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Original Article

Prognostic significance of tumor grade in early-stage endometrioid endometrial cancer

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Abstract

Aim: Although tumor grade has no impact on endometrial cancer stage, it carries prognostic and therapeutic importance. Surgical management and adjuvant treatment following surgery in certain patients depends on a number of factors including tumor grade. Although grade 3 tumors are included in the high-intermediate risk group, there are data demonstrating that there is a slight difference in survival between patients with grade 1 and 2 tumors in early-stage disease. In this study, we aimed to investigate the association of grade with clinicopathological characteristics, recurrence-free and disease-specific survival in patients treated at our clinic and diagnosed with endometrioid endometrial cancer.

Material and Methods: 279 patients with early FIGO Stage endometrioid endometrial cancer treated between 2009-2018 in a University hospital were included in the study. The associations between tumor grade with stage, lymphovascular space invasion (LVSI), myometrial invasion, tumor size, and survival were analyzed.

Results: LVSI, ≥50% myometrial invasion, advanced stage and > 2 cm tumor size were significantly higher in grade 3 tumors compared to patients with grade 1 tumors. Recurrence-free and disease-specific survival were significantly lower in patients with grade 2 and 3 tumors compared to patients with grade 1 tumors. In multivariate analysis of RFS and DSS, tumor grade, LVSI and stage were independent prognostic factors.

Conclusion: According to this study, grade 2 tumors may not differ significantly from grade 3 tumors in terms of survival. Therefore, due to the potential adverse prognosis associated with grade 2 and 3 tumors, vigilance for recurrence is warranted.

Keywords: Endometrioid endometrial adenocarcinoma; grade; survival; prognosis.

INTRODUCTION

Endometrial adenocarcinoma is the most common gynecological cancer in countries with adequate cervical cancer screening programs and endometrioid histology is the most common histological subtype (1). Early diagnosis and treatment result in high survival rates (1,2). Although tumor grade does not alter the stage of the disease, it is thought to carry significant prognostic and therapeutic importance. According to the currently used Federation Internationale de Gynecologie Obstetrique (FIGO) grading criteria, nuclear atypia inconsistent with architectural grade raise the grade by one (3). Adjuvant therapy in stage I disease is given based on certain criteria including tumor grade. Although grade 3 tumors are included in the high-intermediate risk group (4), there are data demonstrating that there is a slight yet statistically significant difference in the survival between patients with grade 1 and 2 early-stage tumors (2,5). Herein, we aimed to investigate the relationship between tumor grades including grade 2 and clinicopathological patient characteristics, relapse-free and disease-specific survival.

MATERIAL and METHODS

A total of 279 patients who were treated surgically at a university hospital between 2009-2018 were included in the study. These 279 patients were included for the investigation of the association of tumor grade with other prognostic factors. Of the 279, only 240 patients who were treated surgically between December 2009 and January 2017 were included for the survival analyses. Patients received a definitive histopathological diagnosis of endometrioid endometrial cancer following hysterectomy and lymphadenectomy and were diagnosed with FIGO stage I or II diseases. They received postoperative adjuvant therapy as indicated. Patient age, histopathological diagnoses, clinicopathological characteristics, surgical notes were accessed from electronic records. Stage and grade were assigned according to the FIGO criteria (3,6). The relationship between tumor grade and stage,

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lymphovascular space invasion (LVSI), myometrial invasion, tumor size and relapse-free survival (RFS) and disease-specific survival (DSS) were investigated.

RFS as the interval from date of completion of primary therapy to date of clinical or radiological evidence of metastatic disease (confirmed by biopsy) and DSS as the interval from the date of diagnosis to time of death due to disease, were calculated from follow-up records and National Death Registry, last checked on June 6, 2019. The study was approved by the Institutional Human Research Ethics Committee

Statistical analyses

The relationship of tumor grade with clinicopathological patient characteristics was compared using the Chi-square test with posthoc Bonferroni adjustments. Kaplan-Meier method was used to investigate the relationship between survival and clinicopathological patient characteristics. The log-rank test was used to determine statistical significance. P-values <0.2 on univariate analyses were included in multivariate analyses. P-value < 0.05 was accepted as statistically significant. Statistical analyses were carried out using SPSS 24.0 statistical software package (SPSS Inc., Chicago, IL).

RESULTS

The average patient age was 58.6 ± 9.2 (33-85). The average follow-up time was 62 months (8-140).

The distribution of clinicopathological patient characteristics is summarized in Table 1. Proportion of grade 1, 2 and 3 tumors was 65.6%, 23.2% and 11.2%, respectively.

Table 1. Distribution of clinicopathological patient characteristics in early stage endometrioid endometrial cancer.

Characteristic		N (%)
Grade	1	186(66.7)
	2	59(21.1)
	3	34(12.2)
Stage	I	232(83.2)
	II	47(16.8)
LVSI	Absent	236 (84.6)
	Present	43 (15.4)
MI	<50%	156 (55.9)
	≥50%	123 (44.1)
Tumor Size	≤2 cm	58(20.8)
	>2 cm	221(79.2)

G, Grade; LVSI, lymphovascular space invasion; MI, myometrial invasion

The relationships between tumor grade and clinicopathological patient characteristics are summarized in Table 2. Grade 3 tumors were significantly associated with the presence of LVSI (p<0.001), ≥%50 myometrial invasion (p=0.02), stage II disease (p<0.001) and > 2 cm tumor size (p=0.02).

Figure 1. Relapse-free survival in patients with endometrioid endometrial adenocarcinoma according to tumor grade.

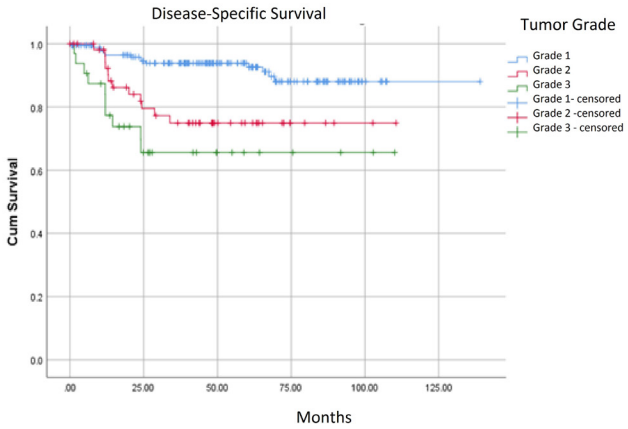

Figure 2. Disease-specific survival in patients with endometrioid endometrial adenocarcinoma according to tumor grade.

Disease-specific death was seen in 5.9%, 21.2% and 29.6% patients, respectively. RFS and DSS for each of the tumor grades are shown in Table 2 and Figure 1, 2 and 3. RFS and DSS in patients with grade 2 and 3 tumors were significantly lower than patients with grade 1 tumors (p <0.001 for both). However, there was no difference in RFS and DSS between patients with grade 2 and 3 tumors (p<0.05).

In multivariate analysis of recurrence-free survival (Table 3), tumor grade [Hazard ratio (HR): 2.4 (%95 Confidence Interval (CI) 1.5-4.0), p < 0.001)], LVSI [HR: 2.3 (%95 CI 1.1-4.6) p=0.01] and stage [HR: 1.4 (%95 CI 1.1-1.9), p = 0.036)] were independent prognostic factors for recurrence-free survival in endometrioid endometrial cancer. However, myometrial invasion was not found to be an independent prognostic factor [HR: 1.1 (%95 CI 0.4-3.1), p = 0.3)].In multivariate analysis of disease-specific survival (Table 4), tumor grade [Hazard ratio (HR): 2.2 (%95 CI 1.3-3.6), p = 0.001)], LVSI [HR: 2.0 (%95 CI 1.2-3.9) p=0.013], stage [HR: 1.5 (%95 CI 0.8-2.5), p = 0.044)] were independent prognostic factors for disease-specific survival in endometrioid endometrial cancer. However, myometrial invasion was not found to be an independent prognostic factor [HR: 1.2 (%95 CI 0.6-3.2), p = 0.44)]

Table 2. Distribution of clinicopathological patient characteristics and survival times based on grade in endometrioid endometrial cancer.

Patient characteristic	Grade 1(%)	Grade 2 (%)	Grade 3 (%)	p
LVSI absent Present	170 (91.5)	48 (81.8)	18 (53.8)	<0.001
	16 (8.5)	11 (18.2)	16 (46.2)	G1 vs 3
<50% MI	117 (63.4)	29 (49.2)	10 (29.4)	0.002
≥50% MI	69 (36.6)	30 (50.8)	24 (70.6)	G1 vs 3
Stage I	166 (89.6)	46 (78.9)	20 (70.6)	<0.001
Stage II	20 (10.4)	13 (21.1)	14 (41.4)	G1 vs 3
Tumor size ≤2cm	49 (26.2)	8 (13.1)	1 (2.9)	0.002
>2 cm	137 (73.8)	51 (86.9)	33 (97.1)	G1 vs 3
Time (Months)				
Relapse-free survival	107.9(%95 CI:100.3-112.4)	77.2(%95 CI:68.7-91.3)	69.4(%95 CI:62.3-79.5)	<0.001*
Disease-specific survival	115.4(95%CI:109.9-128.5)	81.6(95% CI:70.5-93.4)	73.8(95% CI:64.5-85.2)	<0.001**

G, Grade; LVSI, lymphovascular space invasion; MI, myometrial invasion
*Grade 1- Grade 2 p = 0.002, Grade 1-Grade 3 p<0.001, Grade 2- Grade 3 p= 0.18,
**Grade 1 - Grade 2 p <0.001, Grade 1- Grade 3 p< 0.001, Grade 2 - Grade 3 p= 0.11

Table 3. Univariate and multivariate analyses of prognostic factors associated with recurrence free survival in early stage endometrioid endometrial cancer.

	Univariate Analysis			Multivariate Analysis		
	HR	95%CI	P	HR	95% CI	P
Stage	1.2	1.0-1.8	0.018	1.4	1.1-1.9	0.036
Grade	2.1	1.4-3.8	<0.001	2.4	1.5-4.0	<0.001
LVSI	2.1	1.2-4.2	0.001	2.3	1.1-4.6	0.01
≥50% MI	1.0	0.7-2.9	0.048	1.1	0.4-3.1	0.3

LVSI, lymphovascular space invasion; MI, myometrial invasion; HR, Hazard Ratio; CI, Confidence Interval

Table 4. Univariate and multivariate analyses of prognostic factors associated with disease-specific survival in early stage endometrioid endometrial cancer.

	Univariate Analysis			Multivariate Analysis		
	HR	95%CI	P	HR	95% CI	P
Stage	1.1	0.1-1.1	0.021	1.5	0.8-2.5	0.044
Grade	2.1	1.2-3.4	0.001	2.2	1.3-3.6	0.001
LVSI	1.9	1.1-3.2	0.001	2.0	1.2-3.9	0.013
≥50% MI	1.3	0.7-3.1	0.05	1.2	0.6-3.2	0.44

LVSI, lymphovascular space invasion; MI, myometrial invasion; HR, Hazard Ratio; CI, Confidence Interval

DISCUSSION

Endometrial cancer is the most common cancer in certain parts of the world with accessible cervical cancer screening programs and vaccination (1). Five-year survival for endometrial cancer is high (1,2). Even though grade does not alter disease stage, it is accepted as an important prognostic factor for guiding therapeutic management (4). In this study, we sought to evaluate the association between grade and clinicopathological patient characteristics and survival. Grade 3 tumors were significantly associated with the presence of LVSI, advanced stage, outer half myometrial invasion, and > 2 cm tumor size. Patients with grade 1 tumors were found to have a significantly higher RFS and DSS compared to patients with grade 2 and 3 tumors. Although the mean RFS and DSS for patients with grade 3 tumors were lower than those of patients with grade 2 tumors, this difference did not reach statistical significance.

Disease stage, tumor grade, and myometrial invasion are accepted to be among the most important prognostic parameters in endometrial cancer. In 521 patients with early stage endometrioid endometrial cancer, myometrial invasion and tumor grade were independent prognostic factors in FIGO stage IA and IB disease, respectively (7). The researchers reported that the 5-year RFS of patients with stage IB endometrioid endometrial cancer was 94%,79% and 74%, respectively for grades 1, 2 and 3 tumors. Similar to our study a tumor grade of 2 and 3 significantly increasd the risk of recurrence when compared to grade 1 tumors. However, in our study myometrial invasion was not found to be an independent risk factor among other variables such as tumor grade and LVSI. On the other hand, in a retrospective study of 1071 patients, a Cox proportional hazard ratio model including stage, tumor grade and myometrial invasion revealed that only histological grade carried independent prognostic significance associated with poor overall survival and survival after recurrence (8). In another study, age and LVSI were found to be the only independent adverse prognosticators in terms of recurrence-free and overall survival in early stage endometrial cancer patients (9). A study by Turkmen et al. on the prognostic factors and role of lymphadenectomy and adjuvant therapy in patients with stage IB endometrial cancer found no significant impact of tumor grade on survival (10). Our results indicated that grade 2 and 3 tumors may negatively impact survival and that myometrial invasion was not an independent prognostic factor when stage and grade were analyzed.

We were unable to find a statistically significant difference in the mean RFS and DSS between patients with grade 2 and 3 tumors in contrast to a recently published study on this subject (11). In this study of 947 early-stage endometrioid endometrial cancer patients, overall survival for patients with grade 1, 2 and 3 tumors were 62.0 (95% CI 53.8 to 70.2), 48.5 (95% CI 38.2 to 58.8), and 33.5 months (95% CI: 23.1 to 43.8), respectively (11). This study also reported grade to be independent prognostic factors in multivariate survival analyses. In our study, DSS was found to be higher based on tumor grades and in contrast to the study above, survival times in grade 2 and 3 tumors were significantly lower than grade 1 tumors. Similarly, we found the grade to be an independent prognostic factor in early but not the late-stage disease. A study by Gulseren et al. showed that high SUVmax values, which represent more aggressive tumors, were significantly associated with grade 3 but not grade 1 or 2 tumors (12) . This is in contrast to our findings, which associated both grade 2 and 3 tumors with worse outcomes compared to grade 1 tumors. Differences in postoperative treatment may play a role in these results.

Based on the long terms results of our experience at a university hospital, survival of patients with grade 2 tumors did not differ significantly from those of grade 3 patients. Therefore, this study suggests that vigilance for recurrence is warranted in the follow-up of patients with grade 2 and 3 tumors as these histological grades may be associated with unfavorable prognosis compared to grade 1 tumors.

CONCLUSION

Adverse clinicopathological patient characteristics were significantly related to higher tumor grade and the outcome of patients with grade 1 tumors were associated with the most favorable prognosis in our clinic. However, there was no significant difference in the outcome of patients between tumor grades 2 and 3. Therefore, vigilance may be warranted in the follow-up of patients with grade 2 and 3 tumors for recurrence.

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