

# Quantification of recurrence risk based on number of adverse prognostic factors in women with stage I uterine endometrioid carcinoma

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## Abstract

**Objective:** The goal was to develop an updated model to predict the risk of recurrence, based on the number of adverse pathologic features in women with International Federation of Gynecology and Obstetrics stage I uterine endometrioid carcinoma, who did not undergo any adjuvant treatment.

**Material and Methods:** Women at a single center who underwent surgical staging without adjuvant therapy between January 1990 and December 2019 were included. Cox proportional hazards model was used to identify independent predictors of relapse free survival (RFS). Prognostic groups were then created based on the number of independent predictors of recurrence that were identified (0, 1, or 2-3 risk factors). Overall survival (OS) and disease specific survival (DSS) were also calculated for each group.

**Results:** In total 1133 women were eligible for inclusion. Median follow-up was 84 months. Independent prognostic factors of recurrence included: age  $\geq 60$ ; grade 2 or 3 differentiation; and presence of lymphovascular space invasion (LVSI). Due to the small number of patients with either 2 or 3 risk factors, these groups were combined into one (group 2/3). Isolated vaginal cuff recurrence was the most common site of recurrence in all study groups (2%, 7%, and 17% for groups 0, 1, and 2/3, respectively). Five-year RFS rates were 96%, 85%, and 57% for groups 0, 1, and 2/3 ( $p < 0.01$ ), respectively. Five-year DSS rates were 99%, 96%, and 85% and 5-year OS rates were 94%, 85%, and 62% ( $p < 0.01$ ), respectively.

**Conclusion:** We identified older age, high grade, and presence of LVSI as independent predictors of recurrence for women with stage I uterine endometrioid carcinoma. Using these prognostic factors, recurrence risk can be quantified for individual patients, and these factors can be used in deciding the appropriate adjuvant management course. (J Turk Ger Gynecol Assoc 2021; 22: 262-7)

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## Introduction

Endometrial carcinoma (EC) remains the most commonly diagnosed gynecologic cancer in the United States (1). Most women present with early-stage disease, with excellent survival outcomes (2).

Hysterectomy is the standard of care for women with early-stage EC, resulting in most patients being cured. However,

some groups of patients are at risk for cancer recurrence due to the presence of some pathologic risk factors. The Gynecologic Oncology Group-99 (GOG-99) study showed that women with some adverse pathologic features who did not undergo adjuvant treatment have a recurrence risk of 26% at 2 years. This trial solidified the classic definition of high-intermediate risk in stage I EC as follows: age  $\geq 70$  with one risk factor (grade 2 or 3 differentiation, presence of lymphovascular space invasion



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(LVSI), or deep myometrial invasion); age  $\geq 50$  with any two risk factors; and any age with all three risk factors (3). Women with only one of these risk factors experience lower recurrence rates of 5% at 5 years after adjuvant radiation therapy (RT) (4). The National Comprehensive Cancer Network lists observation, RT, and chemotherapy as treatment options for patients with International Federation of Gynecology and Obstetrics (FIGO) stage I EC (5). Given the number of treatment options and their associated toxicities, determining recurrence risk for this group of patients is vital so that appropriate adjuvant treatments can be selected.

Outside of prospective trials, there have been several studies examining recurrence in solely early-stage patients with EC (6-21). However, some of these studies include a heterogeneous group of women with non-endometrioid histologies, such as serous carcinoma, which are known to have a poor prognosis (8,10,11,21,22). All of these studies also include women who received various adjuvant treatments (6-21). Adjuvant therapy is known to significantly impact recurrence rates (3,23). Furthermore, some studies utilized nomograms, which can be cumbersome to use in daily clinical practice (7).

A simplified prognostic model for women with FIGO stage I EC was recently reported based on tumor grade, presence of LVSI, and percent myometrial invasion. While useful, the investigators reported that older age at diagnosis was not an independent risk factor for cancer recurrence (24).

In order to examine recurrence rates in women with FIGO stage I EC accurately, a population of women who did not undergo any adjuvant treatment is needed to answer this question. By including a larger study cohort with a longer follow-up, we sought to analyze independent predictors of recurrence in women with FIGO stage I uterine EC who did not receive any adjuvant therapies.

## Material and Methods

After obtaining Henry Ford Institutional Review Board approval (approval number: IRB 4645), we searched our prospectively maintained database for women with 2009 FIGO stage I EC who underwent hysterectomy and no adjuvant therapy between January 1990 and December 2019. As this was a retrospective study, informed consent was waived. Exclusion criteria were the presence of synchronous malignancies and non-endometrioid histology. After surgery, patients underwent routine follow-up with surveillance testing performed as clinically indicated. Follow-up data, including timing of recurrence, was collected from patients' medical records when available. Patient demographics, surgical pathologic variables, and survival endpoints were collected. Baseline comorbidity burden (Charlson comorbidity score) was also collected for each patient immediately before hysterectomy.

## Statistical analysis

The primary endpoint of the study was relapse free survival (RFS), which included both locoregional and distant recurrences. Univariate (UVA) and multivariate analyses (MVA) were first performed to determine independent predictors of RFS. Cox proportional hazards models were used to identify independent predictors of recurrence using a manual stepwise selection with an entry criterion of  $p < 0.2$  and stay criteria of  $p < 0.05$ . Groups were then created based on the number of recurrence risk factors that were present. Then, for each of these groups, RFS, overall survival (OS), and disease specific survival (DSS) were determined using date of hysterectomy as the start date. Kaplan-Meier plots were generated for each of these outcomes. Nominal and numerical variables were analyzed using a chi-square test and Student's t-test, respectively. All analyses were performed in statistical software SAS version 9.4 (SAS Institute Inc., Cary, NC).

## Results

After considering inclusion and exclusion criteria, a total of 1,133 patients were included with a median (range) follow-up of 86.8 (1-346) months. Table 1 summarizes baseline patient characteristics, pathologic findings, and recurrence patterns for the study cohort. The median age was 60 (26-93) years. There were 75 patients (6.6%) with FIGO stage IB disease. Pelvic lymph node (LN) dissection was performed in 59% (666 patients) with or without para-aortic lymphadenectomy. The median (range) number of LN examined was 2 (0-66). For some patients with adverse prognostic factors, it was not clear in the medical records why they did not receive the recommended adjuvant treatment. Patient refusal was the most commonly reported reason for not receiving adjuvant treatment. There was a total of 71 women (6%) who were diagnosed with cancer recurrence (pathologically, radiologically or both). The sites of their first relapse included isolated vaginal recurrence in 39/71 (54.9%), isolated pelvic recurrence in four (5.6%), vaginal and pelvic recurrence in nine (12.7%), isolated para-aortic recurrence in two (2.8%), and distant recurrence in 17 (23.9%) patients.

For the entire cohort, predictors of worse 5-year RFS on UVA were age (as continuous and dichotomous variables), higher grade, higher stage, and presence of LVSI. On MVA predictors were older age ( $\geq 60$ ), grade 2/3, and presence of LVSI (Table 2). These three independent predictors were then used to design the final recurrence model. A score of 0 was applied if the following factors were present: age  $< 60$ , grade 1, and lack of LVSI. A score of 1 was applied for the following risk factors: age  $\geq 60$ , grade 2/3, and presence of LVSI.

Initially, four risks groups were created (group 0 with no risk factors, group 1 with one risk factor, group 2 with two risk

factors, and group 3 with three risk factors). Due to the small number of patients in groups with 2 or 3 risk factors, these were combined into one group (group 2/3), creating a total of three risk groups.

There were 871 patients (77%) in group 0, 220 patients (19%) in group 1, and 42 patients (4%) in group 2/3. Regarding baseline characteristics among the groups, there were significant differences noted in age, body mass index, characteristics of LN dissection, grade, lower uterine segment involvement, presence of LVSI, and stage (Table 1).

Five-year RFS rates for the three prognostic groups were 96% [95% confidence interval (CI) 95-97%] for group 0, 85% (95% CI 78-90%) for group 1, and 57% (95% CI 38-73%) for group 2/3 ( $p < 0.01$ ) (Figure 1). Independent predictors for RFS included age  $\geq 60$  years, higher tumor grade, and the presence of LVSI.

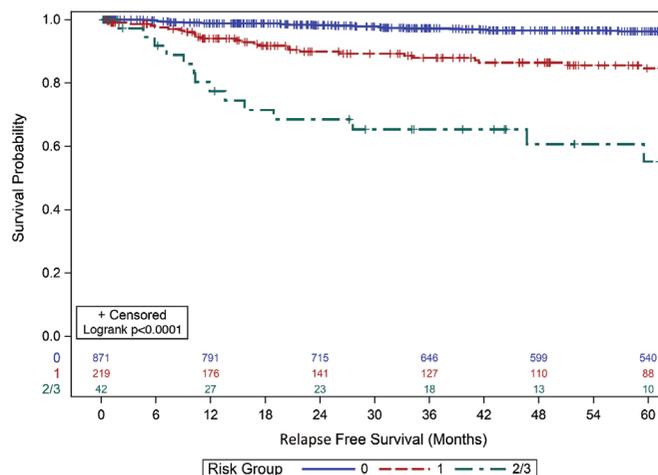


Figure 1. Kaplan-Meier plot comparing 5-year relapse free survival among risk groups

Table 1. Baseline patient characteristics across risk factor groups

Variable	Group 0 (n=871)	Group 1 (n=220)	Group 2/3 (n=42)	P
Age, median (range)	59.0 (26.0-91.0)	62.0 (30.0-92.0)	73.5 (34.0-93.0)	<0.01
Age <60	456 (52%)	89 (40%)	8 (19%)	<0.01
Age >60	415 (48%)	131 (60%)	34 (81%)	
Median (range) body mass index	36.2 (17.9-71.3)	33.4 (15.6-60.3)	30.5 (18.2-59.6)	<0.01
Median (range) Charlson Comorbidity score	0 (0-12)	0 (0-9)	0 (0-4)	0.27
<b>Race</b>				0.39
White	680 (78%)	159 (72%)	34 (81%)	-
African American	160 (18%)	53 (24%)	7 (17%)	-
Other	30 (3%)	8 (4%)	1 (2%)	-
FIGO stage IA	871 (100%)	176 (80%)	11 (26%)	<0.01
FIGO stage IB	0 (0%)	44 (20%)	31 (74%)	-
<b>Tumor grade</b>				<0.01
1	871 (100%)	63 (29%)	6 (14%)	-
2	0 (0%)	131 (60%)	21 (50%)	-
3	0 (0%)	26 (12%)	15 (36%)	-
Lymphovascular space invasion	0 (0%)	19 (9%)	28 (67%)	<0.01
Lower uterine segment involvement	83 (10%)	34 (15%)	10 (24%)	<0.01
Positive peritoneal cytology	12 (1%)	0 (0%)	1 (2%)	0.09
Lymph node dissection	470 (54%)	163 (74%)	33 (79%)	<0.01
Median number of nodes examined	1.0 (0.0-55.0)	5.0 (0.0-66.0)	4.5 (0.0-45.0)	<0.01
Median number of pelvic nodes examined	1.0 (0.0-41.0)	5.0 (0.0-44.0)	3.5 (0.0-36.0)	<0.01
Median number PA nodes examined	0.0 (0.0-32.0)	0.0 (0.0-25.0)	0.0 (0.0-17.0)	<0.01
Tumor recurrence	28 (3%)	29 (13%)	14 (33%)	<0.01
<b>Site of first tumor recurrence</b>				
Isolated vaginal recurrence	17 (2%)	15 (7%)	7 (17%)	0.23
Pelvic only recurrence	1 (0%)	3 (1%)	0 (0%)	0.65
Vaginal and pelvic recurrence	2 (0%)	4 (2%)	3 (7%)	0.35
PA only recurrence	0 (0%)	2 (1%)	0 (0%)	0.28
Distant recurrence	8 (2%)	5 (2%)	4 (9%)	0.67

FIGO: International Federation of Gynecology and Obstetrics, PA: Paraaortic

Five-year DSS rates for the three groups were 99% (95% CI 98-99%) for group 0, 96% (95% CI 91-98%) for group 1, and 85% (95% CI 66-93%) for group 2/3 ( $p < 0.01$ ) (Figure 2). Independent significant predictors for DSS included age  $\geq 60$  years and deep myometrial invasion.

Five-year OS for group 0 was 94% (95% CI 93-96%), 85% for group 1 (95% CI 78-89%), and 62% (95% CI 44-76%) for group 2/3 ( $p < 0.01$ ) (Figure 3). The independent predictors for OS were age  $\geq 60$ , grade 2/3 differentiation, deep myometrial invasion, and high comorbidity burden.

Table 2 summarizes the results of MVA for the different survival endpoints including hazard ratios.

**Discussion**

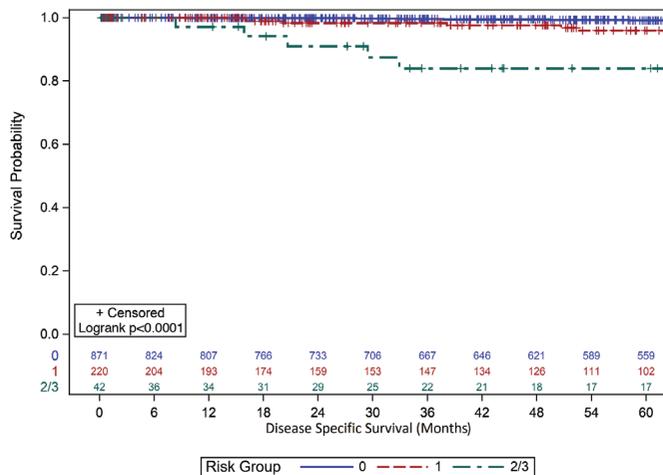
Although prior studies have aimed at creating a method to predict recurrence for early-stage EC, a simplified model is needed that is based on women who were observed following surgery. Given the lack of data to answer this question, some investigators sought to develop a simplified risk stratification method for women with FIGO stage I EC with endometrioid histology who did not undergo any adjuvant therapy. The authors were able to include 976 patients and identified tumor

grade 2/3, presence of LVSI, and stage IB as independent risk factors of recurrence, and three risk groups were established with 0, 1, or 2/3 risk factors (24). The current study further builds on these results, using a larger patient cohort and, importantly, longer follow-up.

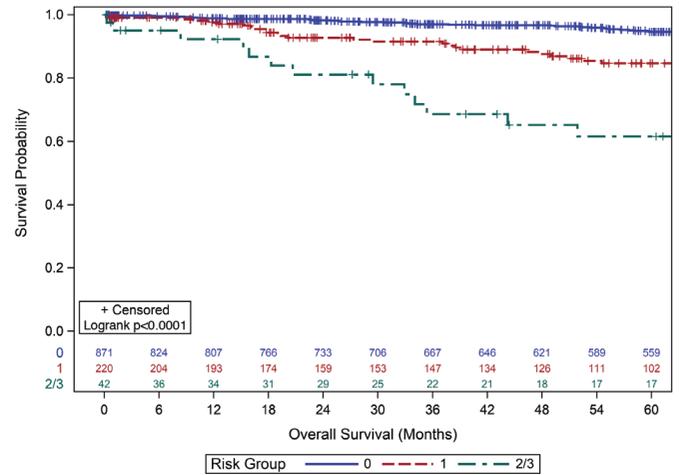
We were able to determine that independent predictors of 5-year RFS were older age, high tumor grade, and presence of LVSI. Utilizing these predictors, we created three separate risk groups based on the number of factors present: 0, 1, and 2/3. The RFS survival endpoints for groups 0, 1, and 2/3 were 96%, 85%, and 57%. This model provides a more individualized approach to determine patients' recurrence risk based on the number of risk factors.

Traditionally, patients with early-stage EC were grouped into low-risk, intermediate-risk, high-intermediate risk, and high risk (3,23,25). These risk stratifications assume that all patients grouped into a specific category have the same risk of recurrence. This assumption is likely inaccurate given the definitions for each group are broad, leading to a heterogeneous cohort.

Also of note, our study confirms that the predominant pattern of first recurrence in women with early-stage EC is in the vagina. Overall, 39 patients (4%) experienced vaginal relapse across



**Figure 2. Kaplan-Meier plot comparing 5-year disease specific survival among risk groups**



**Figure 3. Kaplan-Meier plot comparing 5-year overall survival among risk groups**

**Table 2. Results of multivariate analyses of survival endpoints for the study cohort**

Variable	Relapse free survival			Disease specific survival			Overall survival		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Older age (>60 vs <60)	1.03	1.01-1.05	0.01	1.07	1.02-1.12	<0.01	1.07	1.04-1.09	<0.01
Tumor grade 2/3 vs grade 1	3.00	1.77-5.07	<0.01	2.53	0.90-7.10	0.08	2.36	1.44-3.88	<0.01
Positive lymphovascular space invasion	4.52	2.27-8.97	<0.01	2.12	0.54-8.34	0.28	1.72	0.83-3.60	0.15
FIGO stage IB vs IA	1.44	0.69-3.01	0.33	3.87	1.19-12.57	0.02	2.20	1.17-4.14	0.01
Charlson comorbidity score (as a continuous variable)	-	-	-	-	-	-	1.25	1.12-1.40	<0.01

HR: Hazard ratio, CI: Confidence interval, FIGO: International Federation of Gynecology and Obstetrics

all three risk groups. This finding is in agreement with a large prospective trial (23). This recurrence pattern helps to inform appropriate adjuvant treatment options.

The recurrence rates for our patient population are similar to those that have been identified in prospective studies. For patients with 0 risk factors, we found a 5-year RFS of 96%, which is similar to a study by Sorbe et al. (26) in which women who were deemed low-risk (FIGO stage IA-IB, endometrioid histology, and FIGO grade 1-2) underwent observation and were found to have a recurrence rate of 4.1% at 5 years. Our 5-year OS of 94% was also similar to this cohort, which was found to be 96.1% (26).

For our group with one risk factor, a comparable cohort was studied in the observation arm of Post Operative Radiation Therapy in Endometrial Carcinoma-1 (PORTEC-1), which included women with either <50% myometrial invasion and grade 2/3 disease or >50% myometrial invasion and grade 1-2 disease. Our 5-year RFS for group 1 was 85%, and this study showed a 5-year recurrence rate of 16%. Additionally, our 5-year OS was 85%, which was identical to the endpoint examined in this study (27).

Finally, our group with 2/3 risk factors can be compared to patients in the observation arm studied in GOG-99 (inclusion criteria described earlier). Our 5-year RFS was 57%, which was not as favorable compared to the 5-year recurrence rate of close to 30% in this study. The 5-year OS for our group of 57% is also notably lower than the OS of approximately 75% found in this study. One possible explanation for this discrepancy is that we were able to include only 42 patients in this group while the GOG-99 study observed 70 high-intermediate risk patients (3). Additionally, as our study is retrospective, selection bias may explain the higher recurrence and lower survival in our patient cohort.

Of note, a dissimilar aspect between our study and many of the previously mentioned prospective studies is that myometrial invasion/stage was not found to be a significant predictor for recurrence in our analysis. Depth of myometrial invasion is a well-known predictor for recurrence, as demonstrated in the GOG-33 analysis (28). A possible explanation for us not identifying deep myometrial invasion as a predictor was that only 75 patients (6.6%) had FIGO stage IB disease. It is still likely that myometrial invasion predicts for recurrence and should be considered when determining treatment management.

### Study limitation

Our study does have some other limitations. As noted above, this study is retrospective and prone to selection bias in terms of which treatment the patients received. Also, there were only 42 patients who were included in group 2/3. This small number of patients does limit the power of statistical analyses on this group and the conclusions that can be drawn from this data.

In addition to utilizing these risk factors to determine recurrence risk, a promising future method to help in this effort uses molecular prognostication. The Cancer Genome Atlas identified four molecular subgroups within EC: POLE ultramutated, microsatellite instability hypermutated, copy-number low, and copy-number high (29). PORTEC-4 is an ongoing study determining if these molecular groups are prognostic and if they can guide adjuvant treatment decisions (30). The results of this trial are eagerly awaited and may be practice changing.

### Conclusion

This simplified recurrence model for patients with FIGO stage I EC includes three traditional independent predictors of RFS: older age, high tumor grade, and presence of LVSI. Given that risk groups defined by historical studies for this patient population are very heterogenous, this risk-scoring system can be applied to individual patients and is easy to utilize in daily clinical practice.

**Ethics Committee Approval:** *The study was approved by Henry Ford Institutional Review Board (approval number: IRB 4645).*

**Informed Consent:** *As this was a retrospective study, informed consent was waived.*

**Peer-review:** *Externally peer-reviewed.*

**Author Contributions:** *Surgical and Medical Practices: A.E.C., I.A., M.H., M.A.E.; Concept: I.A., M.H., M.A.E.; Design: I.A., M.H., M.A.E.; Data Collection or Processing: A.E.C., C.B.; Analysis or Interpretation: A.E.C., I.A., C.B., M.H., M.A.E.; Literature Search: A.E.C., M.A.E.; Writing: A.E.C., M.A.E.*

**Conflict of Interest:** *No conflict of interest is declared by the authors.*

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