically beneficial and its main motivation is to more accurately stage and stratify  
36 patients to postoperative adjuvant therapy. However, extensive surgery may cause morbidity and  
37 the rate of unnecessary treatment should be minimized [2]. At most institutions the decision on  
38 lymphadenectomy is made pre- or intraoperatively based on features of the primary tumor,  
39 including histologic type, grade of differentiation, and depth of myometrial invasion, as evaluated  
40 by preoperative histology, frozen section analysis and imaging.

41 The most validated algorithm (so called Mayo criteria, [3]) defines low risk endometrial carcinoma  
42 as endometrioid G1-2 carcinoma with tumor diameter  $\leq 2$  cm and myometrial invasion  $\leq 50\%$ .  
43 When this algorithm is applied, approximately 30% of the patients fall into the category of low risk  
44 for lymphatic dissemination and may avoid lymphadenectomy [4,5]. The remaining 70% of the  
45 patients should undergo lymphadenectomy, yet only 19-22% of them present with lymph node  
46 metastases [4,5]. More recently a risk stratification model was presented, according to which over  
47 40% of the patients could be spared lymphadenectomy with a false positive rate of 57.2% and false  
48 negative rate of 0% [6]. This model is based on tumor grade (G1-2 vs G3), diameter (50-mm cut-  
49 off) and depth of myometrial invasion (MI, three-tiered). A major difficulty related to these  
50 algorithms is the often inaccurate assessment of myometrial invasion by preoperative imaging or  
51 gross visualization [7-9]. Frozen section diagnosis is not readily available in many institutions [10]  
52 and various investigators question its accuracy [11-13]. Intraoperatively assessed tumor diameter  
53 has been proposed as a surrogate for myometrial invasion [6,14,15]

54 Current risk assessment algorithms are burdened with a high frequency of presumably unnecessary  
55 lymphadenectomies. To overcome this problem, attention has been paid to the potential value of  
56 molecular markers (such as ER/PR status in predicting lymph node involvement [16]).  
57 Nevertheless, molecular markers do not have an established role in this setting nor have they been  
58 integrated in randomized clinical trials of surgical therapies.

59 A promising prognostic marker, L1 cell adhesion molecule (L1CAM, CD171) predicts disease  
60 progression and poor prognosis in many types of cancer including endometrial carcinoma [17-23].  
61 The association between L1CAM expression and lymph node involvement of endometrial  
62 carcinoma suggests that L1CAM could be a useful biomarker for stratifying patients to  
63 lymphadenectomy [21-23]. Also, a soluble form of L1CAM (sL1) exists and has been detected in  
64 the serum and ascites of patients carrying a tumor expressing this antigen [17,24-26].

65 Based on the association of L1CAM expression with lymphatic dissemination in endometrial  
66 carcinoma, we wanted to evaluate the power of L1CAM in algorithms aimed at stratifying patients  
67 to lymph node dissection. To further clarify the potentiality of L1CAM as a biomarker, we  
68 compared serum L1CAM concentrations in patients with negative and positive L1CAM expression  
69 in tumor sections.

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## 72 **Material and methods**

73 Patients who underwent primary surgical treatment for endometrial carcinoma at the Department of  
74 Obstetrics and Gynecology, Helsinki University Hospital, between January 1, 2007 and December  
75 31, 2009 were identified. Patients with a preoperative endometrial sample available for L1CAM  
76 analysis were included in the study (n = 241). Approvals of the Institutional Review Board and the  
77 National Authority for Medicolegal Affairs of Finland were obtained. During 2007-09, according to

78 the treatment guidelines of our hospital, bilateral pelvic lymphadenectomy was performed in patients  
79 with grade 1-2 endometrioid carcinoma with <50% myometrial invasion, the depth of invasion being  
80 assessed by vaginal ultrasound and gross visual inspection. In other patients, both pelvic and para-  
81 aortic lymphadenectomies were performed. There was some variation in practice patterns because the  
82 decision to perform lymphadenectomy and the extent of the procedure depended on patient age and  
83 surgical risks. Total rate of lymphadenectomy was 79.7 %. Pertinent patient characteristics and  
84 surgical data are shown in Table 1.

85 Factors selected for statistical analyses were: preoperative L1CAM expression, FIGO  
86 2009 stage [27], lymph node involvement, histologic type (endometrioid/non-endometrioid), grade  
87 of differentiation, depth of myometrial invasion, tumor diameter, cervical stromal invasion, peritoneal  
88 cytology status, patient age at surgery, and body mass index (BMI). The cut off values for the numeric  
89 variables ( $\geq 50\%$  and  $>33\%$  for myometrial invasion, 2cm and 5 cm for tumor diameter, 65 years for  
90 age, 30 kg/m<sup>2</sup> for BMI) were based on earlier reports [6,28-30]. Tumor size was measured  
91 intraoperatively by the surgeon or after formaldehyde fixation by the pathologist. Primary tumor  
92 diameter was defined as the largest dimension of the tumor. If more than 1 lesion was present, the  
93 lesion with the largest diameter was considered. Primary tumor diameter was unknown in 14 patients.  
94 The presence of cervical stromal invasion was unknown in 2 patients. Peritoneal cytology was  
95 considered positive if adenocarcinoma cells were detected in the peritoneal washing, regardless of  
96 the number of cancer cells. One case that was positive due to a concomitant borderline serous ovarian  
97 tumor was considered negative for endometrial cancer. Peritoneal cytology status was unknown in 4  
98 patients.

99 Preoperative L1CAM staining was assessed in tissue samples obtained by uterine aspiration biopsy  
100 or curettage. Uterine biopsy was the primary (>90%) sampling method. Uterine curettage was  
101 performed when biopsy was insufficient for diagnosis or failed due to cervical stenosis. For  
102 immunohistochemical stainings, slides were stained with Ventana Benchmark XT automated slide

103 preparation system (Ventana Medical Systems, Inc., USA) or with Autostainer LV1 (Lab Vision  
104 Corporation, USA). Briefly, slides were deparaffinized and heat-induced epitope retrieval was  
105 performed following standard protocol. Tissue sections were incubated with primary monoclonal  
106 antibodies against L1CAM (CD171; clone 14.10, catalog number SIG-3911-1000, Covance Inc., NJ,  
107 USA). The antibody binding site was visualized using a DAB Detection Kit. Sections were  
108 counterstained with Mayer's hematoxylin, dehydrated, cleared in xylene, and mounted. L1CAM  
109 positivity was defined as >10% of the carcinoma cells staining in one representative slide evaluated  
110 by a pathologist (Supplementary figure 1). Neural cells of an appendix slide served as an external  
111 positive control and myometrial nerves as an internal positive control (for whole sections). For  
112 concordance studies we stained the corresponding hysterectomy sections of all the patients with a  
113 positive (n = 50) and of 25 patients with a negative preoperative sample.

114 Starting from November 2014, we have obtained a preoperative blood sample from voluntary  
115 patients with endometrial carcinoma treated at the Department of Obstetrics and Gynecology,  
116 Helsinki University hospital. Blood fractionation was carried out by centrifugation for 10 min at  
117 2000×g and the samples were stored at -70°C. The serum samples of all the patients with an  
118 immunohistochemically verified L1CAM-positive (n = 17) and 23 patients with an L1CAM-  
119 negative endometrial carcinoma were retrieved. To determine the serum level of L1CAM we used a  
120 commercial enzyme linked immunosorbent assay (ELISA) kit (LifeSpan Biosciences Inc., WA,  
121 USA, Catalog No. LS-F24209). Standards, controls and samples were processed for sandwich  
122 ELISA according to the manufacturer's instructions and duplicate wells were ran for each sample.  
123 Final serum dilution (1:2000) was chosen after running test reactions on serial dilutions. The  
124 absorbance at 450 nm was measured by an automatic ELISA reader (Multiskan EX, Thermo Fisher  
125 Scientific, USA). Results were expressed in ng/ml according to the established standard curve. The  
126 limit of detection was 93.75–6000 pg/ml.

127 Continuous variables (sL1) were compared using the Mann-Whitney U test. Pearson  $\chi^2$   
128 analyses were used to compute odds ratios (OR) along with 95% confidence intervals (CI) for the  
129 associations between preoperative L1CAM staining and various risk parameters in the cohort.  
130 Multiple regression analysis was used to estimate the independent effect of selected risk parameters  
131 on either preoperative L1CAM staining or lymph node/distant metastasis (stage IIIC-IV disease).  
132 Cohen's kappa statistics were calculated to measure the agreement of preoperative L1CAM staining  
133 and tumor histology with corresponding postoperative findings. Based on kappa references outlined  
134 by Landis and Koch [31], the strength of agreement was considered moderate for kappa values  
135 between 0.41 and 0.60 and substantial for kappa values between 0.61 and 0.80.

136 Multivariable models were created to test the capability of preoperative L1CAM to  
137 predict lymph node and distant metastasis in conjunction with other risk parameters. The estimated  
138 weight of each parameter included in a risk model, was determined by rounding statistically  
139 significant odds ratios in the multivariable models to the nearest integer. These risk points of each  
140 factor were summed to generate a risk score potentially predicting the probability of advanced  
141 disease. The risk scores were used to test the discriminating abilities of the risk models with the 2-  
142 tailed receiver operating characteristic (ROC) curve area comparison test. Alternative models were  
143 created by eliminating selected variables from the models. Statistical significance was set at  $P < 0.05$ .  
144 Data were analyzed using IBM SPSS version 22 software (IBM Corp., Armonk, NY, USA).

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## 147 **Results**

148 Of the 241 preoperative endometrial samples, 64 (26.6%) were L1CAM positive. L1CAM expression  
149 was observed in 22.3% (43/193) of grade 1-2 endometrioid carcinomas, 27.6% (8/29) of grade 3  
150 endometrioid carcinomas, and 68.4% (13/19) of non-endometrioid carcinomas ( $P < 0.0001$ ).  
151 According to kappa statistics in 75 sample pairs, preoperative L1CAM staining showed moderate

152 agreement with findings in the whole section ( $\kappa$  0.586,  $P < 0.0001$ ). By comparison, in the whole  
153 study population of 241 patients,  $\kappa$  value was 0.551 ( $P < 0.0001$ ) for the agreement of  
154 preoperative histology with final histology in detecting high risk cases (grade 3 or non-endometrioid  
155 carcinoma). We did not observe any special L1CAM staining pattern, such as preferential positivity  
156 at the myoinvasive front, in the whole sections of hysterectomy specimens.

157           Preoperative L1CAM positivity was associated with disease spread beyond the uterine  
158 corpus, lymph node involvement, non-endometrioid histology, positive peritoneal cytology, and high  
159 age (Table 2). Logistic regression analysis indicated that non-endometrioid histology was  
160 independently associated with L1CAM positivity, whereas the effect of disease spread beyond uterine  
161 corpus, positive peritoneal cytology or high age was not significant (Table 3). Preoperative high risk  
162 histology (grade 3 or non-endometrioid carcinoma), myometrial invasion ( $>33\%$  or  $\geq 50\%$ ), tumor  
163 diameter ( $\geq 2$ cm or  $\geq 5$  cm) and preoperative L1CAM positivity were included in logistic regression  
164 models, with lymph node and distant metastasis as the dependent variable. Patients with available  
165 data for all the variables were included in each model ( $n \geq 225$ ). Tumor size  $\geq 2$ cm was the only  
166 variable that failed to display a significant independent effect on the dependent variable (Table 4).  
167 Addition of L1CAM in the models did not significantly improve the AUCs of the risk stratification  
168 algorithms ( $P > 0.28$ , Table 5). Elimination of myometrial invasion from Cox Bauer's model (TD  $\geq 5$   
169 cm, MI  $> 33\%$ ), did not significantly diminish the AUC of the score ( $P = 0.429$ ).

170 There was no statistically significant difference between the concentrations of soluble L1 (s-L1) in  
171 the serum samples of patients with L1CAM positive or negative tumors ( $P = 0.786$ ). The mean ( $\pm$   
172 SD) soluble L1 concentration was  $3235.49 \pm 808.60$  ng/ml for L1CAM positive cases and  $3163.27 \pm$   
173  $765.90$  ng/ml for L1CAM negative cases. Median (25th and 75th percentiles) soluble L1 values were  
174  $3033.90$  ( $2680.60$  and  $3637.60$  respectively) ng/ml in the patients with L1CAM positive tumor and  
175  $2992.20$  ( $2649.75$  and  $3467.10$  respectively) ng/ml in the L1CAM negative controls.

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177 **Discussion**

178 Modern management of endometrial cancer is based on personalized surgical and adjuvant treatment.  
179 Reliable pre- or intraoperative risk stratification plays a key role in tailoring optimal surgical  
180 treatment. Currently used risk assessment methods suffer from inaccuracy and definite indications  
181 for lymphadenectomy are yet to be established.

182 L1CAM is a promising prognostic marker that independently predicts poor outcome and lymph nodal  
183 involvement in endometrial carcinoma [21-23]. Since L1CAM expression pattern is heterogeneous  
184 in endometrial carcinoma (10-100% of the carcinoma cells staining in a positive  
185 immunohistochemical assay) and endometrial aspiration biopsy represents only a small portion of the  
186 tumor, the true value of L1CAM as a preoperative marker has to be studied on preoperative diagnostic  
187 samples. Despite the heterogeneous staining pattern of L1CAM, we observed a moderate  
188 concordance rate (kappa 0.586,  $P < 0.0001$ ) between L1CAM staining in preoperative and  
189 hysterectomy samples. It is noteworthy, that the concordance between pre- and postoperative L1CAM  
190 staining was superior compared to the concordance of pre- and postoperative histology (low vs high  
191 grade). L1CAM expression was associated with disease spread beyond uterine corpus (OR 2.5,  $P =$   
192  $0.003$ ), but its significant effect was lost once other factors were taken into account. Further, L1CAM  
193 did not significantly improve the performance of risk assessment algorithms based on traditional risk  
194 factors. These results imply, that L1CAM is not a useful tool for preoperative treatment planning of  
195 endometrial carcinoma.

196 Considering the common difficulties in assessing the depth of myometrial invasion preoperatively,  
197 we wanted to test a model without MI as a parameter. Intraoperative tumor diameter is a more feasible  
198 measure since it can be reliably evaluated by gross inspection (by the surgeon) even when frozen  
199 section analysis is not available. In our study cohort the risk assessment model presented by Cox  
200 Bauer et al. performed equally well independently of the presence of MI as a parameter (AUC  $> 0.8$ ;  
201  $P = 0.429$ ), suggesting that intraoperative tumor diameter could be used as an alternative to MI to



202 identify high risk disease, as indicated by previous studies [14,15]. The ideal cut off value for tumor  
203 diameter that determines high risk disease needs to be established by further studies.

204 No serum markers have any established role in the treatment of endometrial carcinoma. Few studies  
205 have addressed the potential clinical usefulness of serum L1CAM. Fogel et al. detected sL1 in the  
206 blood of patients with an advanced L1CAM-positive ovarian or uterine carcinoma, but not in  
207 healthy subjects or patients with other types of tumors, suggesting that sL1 could be used in  
208 diagnostics or follow up of ovarian and uterine carcinoma [17]. Using a commercial ELISA-kit  
209 optimized for serum samples, we were not able to confirm the results of the earlier report. Based on  
210 our results, soluble L1CAM is not a useful marker of L1CAM positivity of endometrial carcinoma.

211 A strength of our study was its unselected cohort of patients with endometrial carcinoma treated at a  
212 single tertiary care center with well-defined diagnostic and operative standards and systematic  
213 follow-up procedures. The relatively high lymphadenectomy rate (192/241, 79.7 %) in the study  
214 cohort improved the diagnostics of occult nodal disease permitting more accurate staging. In our  
215 institution frozen section is not used to determine the depth of MI and data on MI had to be  
216 extrapolated from final pathological reports.

217 In summary, we found a moderate concordance for L1CAM status between endometrial biopsies and  
218 corresponding hysterectomy specimens. Preoperative L1CAM expression was associated with lymph  
219 nodal and distant metastasis, but L1CAM did not significantly improve risk stratification algorithms  
220 based on preoperative histology, tumor diameter and/or myometrial invasion. Interestingly, the  
221 performance of risk stratification models did not depend on the presence of myometrial invasion as a  
222 variable, suggesting that the more feasible tumor diameter could be used as a surrogate variable.  
223 Based on our results, preoperative L1CAM cannot be recommended as a tool for stratifying patients  
224 with endometrial carcinoma to lymphadenectomy.

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229 **Figure legend**

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231 Supplementary figure 1.

232 Figure 1. LICAM immunohistochemical staining patterns in biopsies containing endometrial

233 carcinoma. a) diffuse; b,c) heterogeneous (b and c from the same biopsy)

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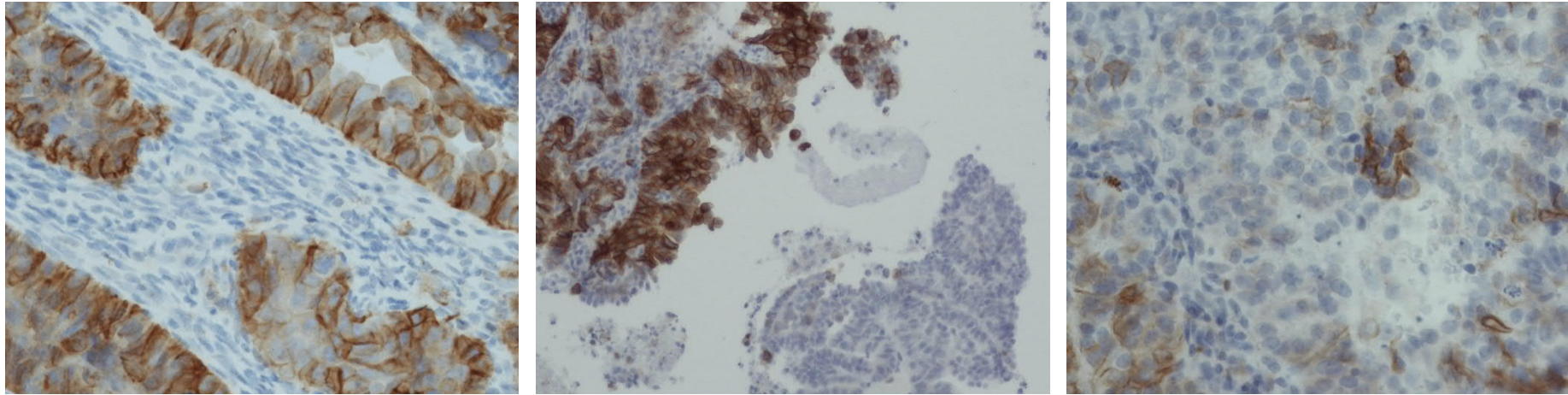


Figure 1. L1CAM immunohistochemical staining patterns in biopsies containing endometrial carcinoma.  
a) diffuse, b,c) heterogeneous (b and c from the same biopsy)

Table 1. Clinicopathologic data (n = 241).

Age (years) (mean $\pm$ SD)	67.3 $\pm$ 10.4
Body mass index (kg/m <sup>2</sup> ) (mean $\pm$ SD)	28.5 $\pm$ 6.5
Pelvic lymphadenectomy (number of cases, percent)	162 (67.2%)
Pelvic-aortic lymphadenectomy (number of cases, percent)	30 (12.4%)
Adjuvant therapy (number of cases, percent)	
Vaginal brachytherapy	133 (55.2%)
Whole pelvic radiotherapy	28 (11.6%)
Chemotherapy	6 (2.5%)
Chemotherapy and vaginal brachytherapy	13 (5.4%)
Chemotherapy and whole pelvic radiotherapy	33 (13.7%)
Histology (number of cases, percent)	
Endometrioid carcinoma	222 (92.1%)
Clear cell carcinoma	7 (2.9%)
Serous carcinoma	4 (1.7%)
Undifferentiated carcinoma	2 (0.8%)
Carcinosarcoma	5 (2.1%)
Neuroendocrine carcinoma	1 (0.4%)
Grade (number of cases, percent) (For endometrioid only, n = 222)	
Grade 1	128 (57.7%)
Grade 2	65 (29.3%)
Grade 3	29 (13.1%)
FIGO 2009 stage (number of cases, percent)	
IA	130 (53.9%)
IB	54 (22.4%)
II	13 (5.4%)
IIIA	12 (5.0%)
IIIB	1 (0.4%)
IIIC1	18 (7.5%)
IIIC2	7 (2.9%)
IVA	0 (0%)
IVB	6 (2.5%)

Table 2. Clinicopathologic characteristics according to L1CAM expression in preoperative endometrial samples, univariate analysis

Variable	Negative L1CAM	Positive L1CAM	OR (95% CI)	P
Stage II-IV	34/177 (19.2%)	24/64 (37.5%)	2.5 (1.3-4.7)	0.003
Positive pelvic and/or para-aortic lymph nodes <sup>a</sup>	12/174 (6.9%)	13/61 (21.3%)	3.7 (1.6-8.5)	0.002
Non-endometrioid carcinoma	6/177 (3.4%)	13/64 (20.3%)	7.3 (2.6-20)	<0.0001
Grade 3 (endometrioid only)	21/171 (12.3%)	8/51 (15.7%)	1.3 (0.55-3.2)	0.526
Myometrial invasion $\geq$ 50%	71/177 (40.1%)	27/64 (42.2%)	1.1 (0.61-1.9)	0.772
Tumor size $\geq$ 2 cm	47/166 (28.3%)	16/61 (26.2%)	0.90 (0.46-1.7)	0.756
Cervical stromal invasion	24/176 (13.6%)	9/63 (14.3%)	1.1 (0.46-2.4)	0.898
Positive peritoneal cytology	7/174 (4.0%)	11/63 (17.5%)	5.0 (1.9-14)	0.001
Age >65 years	94/177 (53.1%)	44/64 (68.8%)	1.9 (1.1-3.6)	0.030
Body mass index $\geq$ 30 kg/m <sup>2</sup>	65/177 (36.7%)	17/64 (26.6%)	0.62 (0.33-1.2)	0.141

<sup>a</sup> Stage IV cancers excluded

Table 3. Clinicopathological characteristics associated with L1CAM expression in preoperative endometrial samples, multivariate analysis

Variable	OR (95% CI)	P
Stage II-IV	1.4 (0.66-2.9)	0.389
Non-endometrioid carcinoma	4.4 (1.4-14)	0.010
Positive peritoneal cytology	2.6 (0.84-8.2)	0.097
Age >65 years	1.8 (0.92-3.3)	0.086



Table 4. Risk factors associated with advanced (stage IIIC-IV) endometrial carcinoma, analysis by multivariate risk models. Patients with available data for all risk factors were included.

	Models with L1CAM		Models without L1CAM	
	OR (95% CI)	P	OR (95% CI)	P
<b>Model HR-TD5cm-MI33%</b>	<i>1 (n = 225)</i>		<i>2 (n = 225)</i>	
Preoperative L1CAM	4.1 (1.5-11)	0.007		
Preoperative histology	3.7 (1.3-10)	0.012	5.2 (2.0-14)	0.001
Tumor size $\geq 5$ cm	3.3 (1.2-8.7)	0.017	3.1 (1.2-7.9)	0.019
Myometrial invasion (MI)				
MI $\leq 33\%$	1		1	
33% < MI $\leq 66\%$	3.3 (0.72-15)	0.125	3.0 (0.67-14)	0.151
MI > 66%	11 (2.7-45)	0.001	8.2 (2.2-32)	0.002
<b>Model HR-TD5cm</b>	<i>3 (n = 228)</i>		<i>4 (n = 228)</i>	
Preoperative L1CAM	3.0 (1.2-7.7)	0.021		
Preoperative histology	4.8 (1.8-13)	0.002	6.6 (2.7-17)	<0.0001
Tumor size $\geq 5$ cm	5.4 (2.2-14)	<0.0001	5.0 (2.1-12)	<0.0001
<b>Model HR-TD2cm-MI50%</b>	<i>5 (n = 227)</i>		<i>6 (n = 227)</i>	
Preoperative L1CAM	3.3 (1.3-8.3)	0.010		
Preoperative histology	4.3 (1.7-11)	0.003	5.8 (2.3-15)	<0.0001
Tumor size $\geq 2$ cm	1.3 (0.33-5.3)	0.687	1.3 (0.33-5.2)	0.701
Myometrial invasion $\geq 50\%$	4.9 (1.7-14)	0.003	4.3 (1.5-12)	0.007
<b>Model HR- MI50%</b>	<i>7 (n = 241)</i>		<i>8 (n = 241)</i>	
Preoperative L1CAM	3.0 (1.2-7.4)	0.015		
Preoperative histology	4.0 (1.6-10)	0.003	5.4 (2.2-13)	<0.0001
Myometrial invasion $\geq 50\%$	6.1 (2.3-17)	<0.0001	5.3 (2.0-14)	0.001

HR = high risk histology (G3 or non-endometrioid); TD = tumor diameter; MI = myometrial invasion

Table 5. Areas under curve (AUC) for risk models predicting stage IIIC-IV endometrial carcinoma.

Risk assessment model	AUC (95% CI)	P (2-tailed)
1. HR-TD5cm-MI33%-L1CAM	0.879 (0.828-0.930)	
2. HR-TD5cm-MI33%	0.870 (0.813-0.928)	P = 0.882 vs. Model 1
3. HR-TD5cm-L1CAM	0.852 (0.778-0.925)	
4. HR-TD5cm	0.818 (0.730-0.906)	P = 0.613 vs. Model 3
5. HR-TD2cm-MI50%-L1CAM	0.841 (0.777-0.905)	
6. HR-TD2cm-MI50%	0.805 (0.717-0.894)	P = 0.602 vs. Model 5
7. HR-MI50%- L1CAM	0.833 (0.770-0.896)	
8. HR-MI50%	0.759 (0.659-0.859)	P = 0.289 vs. Model 7

HR = high risk histology (G3 or non-endometrioid); TD = tumor diameter; MI = myometrial invasion