

High-grade endometrial cancer survival (endometrioid to non-endometrioid histology comparison)

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Summary

Purpose of Investigation: To analyze overall survival (OS) and disease-free survival (DFS) in a retrospective series of 125 patients with serous, clear cell, and high-grade endometrioid carcinoma having undergone complete treatment (primary surgery, oncology treatments, and follow up) at the present institution. **Materials and Methods:** All women with high-grade endometrial cancer having undergone surgery (1998-2012) and postoperatively treated and monitored at Split University Hospital Center, whose tissue samples were stored at Department of Pathology, Split University Hospital Center, were included in the study. Survival time was analyzed with Kaplan-Meier method and the log-rank test was used to assess between-group differences. Cox proportional hazard regression model was used on multivariate survival analysis. Patients were followed from the time of primary surgery until death or last follow up in December 2015. **Results:** Women with serous and clear cell endometrial cancer had similar survival compared to those with high-grade endometrioid endometrial cancer. On multivariate analysis, only earlier stage was an independent predictor of improved survival. **Conclusions:** The present findings suggest that serous and clear cell endometrial carcinomas have a similar prognosis compared to high-grade endometrioid carcinoma of the uterus.

Key words: Uterine cancer; High-grade endometrial cancer; Serous endometrial cancer; Clear cell endometrial cancer; Survival.

Introduction

Endometrial cancer is the most common malignant tumor in gynecology in developed countries [1, 2]. Although it is a disease with good prognosis and overall survival, part of patients are at a high risk of recurrence and unfavorable outcome.

The most common basis for determining the risk of recurrence is division of endometrial cancer into two subtypes proposed by Bokhman in 1983 [3]. Type I, which has good prognosis, accounts for 80% of all endometrial cancer cases. It is associated with estrogen activity, endometrioid histology, and low FIGO Stage. In contrast, type II is associated with poor prognosis and is characterized by non-endometrioid histology, high grade, and higher stage of the disease. The non endometrioid group that includes serous (SC) and clear cell (CC) endometrial cancer accounts for 10%-15% of all endometrial cancer cases, but the mortality from this cancer accounts for 50% of overall endometrial cancer mortality. When relapse occurs, response to systemic therapy is limited and survival is low [4].

Over the last two decades, non-endometrioid histologic types that include SC and CC endometrial carcinomas have been grouped together with grade 3 endometrioid cancer (ECG3). Although belonging to different pathogenetic types, SC, CC, and ECG3 are grouped together as high-risk endometrial cancers and cause the most of endometrial cancer deaths. Recurrence was recorded in 40%-50% of high-

risk endometrial cancer cases [5, 6]. They accounted for 80% of all endometrial cancer deaths [7].

Serous carcinoma is the most aggressive type of nonendometrioid endometrial carcinoma [8-10]. Histologic diagnosis is based on the presence of papillae covered by highly pleomorphic tumor cells with frequent mitoses and necrosis. Myometrial invasion is prominent in most cases and vascular invasion is common. There is a tendency to lymphatic and transperitoneal spread with intra-abdominal involvement, as well as distant spread with a 50% recurrence rate. The incidence is about 10% of all endometrial carcinoma cases [11]. CC endometrial cancer, like uterine SC, is also a rare subtype of endometrial cancer accounting for 2% of endometrial carcinoma and is similarly characterized by a high recurrence rate and poor prognosis [12]. Extra-uterine disease is often found in both histologic subtypes, even in patients without myometrial invasion [13]. While endometrial tumors have a five-year survival of 83%, in case of SS and CC, it is 53% and 62%, respectively [14].

Regarding survival in patients with SC, CC or ECG3 prior studies have yielded different results. Some studies have shown that patients with SS and CC have worse survival as compared to ECG3 [14, 15]. In contrast, some recent studies have shown no difference in SS, CC survival versus ECG3 [7, 16].

The aim of this study was to assess high-grade endome-

trial cancer survival outcome in the present institution, looking separately high-grade endometrioid cancers, SC and CC endometrial carcinomas.

Materials and Methods

All patients with high-grade endometrial cancer having undergone surgery during the 1998-2012 period and postoperatively treated and monitored at Split University Hospital Center, whose tissue samples were stored at Department of Pathology, Split University Hospital Center, were included in the study. Patients with missing tissue samples or samples of inadequate quality were excluded from the study. All patients underwent simple hysterectomy, bilateral salpingo-oophorectomy, and omentectomy. Systematic pelvic with or without para-aortic lymphadenectomy was performed in 57 (47.1%) cases.

Data on the time of diagnosis, stage of disease, histology, adjuvant therapy, and survival were extracted and analyzed. Patients with incomplete clinical data were excluded from the study. Data on the treatment after surgery, chemotherapy, and/or radiotherapy and follow up were collected from Department of Oncology, where patients were postoperatively treated and monitored. Adjuvant radiotherapy or adjuvant chemotherapy was used according to the institutional standards. Radiotherapy included vaginal brachytherapy alone (low dose rate, 30 Gy in two fractions), whole pelvic external beam radiation alone (50 Gy in 25 fractions), or both of them. Chemotherapy included a platinum-based cytostatic in four to six cycles.

After completing surgical and oncologic treatment, patients were monitored at Clinical Department of Oncology, Split University Hospital Center. In the first two years after treatment, follow up examinations were performed every three months, and then every six months and included gynecologic examination, laboratory tests (blood count, basic liver and renal tests), abdominal ultrasound twice a year, computed tomography of the abdomen pelvis once a year, and other medical tests if needed.

Time of recurrence (disease-free survival, DFS) was marked in the months after the date of surgery until the diagnosis of recurrence. Survival time of the patients was calculated as the interval from the date of diagnosis to the date of the last clinical follow up or death from the endometrial carcinoma related causes until December 31, 2015. The outcome of interest was death from endometrial cancer and time to death was censored in women who died from causes other than uterine cancer. The median follow up was 47 months. Stage was defined using the 2009 FIGO classification.

All histopathology slides were revised by an experienced gynecologic pathologist (IKP) to confirm the original diagnosis at the time of surgery. The WHO criteria were used for the diagnosis of high-grade endometrial carcinoma (>50% of solid growth and nuclear grade 3). Immunohistochemical analysis for p53 and ER was employed on routine diagnostic work up for differential diagnosis of ECG3 and other types of carcinoma. When required on slide revision, immunohistochemistry was done using the same markers.

The Kaplan-Meier method was used to estimate survival as a function of time, and survival differences were analyzed with the log-rank test. The Cox proportional hazard regression model was used to examine simultaneously all factors found to be prognostic of survival in univariate analysis. In the analysis of DFS and overall survival (OS), the multifactorial Cox regression analysis was used. In all statistical procedures, the level of significance was set at $p < 0.05$. Analyses were performed using the Statistical Package for Social Sciences, version 10.0. The study

Table 1. — *Clinicopathologic data of study patients.*

Clinical data	Patients (n=125)
Age (years), mean (SD, range)	67±9 (39-86)
FIGO Stage, n (%)	
1	66 (52.8%)
2	20 (16.0%)
3	30 (24.0%)
4	9 (7.2%)
Histologic type, n (%)	
ECG3	47 (37.6%)
Serous endometrial cancer	78 (48.8%)
Clear cell endometrial cancer	17 (13.6%)
Lymphadenectomy, n (%)	
Performed	57 (45.6%)
Not performed	64 (53.4%)
Radiotherapy, n (%)	
Yes	69 (55.2%)
No	56 (44.8%)
Chemotherapy, n (%)	
Yes	46 (37.0%)
No	79 (63.0%)
Myometrial invasion	
No	20 (16.0%)
Yes	105 (84%)
Outcome	
Alive without disease	43 (34.4%)
Death from other causes	17 (13.6%)
Death from disease	51 (40.8%)
Lost for follow up	14 (11.2%)
Observation time (months), mean (range)	47.33 (1-151)

was approved by the Split University Hospital Centre Ethics Committee (500-03/13-01/20).

Results

During the observation period, 143 high-grade endometrial cancer patients were treated in the present hospital. Due to missing patient clinical data (n=10) or insufficient tissue quality (n=8), data sets of 125 (87%) patients were complete for analysis. The study included 61 SC, 17 CC, and 47 ECG3 cases.

Table 1 summarizes clinicopathologic data of the study population. According to histology, study patients were divided into two histologic groups (Table 2). Group 1 included ECG3, while group 2 consisted of SC+CC. There were 47 cases in group 1 and 78 cases in group 2. The mean age at diagnosis was 67.5 (range 39-86) years. There was no significant difference in the mean age between the ECG3 and SC+CC groups (64 and 67, respectively; $p = 0.870$). There was no difference in the distribution of FIGO Stages between groups 1 and 2 ($p = 0.102$). Myometrial infiltration was recorded in 43 (91.5%) ECG3 and 62 (79.5%) SC/CC carcinoma with no between-group difference ($p = 0.21$). A statistically significant between-group difference ($p = 0.035$) was found for myometrial infiltration separately, described as negative or infiltration up to or more

Table 2. — Distribution of clinicopathologic variables between group 1 (grade 3 endometrioid carcinoma, ECG3) and group 2 (serous + clear cell carcinoma, SC/CC)

	ECG3 (n=47)	SC + CC (n=78)	p-value	χ^2
FIGO Stage				
1	22 (46.8%)	44(56.4%)	0.102	6.2
2	11 (23.4%)	9 (11.5%)		
3	13 (27.7%)	17 (21.8%)		
4	1 (2.1%)	8 (10.3%)		
Lymphovascular invasion				
Negative	30 (64.0%)	52 (67.0%)	0.897	0.017
Positive	17 (36.0%)	26 (33.0%)		
Myometrial invasion				
Negative	4 (8.5%)	16 (20.5%)	0.035	6.69
< 50%	15 (31.9%)	33 (42.3%)		
> 50%	28 (59.6%)	29 (37.2%)		
Lymphadenectomy				
Not done	25 (56%)	39 (35.0%)	0.652	0.652
Done	20 (44.4%)	37 (49.0%)		
Lymph nodes				
Negative	7 (30%)	7 (18%)	0.256	1.3
Positive	16 (70%)	32 (82%)		
Age (years)				
≤ 65	25 (53%)	32 (41%)	0.255	1.29
> 65	22 (47%)	46 (59%)		
Radiotherapy				
Not done	19 (40.4%)	50 (64.1%)	0.034	6.7
Complete pelvic RTH	20 (42.6%)	19 (24.4%)		
BRTH only	8 (17 %)	9 (11.5%)		
Chemotherapy				
Not done	12 (25%)	34 (44%)	0.066	3.37
Done	35 (74%)	44 (56%)		

Table 3. — Survival (in months) according to histologic tumor type (histology groups 1-2).

		OS (SE)	95% CI	p Log rank	DFS (SE)	95% CI	p Log rank
All FIGO Stages	Group 1 (n=47)	84.7 (9.5)	66-103	0.829	76 (10)	59-96	0.062
	Group 2 (n=78)	91.5 (7.8)	76-106		86 (8)	70-101	

OS: overall survival; DFS: disease-free survival; SE: standard error; CI: confidence interval; group 1: ECG3; group 2: SC+CC.

than half. The present authors recorded a 2.4-fold higher rate of negative myometrial infiltration in group 2 (SC/CC) and a 1.6-fold higher rate of deeper myometrial infiltration (infiltration >1/2) in group 1 (ECG3) ($p = 0.035$) (Table 2). Lymphovascular invasion was equally represented in groups 1 and 2, with no statistically significant between-group difference ($p = 0.897$) (Table 2).

Among patients with Stage 1-3 disease, lymphadenectomy was performed in 20 (44.45%) group 1 patients. In group 2 (SC/CC), 37 (49%) patients underwent lymph node assessment. Altogether, lymph nodes were removed for histologic analysis in 57 (47.1%) high-grade endometrial cases. The use of radiotherapy (RTH) showed between-group differences. The proportion of patients not receiving RTH was 1.6-fold lower in group 2, while in group 1 (ECG3) there were 1.7-fold more patients that received complete pelvic RTH compared to group 2 ($p = 0.035$) (Table 2). Chemotherapy was equally used in the treatment

of both groups 1 and 2 patients, without a statistically significant difference ($p = 0.066$) (Table 2).

During the study period, recurrence of the disease was recorded in 55/125 (44%) patients, 51 (40%) of which died from endometrial cancer. In groups 1 and 2, disease recurrence was recorded in 21/47 (44%) and 34/78 (43.5%) patients, respectively. Out of 51 deaths, 33/78 (42%) deaths occurred in group 2 and 18/47 (38%) deaths in group 1.

Table 3 shows survival outcome according to histologic groups, including all FIGO stages. The present authors were unable to demonstrate statistically significant difference in survival between the SC/CC and ECG3 groups. There was no significant difference in either OS or DFS between ECG3 and SC+CC ($p = 0.829$ and $p = 0.062$, respectively) (Table 3).

Figures 1 shows the Kaplan-Meier curve for OS of the two histologic groups. Five-year survival was 51% in both groups 1 and 2 including all FIGO Stages, yielding no be-

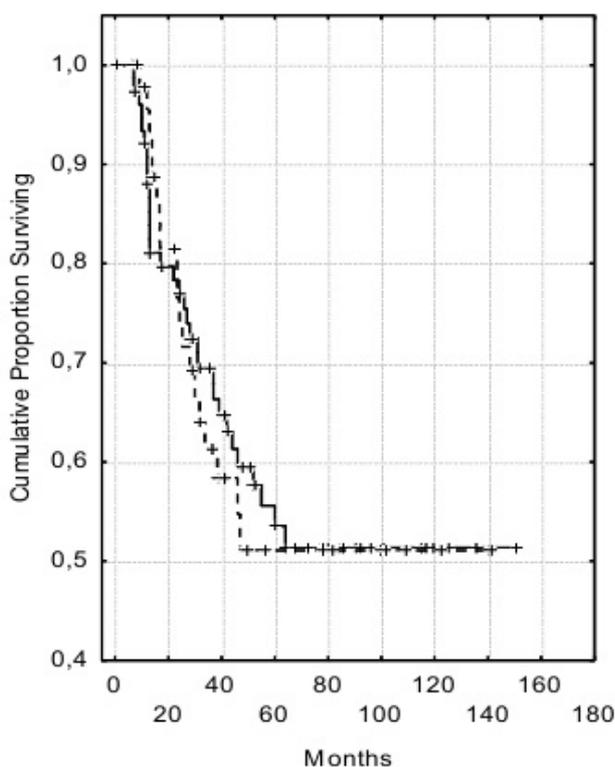


Figure 1. — Overall survival in 125 high-grade endometrial cancer patients. Broken line: high-grade endometrioid carcinoma group; full line: serous/clear cell carcinoma group. Statistical analysis was performed with Kaplan-Meier test.

tween-group difference.

Table 4 shows survival in both histologic groups according to FIGO Stages. The present authors noticed poorer survival in FIGO Stage 2 in ECG3 group compared to survival of FIGO Stage 2 in SC+CC group, which may be explained by the lower percentage of lymphadenectomy performed in group ECG3 FIGO Stage 2 compared with SC/CC FIGO Stage 2, yielding a statistically significant difference ($p = 0.043$).

Using the Cox proportional hazards model, clinicopathologic prognostic factors were investigated as independent predictors of survival in groups 1 and 2 separately (Table 5). On multivariate analysis, advanced stage disease was an independent predictor of poorer survival in both groups ($p = 0.036$ and $p < 0.001$, respectively), while age at the time of diagnosis and lymphovascular invasion were not (Table 5). On multivariate analysis, only chemotherapy correlated with better OS in both groups ($p = 0.045$ and $p = 0.046$, respectively), while there was no such association with radiotherapy ($p = 0.574$ and $p = 0.068$, respectively) (Table 5).

Discussion

Serous carcinoma is the most aggressive type of non-endometrioid endometrial carcinoma, followed by CC carcinoma, which is similar in clinical behavior and prognosis [6]. High-grade endometrioid carcinoma, according to its pathogenesis, does not belong to this group, but clinically shows similar, aggressive tumor biology. Some studies have shown that patients with SS and CC have worse survival compared to ECG3 [14-17], while other studies have shown no difference in SS and CC survival versus ECG3 [7, 18-22]. The mentioned studies analyzed the 1967-2002 period.

The present study analyzed the 1998-2012 period, when diagnostic and therapeutic approach to endometrial carcinoma cancer was modified. Lymphadenectomy has been introduced as part of the complete surgical staging for high-grade endometrial cancer and the rate of lymphadenectomy has increased [23]. Postoperative adjuvant therapy also changed in the mentioned period. There is a worldwide trend of rare application of RTH for carcinoma of the endometrium because of the lack of proven impact of radiotherapy on survival [24]. On the contrary, chemotherapy has been increasingly used as adjuvant treatment of high-risk endometrial cancer, in lower stages of the disease, which is published in the FIGO annual report [24, 25]. Despite changes in therapy, there are studies indicating that the survival of high-grade endometrial cancer worsened in the 20-year period, as well as its incidence [23]. Consequently, in light of new therapeutic approaches, it seemed to be worthwhile to reanalyze survival of this group as the most lethal type of endometrial cancer.

This single-center retrospective analysis showed that there was no survival difference between the ECG3 and SS/CC groups. It is consistent to the report by Voss *et al.*, who showed similar results in a group of comparable size of high-grade endometrial cancer patients [7]. Moreover, the distribution of stages in high-grade endometrial carcinoma was similar in both studies. Similar results have been reported by Soslow *et al.* in 2007, Cirisan *et al.* in 2000, Alektiar *et al.* in 2002, Halperin *et al.* in 2002, and Creasman *et al.* in 2004 [18-22]. Reynaers *et al.* in 2015 compared outcomes between endometrioid and non-endometrioid tumors in patients with early-stage high-grade endometrial cancer. There was no significant difference between the groups [26]. McGunigal *et al.* in 2017 have shown slightly more better survival in ECG3 group, but also not statistically significant [27]. In conclusion, these studies found no significant outcome differences between patients with SC/CC endometrial cancer and those with a similar stage disease, but with ECG3.

Except for survival analysis, the aim in this study was also to determine prognostic value of some clinicopathologic variables in SC/CC and ECG3 separately. Some studies proved the prognostic value of age above 65 for poorer

Table 4. — Survival (in months) according to FIGO stage in group 1, grade 3 endometrioid carcinoma (ECG3) and group 2, serous + clear cell carcinoma (SC/CC).

FIGO Stage	Group 1, ECG3 (n=47)		p	Log rank	Group 2, SC/CC (n=78)		p	Log rank
	OS (SE)	95% CI			OS (SE)	95% CI		
1	116 (11)	93-138	< 0.001	59	125 (8)	108-141	> 0.001	36.5
2	31 (8.7)	14-48			79 (20)	39-119		
3	77 (17)	43-112			36 (5)	26-47		
4	9 (0)				23 (7)	9.4-37		

OS: overall survival; SE: standard error; CI: confidence interval.

Table 5. — Univariate and multivariate analysis on overall survival: high grade endometrioid and serous and clear cell endometrial carcinoma.

High-grade endometrioid endometrial carcinoma	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p
FIGO Stage						
1-4	1.98	1.2-3.3	0.007	1.8	1.04-3.1	0.036
Age (years)						
≤ 65	1.9	0.77-4.7	0.160			0.163
> 65						
Lymphovascular invasion						
Negative	2.6	1.1-6.5	0.036			0.185
Positive						
Radiotherapy						
Yes	1.9 (0.95-3.9)	0.068	0.574			
No						
Chemotherapy						
Yes						
No	2,0	1.2-4.5	0,035	1,5		0,045
Serous and clear cell endometrial ca.						
FIGO Stage						
1-4	2.3	1.7-3.1	< 0.001	1.9	1.3-2.8	< 0.001
Age (years)						
≤ 65	1.9	0.89-4.2	0.093			0.321
> 65						
Lymphovascular invasion						
Negative	2.77	1.4-5.5	0.005			0.944
Positive						
Radiotherapy						
Yes	4.3	1.6-11.2	0.003	2.6	0.93-7.7	0.068
No						
Chemotherapy						
Yes						
No	2,2	1.6-3.1	0.03	2.2	0.81-6.8	0.046

survival in high-grade endometrial cancer patients [6, 14, 18, 28]. Lymphovascular invasion is reported as an independent prognostic parameter in some papers [6, 14, 20]. Usually, all three groups were placed together in the analysis of prognostic parameters; although they belonged to different pathogenetic groups, the study did not confirm the prognostic value of age and lymphovascular invasion in either ECG3 or SC/CC group. The adjuvant chemotherapy had prognostic value on OS in both histologic groups, in the present study, what has also been shown in recent meta-analysis on endometrial cancer [25, 29].

The possible limitation of the present study was incompleteness of optimal surgical staging, which refers to lym-

phadenectomy. At the present institution, according to the FIGO recommendations, it is agreed that lymphadenectomy be performed as part of complete surgical staging for high-grade endometrial cancer. This practice was introduced in 2002 and the rate of lymphadenectomy performed increased from 20% in 2002 to 77% in 2012. Consequently, altogether, in the 1998-2012 period, lymphadenectomy was performed in 49.1% of high-grade endometrial cancers Stages 1-3. Yet, other similar studies report relatively few lymphadenectomy procedures, e.g., 20% [7] and 28% [20]. Another limitation of the present study was the relatively small number of patients, which may have influenced the results, but the study population included all cases of high-

grade endometrial carcinoma treated at the present institution during the 1998-2012 period. Also, despite the small number of patients, the results are consistent with some previously mentioned studies.

Although survival was similar in the two groups, there still remains an open and more important issue, i.e. the molecular basis of endometrial serous carcinogenesis and/or endometrioid carcinogenesis. In support to this is the similar immunohistochemical profile of ECG3, as well as SC and CC carcinomas, as demonstrated by recent research [7, 30].

Conclusions

In conclusion, the five-year survival of SC/CC and ECG3 patients treated at the present institution was 51% in both groups. This study showed no difference in survival between the SC/CC and ECG3 groups. In these groups, higher FIGO stages and chemotherapy proved to be prognostic on multivariate analysis.

Also, a proposal for further researches is to analyze the molecular basis of grade 3 (in separate from group type 1) and compare it with non-endometrioid carcinoma. It is necessary to clarify, by this knowledge on their similar survival, whether there are similarities in their molecular profile that lead to increased invasiveness.

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