Current Problems in Cancer 43 (2019) 160–166

Contents lists available at ScienceDirect

Current Problems in Cancer

journal homepage: www.elsevier.com/locate/cpcancer

Comparison of clinicopathologic and survival characteristics of high grade endometrial cancers; single center experience

Ozlem Ercelep[a,*], Mahmut Gumus[b]

[a] Department of Medical Oncology, Dr. Lutfi Kirdar Kartal Education and Research Hospital, Istanbul, Turkey
[b] Department of Medical Oncology, Faculty of Medicine, Bezmi Alem Vakif University, Istanbul, Turkey

ARTICLE INFO

Keywords:
Grade 3 Endometrioid Carcinoma
Uterine Serous Carcinoma
Clear Cell Carcinoma
Nonendometrioid Carcinoma

ABSTRACT

Purpose: Approximately a quarter of endometrial cancers are of high grade. We aimed to perform clinicopathologic and survival evaluation of high grade endometrial cancer in our study.

Method: We evaluated the data of 78 high grade patients; 30 G3EC (Grade 3 Endometrioid Carcinoma), 48 nonendometrioid carcinomas; 32 USC (uterine serous carcinoma), 16 CCC (clear cell carcinoma), from 312 patients who were followed with endometrial cancer between years 2006 and 2016.

Results: Mean age was 62 years (range 43-83) in all patients, the age in histologic subtypes was 56.5, 65, 66.3, years for G3EC, USC, and CCC, respectively. The G3EC mean age is significantly smaller than other histologic subtypes ($P = 0.00$). The median follow-up time was 39 months (range 6-136). The 5-year overall survival was 55%, 44%, G3EC, and nonendometrioid carcinoma (USC and CCC), respectively ($P = 0.127$). In the univariate model; age $>$ 65, ECOG-PS $\geq$ 2, stage 3-4 disease, LVI presence were poor prognostic factors ($P < 0.05$). Effect of the stage of the disease, the age of the patients and ECOG-PS on survival was demonstrated with multivariate analysis. The clinicopathologic features of the patients were similar.

☆ Conflicts of interest: None.

☆☆ Ethical statement: Not applicable because the study was retrospective.

* Correspondence to: Department of Medical Oncology, Pendik Education and Research Hospital, Marmara University, Istanbul, Turkey.

E-mail address: ozlembalvan@yahoo.com (O. Ercelep).

https://doi.org/10.1016/j.currproblcancer.2018.07.004

Conclusion: G3EC is seen at a younger age than other high grade endometrial carcinomas. Grade 3 endometrioid carcinomas have an increasing trend in survival compared to high grade nonendometrioid carcinomas.

Background

Endometrial cancer is the most common gynecologic cancer in developed countries and is the second most common in developing countries. Its incidence is increasing; in 2012, around 320,000 new cases of endometrial cancer were diagnosed worldwide, which is associated with a mortality rate of approximately 20%. Endometrial cancer contains a large number of diseases with different genetic and molecular characteristics.[1,2]

In the past 30 years, endometrial cancers have roughly divided into 2 subtypes according to their histologic characteristics, hormone receptor expression and grade.[3]

The most common subtype is type I endometrial cancers which include good and moderately differentiated endometrioid endometrial cancers. Clinicopathologic features and molecular profile differ from type II cancer.[4-9]

Type II endometrial cancers contain non-endometrioid (serous, clear cell carcinoma), high grade, TP53 mutated, hormone receptor negative cancers. It is associated with a higher risk of metastasis and a poor prognosis.[3]

G3EC contains genomic and epigenomic alterations of both histologic subtypes.[12,13] The clinical behavior of Grade 3 EC and type II cancers is similar and often coexists. Hence there has been debate about the classification of G3EC as type I or type II EC.[10-15]

Comparative clinical analyses of G3EC, uterine serous carcinoma (USC), and clear cell carcinoma (CCC) are very limited, due to the low prevalence of these histologic subtypes. The aim of our study was to compare the outcomes between patients with G3EEC and nonendometrioid carcinomas (USC and CC).

Materials and methods

The data of 312 endometrium cancer patients followed in our medical oncology clinic between 2006 and 2016 were retrospectively analyzed. The results of 78 patients with high-grade endometrium cancer were evaluated. The patients were divided into 3 groups according to histologic subtypes G3EC, USC, CCC, and 2 subtypes endometrioid (G3EC) and nonendometrioid carcinomas. Patient characteristics (age stage, lymphovascular invasion [LVI], lymphadenectomy, Eastern Cooperative Oncology Group-Performance Status [ECOG-PS], body mass index, adjuvant therapy, diabetes mellitus, hypertension) and survival were compared between the groups. Survival analysis was performed in early stage (stage I-II) and advanced stage (stage III-IV).

Overall survival (OS) and progression free survival were calculated using the Kaplan-Meier method. For descriptive statistics of the data, mean, and frequency were used. Prognostic factors were compared using the log-rank test in univariate analysis. Hazard ratios with 95% confidence intervals were also calculated. All *P* values were 2-sided in the tests, and *P* values of 0.05 were considered to be statistically significant. Multivariate analysis was carried out using the Cox proportional hazards model to assess the effect of prognostic factors on survival. For statistical analysis, SPSS version 17.0 was used.

Results

We retrospectively evaluated the data of 78 (25%) high grade patients; 30 G3EC (Grade 3 Endometrioid Carcinoma), 32 USC, 16 CCC. There was no statistically significant difference in

Table 1
Clinicopathological data of G3EEC, USC, CCC patients.

		G3EEC (n:30)	USC (n:32)	CC (n:16)	All Patients (n:78)	*P*
Age (mean)		56.5	65	66.3	62.0	0.001
Stage						0.583
	1A	3	7	6	16	
	1B	9	2	1	12	
	2	1	8	1	10	
	3	10	12	5	27	
	4	7	3	3	13	
Stage-group						
	1-2	13	17	8	38	0.588
	3-4	17	15	8	40	
LVI						0.098
	no	12	19	8	39	
	yes	15	19	6	30	
	unknown	3	4	2	9	
Lymphadenectomy						0.079
	no	8	12	8	28	
	yes	22	19	7	47	
ECOG-PS						0.217
	0-1	28	28	13	69	
	≥2	2	4	3	9	
BMI (mean)		30.99	31.52	32.58	31.53	0.358
Adjuvant Therapy						0.136
	observation	4	2	6	12	
	chemotherapy only	8	10	5	23	
	EBRT only	7	7	2	16	
	chemotherapy and EBRT	11	13	3	27	
Surgery						0.566
	no	0	1	1	2	
	TAH + BSO	8	12	8	28	
	TAH + BSO + staging	22	19	7	48	
Diabetes Mellitus, no. (%)						0.791
	no	13	12	5	30	
	yes	7	9	3	19	
Hypertension, no. (%)						0.976
	no	8	11	3	22	
	yes	13	11	6	30	

BSO, Bilateral Salpingo Oophorectomy; EBRT, External Beam Radiotherapy; TAH, Total Abdominal Hysterectomy.

terms of demographic characteristics (stage, LVI, lymphadenectomy, ECOG-PS, body mass index, adjuvant therapy, diabetes mellitus, hypertension) except age (Table 1). Seventy-six patients underwent surgery. After surgery, 50 patients (65%) received adjuvant chemotherapy—carboplatin (area under the curve; 5-6) and paclitaxel (175 mg/m^2) based systemic combination chemotherapy, every 3 weeks for 3-8 cycles, median 6 cycles. Forty-three patients (57%) received adjuvant external beam radiotherapy. Eighty-nine percent of our patients were postmenopausal while 11% were premenopausal.

Mean age was 62 years (range 42-83) in all patients; the mean age in histologic subtypes was 56.5, 65, for 66.3 G3EC, USC, and CCC, respectively. The G3EC mean age is significantly smaller than other histologic subtypes ($P = 0.000$). The mean follow-up was 39 months (range 6-136). At the time of analysis, 38 patients died (49%) and 40 patients were alive (51%).

The median survival time was 54 months in all patients. The 5-year overall survival in all stages was 55%, 44% for G3EC, and nonendometrioid carcinomas, respectively ($P = 0.127$) (Figs. 1 and 2) (Table 2). Forty-nine percent of the patients were stage I-II, while 51% were stage III-IV. The 5-year survival rate in the early stage was 63%, while in the advanced stage it was 31% ($P = 0.003$). The 5-year overall survival in early stage (stage I-II) was 72%, and 59% for G3EC,

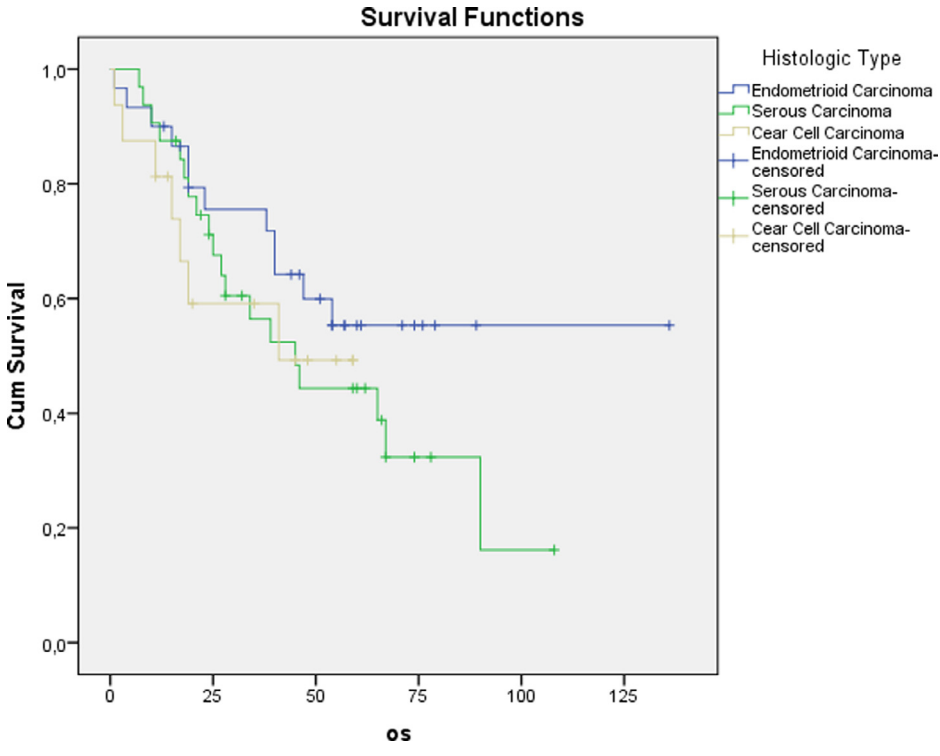

Fig. 1. Overall survival (OS) according to histological subtypes.

Table 2
Overall survival (OS) and relapse free survival (RFS), according to histological subtypes in high grade endometrial cancer.

		G3EEC	USC	CC	All Patients	*P*
OS Rate (5 year) (%)	all stages	55	44	49	49	0.376
	stage I-II	72	61	58	63	0.512
	stage III-IV	43	24	45	35	0.522
RFS (5 year) (%)	stage I-III	65	39	77	56	0.233

Kaplan-Meier (Log-rank).

nonendometrioid carcinomas, respectively ($P = 0.218$). The 5-year overall survival in advanced stage (stage III-IV) was 43%, 27%, and for G3EC, nonendometrioid carcinomas, respectively ($P = 0.258$). The 5-year progression free survival in all stages was 67%, 48%, for G3EC and nonendometrioid carcinomas, respectively ($P = 0.404$).

In the univariate model; the age of the patients (≤ 65, >65), the stage of the disease (I-II, III-IV), ECOG-PS (0-1, ≥ 2), LVI (no and/or yes) had significant effects on survival time. Age > 65, ECOG-PS ≥ 2, stage III-IV disease, LVI presence were poor prognostic factors ($P < 0.05$). Effect of the stage of the disease, the age of the patients and ECOG-PS on survival was demonstrated with multivariate analysis (Table 3).

Discussion

High grade endometrial cancers are a heterogeneous group of tumors and include G3EC, USC, and CCC. The 5-year survival rate is approximately 87% for International Federation of

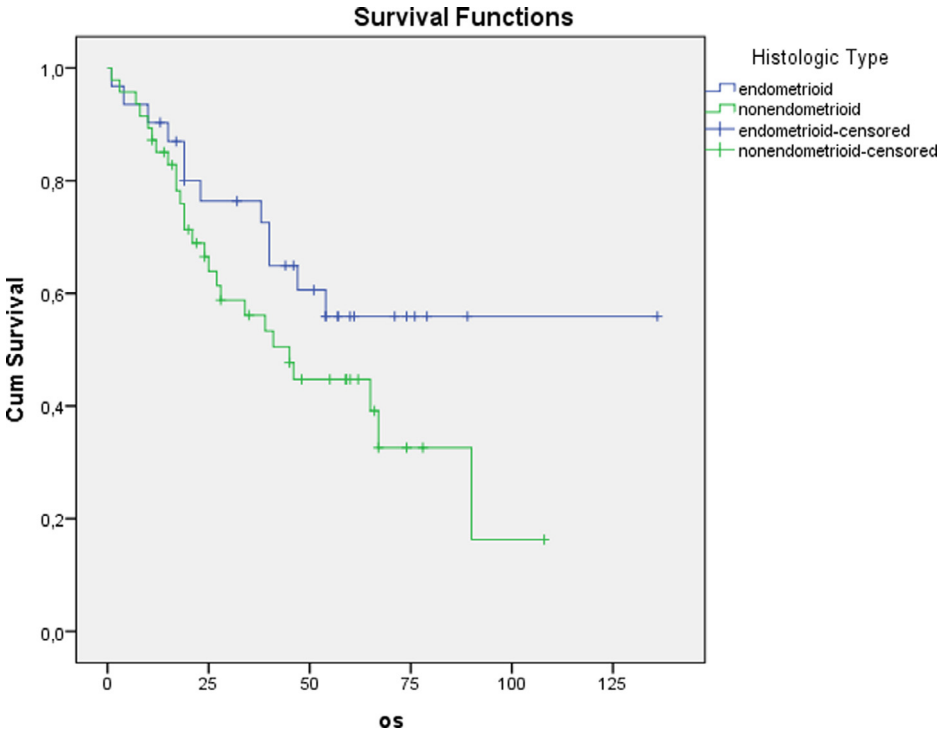

Fig. 2. Overall survival (OS) according to histological subtypes (endometrioid or nonendometrioid carcinoma).

Table 3
Cox-regression model of overall survival (OS) in high grade endometrial cancer.

	Univariate Analysis				Multivariate Analysis			
	HR	95 % CI		*P*	HR	95 % CI		*P*
		Lower Bound	Upper Bound			Lower Bound	Upper Bound	
Age (≤65 / >65)	3.56	1.86	6.84	***0.000***				***0.009***
Stage (I-II / III-IV)	2.75	1.37	5.51	***0.004***				***0.009***
Operation Type (Non-lymphadenectomy / Lymphadenectomy)	1.09	0.55	2.14	0.810				
LVI (no / yes)	1.44	1.06	1.95	***0.018***				
ECOG (0-1 / ≥2)	6.74	2.96	15.33	***0.000***				***0.050***
Histological Type (Endometrioid / Non endometrioid)	1.32	0.85	2.05	0.200				

Cox-regression.

Gynecology and Obstetrics stage I, 76% for stage II, 57% for stage III, and 18% for stage IV endometrial cancer.[16,17] The 5-year survival rate is lower in type II cancers, 53% in USC, 62% in CCC, and 83% in type I cancers.[18] Prognosis of endometrial cancer patients is also related to the histologic tumor type, differentiation grade, patient age, myometrial invasion, lymphovascular invasion, and therapeutic possibilities.[16,19]

The majority of endometrial cancers are early stage, low grade, with a good prognosis. Type II cancers are generally associated with more aggressive clinical behavior than type I tumors. Only

14% of type I cancers were at stages III-IV at diagnosis, while 41% of papillary serous carcinomas and 33% of clear cell carcinomas were diagnosed at these advanced stages.[20]

There was no difference in survival between histologic subtypes in our study. The 5-year overall survival in all stages was 55%, 44%, and 49% for G3EC, USC, and CCC, respectively. There was no significant OS difference in both early-stage and advanced-stage patients compared to histologic subtypes (endometrioid or nonendometrioid). But OS in patients with G3EC did not reach statistical significance, although it was numerically better, which may be due to the inadequate number of cases.

There is no consensus on the prognosis of these 3 high-risk endometrial cancers in the literature.[21-28] In the analysis of SEER made in 2006, Hamilton et al. described a superior prognosis for G3EC compared with type II cancers (USC, CCC).[21] Cirisano et al. performed a retrospective study on the outcome of 574 stage I-II endometrial cancer patients. Subset analyses showed that patients with serous papillary or clear cell tumors have a shorter survival and they are older than those with endometrioid cancers ($P = 0.001$).[22] In this study, USC and CCC frequencies were higher in stage III-IV and G3EC frequency was higher in stage I-II. In our study, there was no difference in histologic subtype frequency according to the stage. Creasman et al. retrospectively analyzed data and showed that 5-year survival was 72% and 81% for early stage serous papillary and clear cell carcinomas, respectively, which was similar to the 76% found for grade III endometrioid carcinomas.[28] In another study, Ayeni et al. published a retrospective study on 370 (stage I-IV) endometrial cancer patients, of which 119 patients had grade III endometrioid type, 211 had papillary serous type, and 40 had clear cell type carcinomas. Overall survival was similar among different subtypes and stages.[29] Robert A. Soslow and colleagues showed that 187 high grade endometrial carcinoma patients had similar clinical outcomes compared to histologic subtypes. They also found that patients with USC and CCC histology were older.[30] Similar results were seen in our study. Reynaers and colleagues found no significant difference between endometrioid and non-endometrioid (USC, CCC) groups in the 5-year recurrence-free survival study in early-stage high-grade 123 patients in 2015.[31]

In our study, the ratio of high grade endometrial cancers to all endometrial cancers was 25% (78/312), which is similar to the results in the literature. Previous trials[20,29,32] have shown a negative effect of lymphovascular invasion on survival and our study showed that LVI is a poor prognostic factor.

Because of the limited number of studies in the literature on high grade endometrial cancers and the lack of literature on this topic in our country before, we wanted to report the survival and clinicopathologic features of high grade endometrial cancer in our patient population. The shortcoming of our study is that it is a retrospective study and molecular characteristics are not examined.

Conclusion

Although high grade endometrial cancers constitute approximately 25% of all endometrial cancers, they are responsible for most of the deaths. High grade endometrioid carcinomas have an increasing trend in survival compared to nonendometrioid carcinomas. Advanced age, late stage and presence of LVI is associated with poor prognosis.

References

1. Kandoth C, Schultz N, Cherniack AD, et al. the Cancer Genome Atlas Research Network. Integrated genomic characterization of endometrial carcinoma. *Nature*. 2013;497:67–73.
2. Hussein YR, Soslow RA. Molecular insights into the classification of high-grade endometrial carcinoma. *Gyneco Pathology*. 2018;50:151–161.
3. Bokhman JV. Two pathogenetic types of endometrial carcinoma. *Gynecol Oncol*. 1983;15:10–17.
4. Hecht JL, Mutter GL. Molecular and pathologic aspects of endometrial carcinogenesis. *J Clin Oncol*. 2006;24:4783–4791.
5. Lax SF, Kendall B, Tashiro H, et al. The frequency of p53, K-ras mutations, and microsatellite instability differs in uterine endometrioid and serous carcinoma: evidence of distinct molecular genetic pathways. *Cancer*. 2000;88:814–824.

6. Prat J. Prognostic parameters of endometrial carcinoma. *HumPathol*. 2004;35:649–662.
7. Lax SF. Molecular genetic pathways in various types of endometrial carcinoma: from a phenotypical to a molecular-based classification. *Virchows Arch*. 2004;444:213–223 [Epub 2004 Jan 28].
8. Bansal N, Yendluri V, Wenham RM. The molecular biology of endometrial cancers and the implications for pathogenesis, classification, and targeted therapies. *Cancer Control*. 2009;16:8–13.
9. Alvarez T, Miller E, Duska L, et al. Molecular profile of grade 3 endometrioid endometrial carcinoma: is it a type I or type II endometrial carcinoma? *Am J Surg Pathol*. 2012;36:753–761.
10. Cirisano Jr FD, Robboy SJ, Dodge RK, et al. The outcome of stage I–II clinically and surgically staged papillary serous and clear cell endometrial cancers when compared with endometrioid carcinoma. *Gynecol Oncol*. 2000;77:55–65.
11. Halperin R, Zehavi S, Langer R, et al. Uterine papillary serous carcinoma (pure and mixed type) compared with moderately and poorly differentiated endometrioid carcinoma: a clinicopathologic study. *Eur J Gynaecol Oncol*. 2002;23:300–304.
12. Alektiar KM, McKee A, Lin O, et al. Is there a difference in outcome between stage I–II endometrial cancer of papillary serous/clear cell and endometrioid FIGO grade 3 cancer? *Int J Radiat Oncol Biol Phys*. 2002;54:79–85.
13. Boruta 2nd DM, Gehrig PA, Groben PA, et al. Uterine serous and grade 3 endometrioid carcinomas: is there a survival difference? *Cancer*. 2004;101:2214–2221.
14. Soslow RA, Bissonnette JP, Wilton A, et al. Clinicopathologic analysis of 187 high-grade endometrial carcinomas of different histologic subtypes: similar outcomes belie distinctive biologic differences. *Am J Surg Pathol*. 2007;31:979–987.
15. Voss MA, Ganesan R, Ludeman L, et al. Should grade 3 endometrioid endometrial carcinoma be considered a type 2 cancer: a clinical and pathological evaluation. *Gynecol Oncol*. 2012;124:15–20.
16. Van Driel W, Creutzberg C, Grimbergen C, et al.: National guideline 'endometrial cancer'. Approved by the Dutch society of Obstetrics and Gynaecology (NVOG) in. February February 2011;2011.
17. Cooke EW, Pappas L, Gaffney DK. Does the revised international federation of gynecology and obstetrics staging system for endometrial cancer lead to increased discrimination in patient outcomes. *Cancer*. 2011;117:4231–4237.
18. Hinshaw HD, Smith A, Rungruang B, et al. The risk of subsequent malignancies in women with uterine papillary serous or clear cell endometrial cancers. *Int J Gynecol Cancer*. 2013;23:1044–1049.
19. Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with, stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post operative radiation therapy in endometrial carcinoma. *Lancet*. 2000;355:1404–1411.
20. Sert F, Yilmaz U, Alanyali S, et al. Evaluation of unusual and highly aggressive variant of endometrium cancer: nonendometrioid endometrium carcinoma of the uterus. *Tumori*. 2017;103:551–556.
21. Hamilton CA, Cheung MK, Osann K, et al. Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers. *Br J Cancer*. 2006;94:642–646.
22. Cirisano Jr FD, Robboy SJ, Dodge RK, et al. The outcome of stage I–II clinically and surgically staged papillary serous and clear cell endometrial cancers when compared with endometrioid carcinoma. *Gynecol Oncol*. 2000;77:55–65.
23. Boruta 2nd DM, Gehrig PA, Groben PA, et al. Uterine serous and grade 3 endometrioid carcinomas: is there a survival difference? *Cancer*. 2004;101:2214–2221.
24. Voss MA, Ganesan R, Ludeman L, et al. Should grade 3 endometrioid endometrial carcinoma be considered a type 2 cancer: a clinical and pathological evaluation. *Gynecol Oncol*. 2012;124:15–20 [Epub 2011 Aug 23].
25. McMeekin DS, Filiaci VL, Thigpen JT, et al. Gynecologic Oncology Group study. The relationship between histology and outcome in advanced and recurrent endometrial cancer patients participating in first-line chemotherapy trials: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2007;106:16–22.
26. Greggi S, Mangili G, Scaffa C, et al. Uterine papillary serous, clear cell, and poorly differentiated endometrioid carcinomas: a comparative study. *Int J Gynecol Cancer May*. 2011;21:661–667.
27. Creasman WT, Kohler MF, Odicino F, et al. Prognosis of papillary serous, clear cell, and grade 3 stage I carcinoma of the endometrium. *Gynecol Oncol*. 2004;95:593–596.
28. Fader AN, Starks D, Gehrig PA, et al. UPSC Consortium. An updated clinicopathologic study of early-stage uterine papillary serous carcinoma (UPSC). *Gynecol Oncol*. 2009;115:244–248 (Epub 2009 Aug 26).
29. Ayeni TA, Bakkum-Gamez JN, Mariani A, et al. Comparative outcomes assessment of uterine grade 3 endometrioid, serous, and clear cell carcinomas. *Gynecol Oncol*. 2013;129:478–485.
30. Soslow RobertA, Bissonnette JohnP, Wilton Andrew, et al. Clinicopathologic analysis of 187 high-grade endometrial carcinomas of different histologic subtypes: similar outcomes belie distinctive biologic differences. *Am J Surg Pathol*. 2007;31:979–987.
31. Reynaers EAEM, Ezendam NPM, Pijnenborg JMA. Comparable outcome between endometrioid and non-endometrioid tumors in patients with early-stage high-grade endometrial cancer. *J Surg Oncol*. 2015;111:790–794.
32. Kim HJ, Kim TJ, Lee YY, et al. A comparison of uterine papillary serous, clear cell carcinomas, and grade 3 endometrioid corpus cancers using 2009 FIGO staging system. *J Gynecol Oncol*. 2013;24:120–127.