



Prognosis Trend of Grade 2 Endometrioid Endometrial Carcinoma: Toward Grade 1 or 3?

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Received: 15 May 2020 / Accepted: 27 May 2020 / Published online: 2 June 2020
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Abstract

Although the prognostic significance of grade in endometrial cancer is well known, grade 2 cases have not been evaluated separately in most of the previous studies. In this study, we aim to investigate whether the oncologic outcomes of grade 2 endometrioid endometrial carcinomas trend towards grade 1 or 3 tumors. Patients' records and pathological reports were reviewed retrospectively and eligible patients with endometrioid endometrial carcinoma were determined and distributed into 3 groups according to their 1988 International Federation of Gynecology and Obstetrics (FIGO) grade. Groups' characteristics and oncologic outcomes were compared. Differences between grades were tested with z-test and adjusted by Bonferroni method. Kaplan–Meier method was performed for the survival analysis. In total, 776 patients of endometrioid endometrial carcinoma were included in this study. Mean follow-up time was 52 ± 14 months. Patients' mean age was 56.3 ± 10.8 years. Even though grade 2 endometrioid endometrial carcinomas were different from both grade 1 and 3 in terms of the pathological features, survival analyses demonstrated that their oncologic outcomes trended towards grade 1. The grade was determined as an independent prognostic factor for overall survival (OS). The interobserver reproducibility will be improved among pathologists by combining FIGO grade 1 and 2 endometrioid endometrial carcinomas, while prognosis prediction is not likely to be affected.

Keywords Endometrioid endometrial carcinoma · FIGO grade · Oncologic outcomes · Interobserver reproducibility

Introduction

The International Federation of Gynecology and Obstetrics (FIGO) ternary grading system is the most widespread system used for grading the endometrioid endometrial cancers [1]. The prognostic significance of the tumor grade has been previously described in various studies [2, 3]. Nevertheless, grade 2 tumors were combined with grade 1 and compared together with grade 3 tumors in most of these studies [2, 4]. Clearly, favorable prognosis is expected for grade 1 endometrioid endometrial cancers while the opposite is expected for grade 3 tumors [2, 4, 5]. However, for grade 2 endometrioid carcinomas, there are no sufficient data in the literature and the situation is conflicted actually. The conflict regarding grade 2 endometrioid endometrial carcinomas is not only linked to their prognosis but begins firstly with their diagnosis which is based upon a relatively subjective and arbitrary grading system [1, 3].

The FIGO grading system has several pitfalls, which complicate its application and reduce the interobserver reproducibility [1, 3]. The discrimination between exact solid growth

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and squamous areas, determining the precise percentage of the solid growth especially when close to the cut-points are the obvious problems of this grading system. Additionally, designation of the notable nuclear atypia maybe subjective due to the lack of meticulous criteria [1, 3].

The question “Is grade 2 endometrioid endometrial tumors’ prognosis absolutely similar to that with grade 1?” occurred to us since grade 1 and 2 endometrioid endometrial carcinomas were identified together in the same categories of the recent 2016 ESMO-ESGO-ESTRO risk classification system [6]. If the answer is affirmative, we can harmonize both of them in the same grade and thus overcome the difficulties of the histopathological assessments. Based on these assumptions, we have aimed in this study to investigate the oncologic outcomes of grade 2 endometrioid endometrial carcinomas compared with grade 1 and 3 tumors.

Materials and Methods

The present retrospective study was conducted in the Gynecologic Oncology Department of Çukurova University Balcalı Hospital between January 1996 and December 2018. The pathologic reports, electronic and archival records of the department were retrospectively reviewed. The patients’ demographic, pathologic and follow-up characteristics were obtained. Patients with endometrioid endometrial cancer histology were the subject of the study, and hence, the other histologies were excluded, and the remaining 776 cases were recruited for this study. Patients were divided into three groups according to their grade. Groups’ clinical and pathological characteristics and oncological outcomes were compared. All patients were operated and pathologically evaluated in the same center by expert gynecological pathologists. The main surgical procedures were total hysterectomy- bilateral salpingo-oophorectomy (via laparotomy or laparoscopy) with or without pelvic and para-aortic lymphadenectomy according to the intraoperative frozen section result. FIGO 2009 staging guidelines for endometrial cancer was used. Stages of cases operated before 2009 were rearranged accordingly. The grade was identified according to 1988 FIGO grading system in which non-squamous solid areas percentage is taken into account as follows: $\leq 5\%$, 6–50% and $> 50\%$ solid growth for grade 1, 2 and 3, respectively. Patients were upgraded in case of determining notable nuclear atypia. Patients were followed-up every 3 months in the first 2 years and every 6 months in the following 3 years and then annually. The period between date of the histopathologic diagnosis and recurrence was identified as disease-free survival (DFS). Overall survival (OS) was considered to be the time between date of histopathologic diagnosis and date of death.

Statistical Analysis

Data were analyzed using SPSS software version 23.0 (IBM, Armonk, NY, USA). Descriptive analyses were presented as mean \pm standard deviation, median and minimum-maximum values. Categorical data were analyzed using Chi-square test or Fisher’s exact test. Difference between grades was tested with z-test and adjusted by Bonferroni method. Survival analyses were realized with Kaplan–Meier method and the differences in the survival curves were calculated through the log-rank test. The significance of multiple variables was assessed using the Cox proportional hazard model. *P* value was considered significant at the level < 0.05 .

Results

During the study period, 1110 patients were operated because of endometrial cancer. Records of 776 cases with endometrioid endometrial cancer were determined and included in the study. Median of follow-up time was 41 (1–209) months. Median age of the entire cohort was 57 (26–91) years. Mean age of grade 2 (58.7 ± 10.2) patients was significantly higher than grade 1 (54.5 ± 11.0) and similar to grade 3 (59.4 ± 9.3) ($p < 0.001$). Body mass index (BMI) did not vary between the grade groups ($p = 0.069$). Patients’ clinical and pathological characteristics are summarized in Table 1. Deep myometrial invasion ($MI \geq 50\%$) was reported in 17.1%, 42.8% and 78.7% of grade 1, 2 and 3 cases, respectively ($p < 0.001$). Lymphovascular space invasion (LVSI) was determined to significantly vary between grades (14.6%, 39.2%, and 76.6% for grade 1, 2 and 3, respectively). Cervix was invaded in 6% of grade 1 while it was invaded in 13.2% and 29.8% of grade 2 and 3 patients ($p < 0.001$). Lymph nodes (LN) were involved in 2.8%, 8.6% and 30.4% of grade 1, 2 and 3 patients, respectively ($p < 0.001$). Stage 3–4 cases (extrauterine spread) were recorded to significantly vary among grade groups (5.3%, 13% and 32.6% for grade 1, 2 and 3, respectively). The above-mentioned variables; MI, LVSI, cervical invasion, LN involvement and stage were significantly different at the level of each grade’ group. Omental metastases were reported in 11.1% of grade 2 patients. This ratio was not statistically different from grade 1 (4.2%) or 3 (17.4%) groups, whereas it was significantly different between grade 1 and 3 cases. Proportions of positive cytology were also found to significantly vary between grade 1 and 3 patients. Positive cytology ratio of grade 2 group was neither different from grade 1 nor 3 groups. Adjuvant treatments were administered to 45.3% of grade 2 patients and this rate was significantly different from both grade 1 (17.5%) and 3 (93.6%). There was no statistically-significant difference regarding the recurrence between grade 1 and 2 patients (13.2% and

Table 1 Patients' clinical and pathological characteristics

Variable, total N		Grade				P
		1 N (%)	2 N (%)	3 N (%)	Total N (%)	
Recurrence, 745	No	374 (86.8) a	230 (85.8) a	34 (73.9) a	638 (85.6)	0.061
	Yes	57 (13.2) a	38 (14.2) a	12 (26.1) b	107 (14.4)	
Status, 746	Alive	372 (86.1) a	215 (80.2) a	28 (60.9) b	615 (82.4)	0.001
	Dead	19 (4.4) a	23 (8.6) a.b	8 (17.4) b	50 (6.7)	
	Unknown	41 (9.5) a	30 (11.2) a.b	10 (21.7) b	81 (10.9)	
Cytology, 728	Negative	110 (25.9) a	55 (21.3) a	11 (23.9) a	176 (24.2)	0.002
	Positive	1 (0.2) a	5 (1.9) a.b	3 (6.5) b	9 (1.2)	
	Unknown	313 (73.8) a	198 (76.7) a	32 (69.6) a	543 (74.6)	
LVSI, 741	No	364 (85.4) a	163 (60.8) b	10 (21.3) c	537 (72.5)	<0.001
	Yes	62 (14.6) a	105 (39.2) b	36 (76.6) c	203 (27.4)	
	Unknown	67 (95.8) a	64 (88.9) a.b	19 (82.6) b	150 (91.0)	
Omental met., 673	No	3 (4.2) a	8 (11.1) a.b	4 (17.4) b	15 (9.0)	<0.001
	Yes	354 (82.5) a	145 (54.7) b	3 (6.4) c	502 (67.7)	
Adjuvant treat., 741 MI, 714	No	75 (17.5) a	120 (45.3) b	44 (93.6) c	239 (32.3)	<0.001
	Yes	334 (82.8) a	151 (57.2) b	10 (21.3) c	495 (69.2)	
	<50	69 (17.1) a	113 (42.8) b	37 (78.7) c	219 (30.7)	
LN invasion, 696	Yes	384 (97.2) a	233 (91.4) b	32 (69.6) c	649 (93.2)	<0.001
	<50	11 (2.8) a	22 (8.6) b	14 (30.4) c	47 (6.8)	
	= > 50	413 (94.7) a	234 (87.0) b	31 (67.4) c	678 (90.3)	
Cervical inv., 742	No	23 (5.3) a	35 (13.0) b	15 (32.6) c	73 (9.7)	<0.001
	Yes	404 (94.0) a	230 (86.8) b	33 (70.2) c	667 (89.9)	
Age (mean ± SD)		54.46 ± 11.0 a	58.73 ± 10.2 b	59.36 ± 9.3 b	56.29 ± 10.8	<0.001
BMI (mean ± SD)		26 (6.0) a	35 (13.2) b	14 (29.8) c	75 (10.1)	<0.001
Stage, 751	Uterus confined (1–2)					<0.001
Cervical inv., 742	Extrauterine spread (3–4)					<0.001
	No					
	Yes					

N count, LVSI lymphovascular space invasion, met. metastasis, treat. treatment, MI myometrial invasion, LN lymph node, inv. invasion, SD standard deviation

(a,b,c): Each subscript letter denotes a subset of grade categories whose column proportions do not differ significantly from each other at the 0.05 level

14.2%, respectively) whereas both of them were significantly different from grade 3 group (26.1%).

Survival rates are compared between grade groups and illustrated in Table 2. Five years OS, DFS rates were 95.1%, 83.3% and 91.6%, 79.1% for grade 1 and 2, respectively. These rates were not statistically-significant (OS: $p = 0.075$, DFS: $P = 0.939$). The statistically-significant difference between grade groups in terms of OS and DFS was mainly noticed between grade 1 and 3 (OS: 75.6%, DFS: 60.3%) (Fig. 1). However, OS rate of grade 2 had a robust tendency to be significantly different from grade 3 ($p = 0.053$). Similar difference but with weak tendency was also noticed between grade 1 and 2 cases ($p = 0.075$). Sub-analysis of survival comparison among grade groups was performed considering various clinical and pathological variables (Table 2). In case of uterus-confined disease (stage 1–2), negative LN, negative LVSI, $\geq 50\%$ MI and not receiving adjuvant treatments, significant differences between OS of the groups were found. For

DFS, significant difference between groups were determined in case of uterus-confined disease, negative LN and negative LVSI. When these variables were taken into account, five years OS and DFS rates were similar for grade 1 and 2 patients. On the other hand, OS and DFS rates of grade 3 were significantly different from both grade 1 and 2 cases. On multivariate analysis, the grade beside age, stage, and recurrence were found to be independent prognostic factors for OS. In addition, age, stage, LVSI, omental metastasis and adjuvant treatment were determined as independent factors for DFS (Table 3).

Discussion

The importance of grade in predicting prognosis of the endometrial cancer has been stated in numerous previous studies for years [3, 7]. Nevertheless, grade 2 tumors were combined

Table 2 Comparison of overall and disease-free survival between grade groups

	Grade 1		Grade 2		Grade 3		P for OS	P for DFS
	Total / Dead n	OS/DFS 5 years survival %	Total / Dead n	OS/DFS 5 years survival %	Total / Dead n	OS/DFS 5 years survival %		
Grade	408/19	95.1/83.3	260/23	91.6/79.1	42/8	75.6/60.3	0.003	0.005
Stage								
Uterus confined (1–2)	387/15	96.2/83.7	225/16	94.2/81.7	27/5	79.7/57.7	0.015	<0.001
Extrauterine (3–4)	21/4	81.4/69.4	33/7	73.1/51.8	15/3	65.2/45.5	0.636	0.091
LN involvement								
Negative	361/17	95.7/83.5	225/21	91.9/80.0	28/5	81.1/60.3	0.030	0.003
Positive*	10/1	87.5/78.8	20/2	85.1/68.8	14/3	59.1/43.5	0.461	0.226
Myometrial invasion								
<%50	314/15	95.3/84.6	148/15	92.3/83.0	9/1	72.9	0.199	0.602
>%50	62/4	92.5/77.2	105/8	88.2/73.3	33/7	69.3/48.6	0.018	0.095
Lymphovascular space invasion								
No	339/14	95.7/83.3	159/9	94.3/81.6	8/3	68.6/28.6	0.001	0.003
Yes	58/5	91.5/81.2	98/14	85.6/75.4	33/5	78.3/68.3	0.597	0.692
Adjuvant treatment								
No	332/11	96.5/85.9	141/11	95.7/89.5	3/1	50/–	0.035	0.481
Yes	69/6	90.9/77.7	113/12	82.7/63.7	39/7	77.0/60.7	0.470	0.671

*: 3 years survival, n: count, OS overall survival, DFS disease-free survival, LN lymph node

with grade 1 and compared together with grade 3 tumors in most of these studies [2, 4]. Therefore, sufficient data focusing on grade 2 endometrial cancer are not available in the literature. Lack of sharp discrimination between the grades and hence the low interobserver reproducibility are the main restrictions of the FIGO ternary grading system [1, 3]. The recent ESMO-ESGO-ESTRO consensus combined grade 1 and 2 of stage 1 endometrioid endometrial cancer in the same risk categories [6]. In the present

study, we investigate whether grade 2 endometrioid endometrial cancer prognosis tends towards grade 1 or 3. The main results of our study demonstrated that even major pathological parameters (MI, LVSI, LN involvement, cervical invasion, and stage) significantly varied among the three grade groups, survival indicators were comparable between grade 1 and 2 cases. Survival rates of patients with grade 3 were significantly different from both grade 1 and 2 groups. Moreover, these results were valid even after a

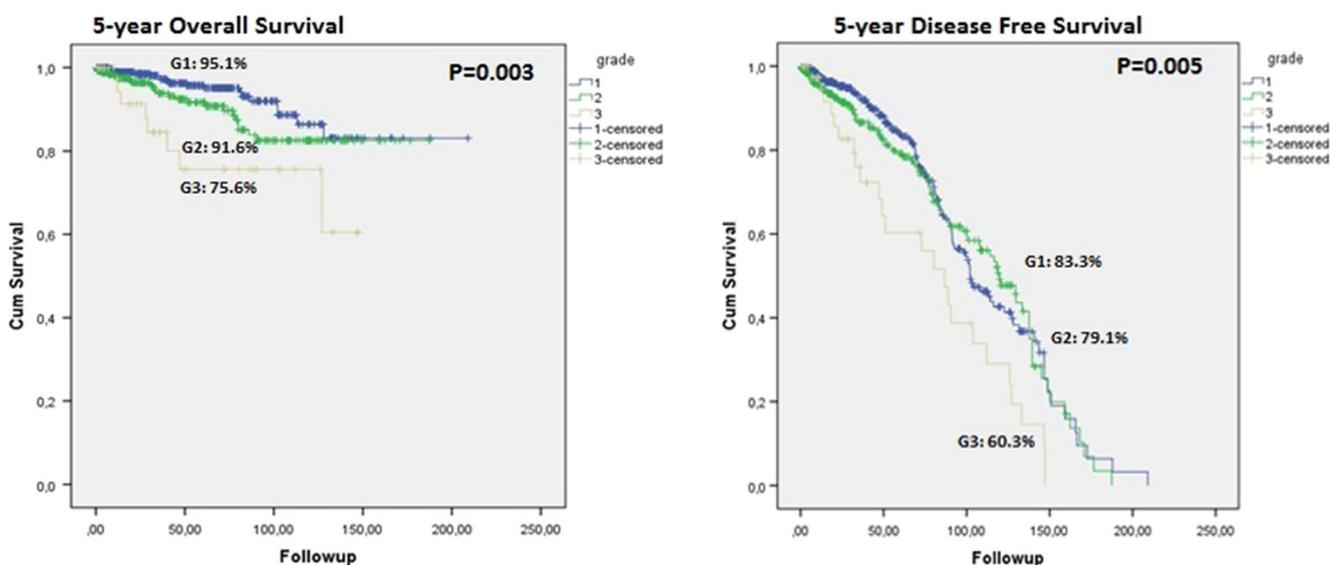


Fig. 1 Comparison of overall and disease free survival between grade groups

Table 3 Multivariate analysis of OS and DFS

Variable	OS				DFS			
	P	HR	95% CI		P	HR	95% CI	
			Lower	Upper			Lower	Upper
Grade	0.008	1.884	1.176	3.019	0.872	1.020	0.805	1.291
Cytology	0.933	0.984	0.669	1.446	0.805	1.024	0.850	1.233
LVSI	0.929	0.968	0.481	1.951	0.000	1.156	1.076	1.241
Omental metastasis	0.784	0.951	0.662	1.365	0.001	1.385	1.152	1.666
Adjuvant treatment	0.272	1.667	0.670	4.148	0.001	1.953	1.317	2.896
MI	0.007	0.334	0.151	0.740	0.862	0.966	0.657	1.421
LN involvement	0.568	0.707	0.215	2.327	0.113	0.534	0.245	1.160
Stage	0.011	3.807	1.360	10.654	0.044	1.915	1.018	3.605
Age	0.000	1.102	1.066	1.139	0.000	1.034	1.017	1.051
Recurrence	0.033	1193	1.014	1.402				

OS overall survival, DFS disease-free survival, CI confidence interval, HR hazard ratio, LVSI lymphovascular space invasion, MI myometrial invasion, LN lymph node

sub-analysis was performed between groups according to the abovementioned pathological parameters.

Many investigators reported that increasing grade of endometrial cancer was related to increasing myometrial invasion, positive lymph nodes and extra-uterine spread [8, 9]. Compatible with the literature, increasing grade was associated with MI, LVSI, LN involvement, cervical invasion, positive cytology, omental metastases and advance stage in our study.

Numerous studies have failed to demonstrate significant difference between grade 1 and 2 endometrial carcinoma prognosis [1, 4, 10]. Alkushi and colleagues declared that there was no significant difference between grade 1 and 2 endometrial carcinoma outcomes in their study [3]. Scholten et al. [4] stated in their study of 253 endometrial cancer cases that 5-year disease specific survival (DSS) of grade 1 and 2 was identical (92% and 94%, respectively) and it was significantly better from grade 3 (63%). Authors had also reported similar results in their next work [11]. Grade 1 and 2 of stage 1 endometrial cancer were considered eligible to be evaluated together in the PORTEC 1 study, due to the small difference between them [12]. Furthermore, uterus-confined grade 1 and 2 patients were stratified together into the same risk groups in the last ESMO-ESGO-ESTRO risk classification system [6]. Comparable to these results, statistically equal OS and DFS rates of grade 1 and 2 cases were determined in our study. On the other hand, grade 3 tumors were linked to significantly worse outcomes. Unlike the studies in the literature, all stages were included in the present study. However, a sub-analysis concerning various parameters including the stage was performed and identical results were noticed for the uterus-confined patients (stage 1–2). In stage 3–4 disease, no difference between grade groups was noted regarding both OS and DFS. Similarly, there was no significant difference in the

survival rates between grade groups in terms of LN positive patients, whereas the difference was significant in case of negative LNs.

A debate about the best reproducible grading system for endometrial cancer has been carried out for years [1, 3, 4, 10, 11, 13–16]. Lax and co-workers [10] described a binary grading system based on an assessment of solid areas, invasion pattern and necrosis coexistence and they compared this system with the FIGO ternary grading system. Authors concluded that a superior interobserver and intraobserver reproducibility was achieved with the binary grading system [10]. Scholten et al. [11] compared the FIGO ternary and Lax binary grading systems in 800 cases of endometrial carcinoma. Investigators determined that both grading systems were with robust prognostic significance, but the binary system was superior in terms of reproducibility [11]. However, the combination of FIGO grade 1 and 2 as low grade and considering grade 3 as high grade was suggested to be comparable to the two-tiered grading system in addition to the long practice and familiarity in the FIGO system application [3, 11]. On the other hand, Scholten concluded that their simple architectural grading method by segregating the patients into two groups according to the presence of more or less than 50% solid growth, was as reproducible as the FIGO 2-tiered system and had more prognostic value [11]. Taylor and colleagues, [13] suggested that subgrouping the endometrial carcinoma grade based on a cut-off value of 20% solid growth was at least with equal prognostic significance to the FIGO grading system.

Variability in the pathologic diagnosis of the endometrial cancer grade leads to under- and overtreatment conditions. Consequently, the controversy regarding how to stratify and categorize the grade of the endometrial cancer is bound to continue unless the clinical reactions of these classifications

is focused upon beside the pathologic point of view. For instance, studies in order to validate the recent ESMO-ESGO-ESTRO risk classification system may be planned for improvement in this issue. In our study, FIGO grade 1 and 2 endometrial cancer had identical good prognosis while grade 3 had significantly worse outcomes compared with grade 1 and 2. In addition, the grade was found to be an independent prognostic factor for OS. Ultimately, with respect to our findings, referring FIGO grade 1 and 2 endometrioid endometrial carcinomas in one category (e.g low grade) would be able to reflect the clinical aspects thoroughly. Even though simplifying the grading system of the endometrioid endometrial carcinomas is not a novel idea, this study establishes the possibility of combining FIGO grade 1 and 2 tumors, parallel to the recent ESMO-ESGO-ESTRO risk classification system.

The main disadvantage of our study is its retrospective design. On the other hand, high number of patients, assessment of the cases by the same expert team of gynecologic pathologists and gynecologic oncologists from an academic cancer center and the long follow-up period are the main strengths.

In conclusion, survival indicators were comparable between grade 1 and 2 cases, while survival rates of patients with grade 3 were significantly different from those of both grade 1 and 2 groups. The present study has shown that combining FIGO grade 1 and 2 endometrioid endometrial carcinomas may improve the variability and reproducibility among pathologists without affecting the interpretation of prognosis. However, prospective validation studies are required on this subject.

Acknowledgements Authors thank Professor Naki Tutuncu for editing the paper.

Author Contributions Conceptualization: UKG, MAV, GK; Methodology: UKG, MAV, GK; Validation: GK; Formal analysis and investigation: GK, UKG, ABG; Writing - original draft: UKG, GK; Writing - review and editing: UKG, MAV, ABG, GK, SP, EB; Funding acquisition: none; Resources, and Supervision: UKG, MAV, ABG, GK, EB, SP.

Data Availability Available and can be shared based on reasonable request.

Code Availability Not applicable.

Compliance with Ethical Standards

Conflict of Interest None.

Ethics Approval Not applicable.

Consent to Participate Informed Consent A written informed consent was taken from all participants in the study.

Consent for Publication A routinely written consent was taken for academic purposes from all participants.

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