

## Histological Grade Predicts for Recurrence in Patients with Uterine Endometrioid Carcinoma without Myometrial Involvement

MARK A. ZAKI<sup>1</sup>, JARED R. ROBBINS<sup>1</sup>, SAIF FATTEH<sup>1</sup>, MEREDITH G. MAHAN<sup>2</sup>,  
RABBIE K. HANNA<sup>3</sup> and MOHAMED A. ELSHAIKH<sup>1</sup>

<sup>1</sup>Department of Radiation Oncology, <sup>2</sup>Public Health Science, <sup>3</sup>Division of Gynecologic Oncology,  
Department of Women's Health Services, Henry Ford Hospital, Detroit, MI, U.S.A.

**Abstract.** Aim: To evaluate clinical outcomes and identify factors predictive for recurrence in patients with 1988 (FIGO) stage IA uterine endometrioid carcinoma. Patients and Methods: Patients who underwent hysterectomy for stage IA carcinoma were identified in our database. Fisher's exact and  $\chi^2$  tests were used to identify factors that influenced outcome. Survival plots were generated according to Kaplan-Meier product-limit method and the log-rank test was used to determine significance. Results: A total of 121 patients were identified. Eighty-seven percent (n=105) had tumor FIGO grade 1, 9% (n=11) grade 2, and 4% (n=5) grade 3 tumors. Six patients (5%) experienced recurrence. The 5-year recurrence-free survival (RFS), disease-specific survival (DSS) and overall survival (OS) were 93%, 95%, and 85%, respectively. On univariate analysis, tumor FIGO grade 2/3 was strongly associated with tumor recurrence ( $p=0.003$ ), DSS ( $p=0.016$ ), and OS ( $p=0.023$ ). The 5-year RFS, DSS, and OS were 65.1%, 73.9%, and 63.9% respectively for patients with grade 2 and 3 tumors, which were significantly less than the corresponding rates of 97.5% ( $p\leq 0.0001$ ), 98.6% ( $p=0.001$ ), and 87.7% ( $p=0.024$ ) for patients with grade 1 tumors. Conclusion: In this large cohort of patients, RFS, DSS and OS were excellent. Patients with FIGO grade 2/3 tumors had worse outcomes compared to those with grade 1 tumors. Therefore, while most patients with stage IA disease do not need adjuvant treatment after hysterectomy, our results suggest that patients with higher-grade tumors have

an increased likelihood for recurrence and they may benefit from counseling regarding adjuvant therapies.

Endometrial carcinoma (EC) is the most common gynecological malignancy in the United States, with 47,130 estimated new cases in 2012 (1). Total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO), with or without pelvic or para-aortic lymphadenectomy is curative in most patients with early EC, with an overall recurrence rate of 11-13% (2).

Adjuvant treatment is utilized in selected patients with early-stage EC to reduce the rate of tumor recurrence and improve disease-specific survival (DSS). The overall recurrence-free survival (RFS) for patients with early-stage EC is excellent, approaching 90% (3, 4). This depends on a number of factors, such as the stage of the disease, histology, tumor grade and depth of myometrial invasion (3, 5).

Two major randomized studies showed that adjuvant radiation treatment after hysterectomy reduced the rate of recurrence in patients with early-stage EC (6, 7). However, patients with tumor confined to the endometrium 1988 (FIGO) stage IA were not included in these studies secondary to the low risk of recurrence. In patients without myometrial invasion, the 5-year overall survival (OS) is excellent, reaching 91% according to Quinn *et al.* (8). However, there are limited data examining prognostic factors and patterns of failure for this group of patients.

Considering the highly significant prognostic impact of FIGO grade on recurrence (7), patients with uterine endometrioid carcinoma grade 3 with no myometrial invasion were included in one of the largest prospective studies (3). However, the number of patients with stage IA in that study was limited. Therefore, we aimed to study the clinicopathological factors associated with favorable outcomes and to determine factors that may predict recurrence in patients with uterine endometrioid carcinoma confined to the endometrium.

Correspondence to: Mohamed A. Elshaikh, MD, Department of Radiation Oncology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI 48202, U.S.A. Tel: +1 3139161021, Fax: +1 313 9163235, e-mail: melshai1@hfhs.org

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**Patients and Methods**

After Institutional Review Board approval, we reviewed the medical records of 775 patients in our prospectively maintained database of patients with EC. One hundred and twenty-one patients with 1988 FIGO stage IA uterine endometrioid adenocarcinoma were identified. All patients underwent TAH-BSO, with or without peritoneal cytology and/or pelvic or para-aortic lymph node dissection at our institution between 1985 and 2011. The medical records were retrospectively reviewed to collect demographic, clinical, and pathological data. Data on adjuvant therapy, recurrence, and salvage treatment were also collected. Patients with mixed and non-endometrioid histologies, as well as patients with any myometrial invasion, were excluded from this study.

The following factors were assessed: age, race, FIGO tumor grade, cytology, lower uterine segment (LUS) involvement, and lymphovascular space invasion (LVSI). Fisher exact and  $\chi^2$  tests were used to identify factors that influenced outcome. Due to the low frequency of events, multivariate analysis (MVA) was not included. Survival plots were generated according to the Kaplan Meier product-limit method calculated from the date of hysterectomy, and the log-rank test was used to determine significance. A *p*-value of <0.05 was considered to be statistically significant.

**Results**

One hundred twenty-one patients with 1988 stage IA uterine endometrioid EC were identified. The median follow-up time calculated from the date of hysterectomy was 65 months (range 13-250 months). All patients underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy (TAH-BSO), with or without lymph node dissection. Table I shows the patients' characteristics included in this study. Thirty-five patients (29%) did not undergo pelvic lymph node dissection and only eight patients (6.6%) did not have peritoneal cytology.

In our cohort, 16 patients (13%) had FIGO grade 2-3 EC, while the remaining 105 patients (87%) had grade 1 tumors. Only eight patients (6.6%) received adjuvant radiation with either vaginal cuff high-dose rate (HDR) brachytherapy alone (six patients) or pelvic external beam radiation treatment (two patients). Five out of the 16 patients with tumor grade 2-3 received adjuvant RT compared to three out of the 105 patients with tumor grade 1. Adjuvant RT was recommended based on the discretion of the managing multidisciplinary team. Intravaginal HDR brachytherapy was delivered to the surface of the vaginal cuff. Treatment was delivered once or twice per week using a single-channel vaginal cylinder to a dose of 35-45 Gy in three to six fractions. External beam RT was delivered in daily fractions of 1.8 Gy to a total dose of 45 Gy.

For the entire study cohort, the 5-year RFS, DSS and OS were 93%, 95%, and 85%, respectively. Only six patients (5%) developed a recurrence. Two percent of patients (2 out of 105) with grade 1, 18% of patients (2 out of 11) with grade 2, and 40% of patients (2 out of 5) with tumor grade 3 experienced a recurrence. Two recurrences were locoregional-only, while the remaining four had a distant component with or without a

Table I. Patient characteristics.

Median age (years)		58 (range 31-86)
Race	Caucasian	84 (69.4%)
	African-American	32 (26.5%)
	Other	5 (4.1%)
FIGO Tumor grade	1	105 (86.8%)
	2	11 (9.1%)
	3	5 (4.1%)
LUS involvement	Negative	115 (95.0%)
	Positive	6 (5.0%)
LVSI	Negative	120 (99.2%)
	Positive	1 (0.8%)
Median no. of pelvic lymph nodes examined		5 (range 0-34)
Peritoneal cytology	Negative	113 (93%)
	Not performed	8 (7%)
Adjuvant radiation treatment	None	113 (93.4%)
	Yes	8 (6.6%)

LUS, Lower uterine segment; LVSI, lymphovascular space invasion; FIGO, International Federation of Gynecology and Obstetrics.

locoregional component. The median time to recurrence was 15 months (range 5-40 months). A summary of the six patients in whom tumor recurred is included in Table II.

All patients who had tumor recurrence except one, received salvage treatment with chemotherapy, radiation, surgery or a combination of these modalities, and four out of five (80%) eventually succumbed to their disease. One patient with a grade 2 tumor received no adjuvant therapy and later developed a vaginal recurrence; the patient underwent salvage RT and she currently has no evidence of disease 5 years after salvage therapy.

On univariate analysis, tumor grade 2 or 3 was strongly associated with tumor recurrence (*p*=0.003), DSS (*p*=0.016), and OS (*p*=0.023). The 5-year OS, DSS, and RFS were 63.9%, 73.9%, and 65.1%, respectively for patients with grade 2 and 3 tumors, which were significantly less than the corresponding rates of 87.7% (*p*=0.024), 98.6% (*p*=0.001), and 97.5% (*p*≤0.0001) for patients with grade 1 tumors. Kaplan Meier plots of OS (Figure 1) and RFS (Figure 2) illustrate the impact of higher grade on clinical outcome. Age was also an important factor, as the median age of patients who experienced disease recurrence was 72.3 years compared to the age of those without recurrence, 57.8 years (*p*=0.019). Race, cytology, LVSI, and LUS involvement were not significant for tumor recurrence in the study cohort (Table III).

**Discussion**

In this retrospective series of patients with uterine endometrioid carcinoma without myometrial involvement, tumor grade was the only significant pathological factor predictive of tumor recurrence. The overall recurrence rate

Table II. Summaries of the cases of six patients who developed a tumor recurrence.

Tumor grade	Age (years)	LVSI	LUS involvement	Number of LN examined	Adjuvant treatment	Initial site of recurrence	Time to recurrence (months)	Initial salvage	Status at the time of analysis	Survival (months)
1	85	No	No	0	Observation	Liver	9	Chemotherapy	DOD	11
1	73	No	Yes	5	WPRT	Liver, peritoneal	5	None	DOD	8
2	62	No	No	2	Vaginal Brachytherapy	Pelvic mass	40	RT and chemotherapy	DOD	59
2	64	No	No	4	Observation	Vaginal	22	RT	NED	87
3	64	No	No	16	WPRT	Omentum/ abdominal wall	20	Surgery, chemotherapy and RT	DOD	31
3	86	No	No	13	Vaginal Brachytherapy	Pelvic mass, liver	5	RT	DOD	9

LVSI, Lymphovascular space invasion; LUS, lower uterine segment; LN, lymph node; WPRT, whole pelvic radiation therapy; DOD, dead of disease; NED, no evidence of disease.

for all patients was 5%. Patients with disease of grade 2 and 3 had a recurrence rate of 25%, compared to the 2% recurrence rate of grade 1 patients. Two-thirds of the recurrences were distant and could not be effectively salvaged. In fact, the only case with successful salvage was an isolated vaginal recurrence. These results suggest that patients with higher grade disease are more likely to experience tumor recurrence and suffer worse outcomes.

The recurrence rate for stage IA EC has been demonstrated to be from 1.8-8%, depending on grade and choice of adjuvant therapy. Salani *et al.* showed a recurrence rate of 2.6% for patients with stage IA, grade 1 disease who did not receive any adjuvant therapy (9). Rasool *et al.* showed an 8% recurrence rate in patients with stage IA, grade 3 disease, of whom half underwent adjuvant RT (10), while Straughn *et al.* found a 1.8% recurrence rate for patients with the same stage and grade 3 who did not undergo adjuvant RT (11). Konski *et al.* found a 2.3% overall recurrence rate. The only patient who experienced recurrence in this study had stage IA, grade 2 disease (12).

The 5-year OS for our cohort of patients with EC confined to the endometrium was 85%, which was less than that of 100% by Rasool *et al.* (10), 98.8% by Straughn *et al.* (11) and 92.4% by Abu-Rustum *et al.* (13). However, the DSS for our cohort was 95%, suggesting that many patients in our population died of other co-morbid conditions.

Many studies suggest that grade is a very important prognostic factor in terms of recurrence and outcome of patients with uterine endometrioid carcinoma. Grigsby *et al.* demonstrated that higher tumor grade was a prognostic factor for both local and distant failure (14). Fujimoto *et al.*

demonstrated that variously staged grade 3 tumors had higher locoregional recurrence rates than similarly staged lower grade disease (15). Esselen *et al.* demonstrated that histological grade was the only independent variable associated with an increased risk for recurrence and worse OS (5). Additionally, Creutzberg *et al.* confirmed that grade 3 disease was the most important adverse factor for recurrence and death as a result of EC, with a hazard ratio of 5.4 ( $p < 0.0001$ ) (16). These studies established tumor grade as being a poor prognostic factor for EC. Furthermore, in assessing patients with very early-stage EC confined to the endometrium, our results confirm grade an adverse factor for recurrence and survival.

Some authors have suggested that other factors may additionally play a role in prognosis. Abu-Rustum *et al.* predicted for OS by creating a nomogram that included five readily assessable features: age, stage, number of negative lymph nodes, final grade, and histological subtype (17). Based on this algorithm, a 60-year-old woman with stage IA endometrial adenocarcinoma who underwent TAH-BSO without lymphadenectomy would have an estimated 3-year OS of over 95% if she had had a grade 1 tumor but about 88% if she were to have a grade 3 tumor.

Risk stratification for stage I uterine endometrioid carcinoma using 2009 FIGO staging has been defined: low risk as any patient with stage IA, grade 1 or 2; intermediate risk as stage IA, grade 3 or stage IB, grade 1 or 2; and high risk as stage IB, grade 3 or any stage I with LVSI (18). Based on this stratification, 1988 FIGO stage IA, grade 3 EC would be categorized as intermediate risk with recommendations for adjuvant vaginal brachytherapy (18). However, stage IA,

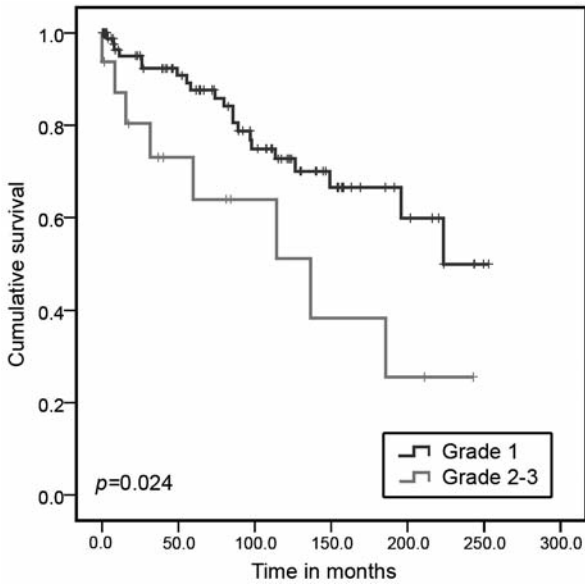


Figure 1. Overall survival (OS) after hysterectomy by tumor grade (Grade 1 compared to Grade 2-3).

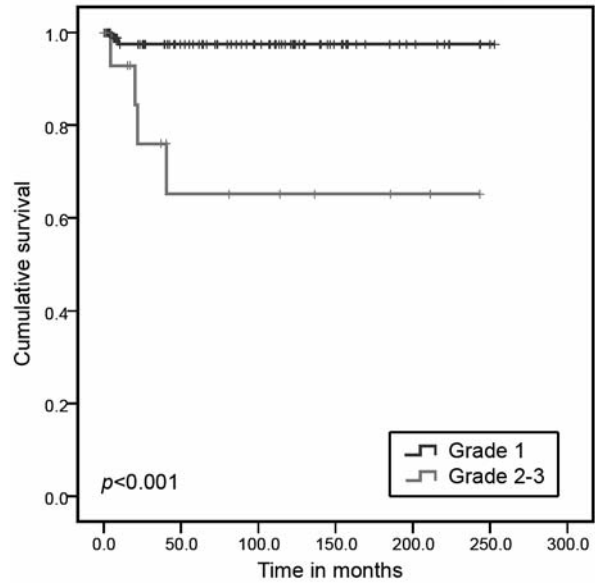


Figure 2. Recurrence-free survival (RFS) after hysterectomy by tumor grade (Grade 1 compared to Grade 2-3).

Table III. Univariate analysis for factors associated with clinical outcomes.

Variable	Recurrence-free survival			Disease-specific survival			Overall survival		
	No recurrence (n=115)	Recurrence (n=6)	p-Value	Alive/dead from other cause (n=116)	Dead of disease (n=5)	p-Value	Alive (n=92)	Dead (n=29)	p-Value
Median age in years	57.8	72.3	0.019	57.8	74.0	0.035	55.7	66.9	<0.001
Race									
White	81 (96%)	3 (4%)	0.494	81 (96%)	3 (4%)	0.725	65 (77%)	19 (23%)	0.679
AA	29 (97%)	3 (3%)		30 (94%)	2 (6%)		24 (75%)	8 (25%)	
Other	5 (100%)	0 (0%)		5 (100%)	0 (0%)		3 (60%)	2 (40%)	
Grade									
1	103 (98%)	2 (2%)	0.003	103 (98%)	2 (2%)	0.016	84 (80%)	21 (20%)	0.023
2-3	12 (75%)	4 (25%)		13 (81%)	3 (19%)		8 (50%)	8 (50%)	
LUSI	5 (4%)	1 (17%)	0.268	5 (83%)	1 (17%)	0.228	4 (67%)	27 (23%)	0.629
LVSI	1 (1%)	0 (0%)	1.000	1 (100%)	0 (0%)	1.000	1 (100%)	0 (0%)	1.00

AA, African-American; LUSI, lower uterine segment involvement; LVSI, lymphovascular space invasion.

grade 2 disease would be stratified in the low-risk category and receive no adjuvant RT (18).

Due to the risk of recurrence after hysterectomy, patients with endometrioid carcinoma grade 2 or 3 with no myometrial invasion are eligible to participate in the Gynecology Oncology Group (GOG) 0249 study. Patients in this study are randomized to adjuvant RT with or without systemic chemotherapy (19).

The strengths of our study are the large cohort of patients with only endometrioid adenocarcinoma without myometrial

invasion and a comprehensive prospectively maintained database with well-documented demographic, clinical, and pathological features. This allowed us to examine prognostic significance of various clinical and pathological factors. Yet there are some limitations to our study. Firstly, the inherent biases of any retrospective study. Secondly although there were a large number of patients, there were only a small number of events (recurrences), thus a multivariate analysis could not be effectively performed for this study population.

## Conclusion

In this large series of patients with 1988 FIGO stage IA uterine endometrioid adenocarcinoma, OS, DSS, and local control were excellent. Patients with grade 2 or 3 tumors had worse RFS, DSS, and OS than patients with grade 1 tumors. Therefore, while most patients with EC without myometrial involvement do not need adjuvant treatment after hysterectomy, our results suggest that patients with higher grade tumors have an increased risk of tumor recurrence and should be counseled about the potential benefit of adjuvant therapies.

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