Prognosis of high-grade endometrial cancer: a comparison of serous-type and clear cell type to grade 3 endometrioid-type

T. Goto, M. Takano, T. Aoyama, M. Miyamoto, A. Watanabe, M. Kato, N. Sasaki, J. Hirata, H. Sasa, K. Furuya

Department of Obstetrics and Gynecology, National Defense Medical College, Tokorozawa, Saitama (Japan)

Summary

Objective: To evaluate prognosis of high-grade endometrial cancers, comparing serous (SC) and clear cell (CCC) types to grade 3 endometrioid carcinoma (ECG3). *Methods:* Among patients with endometrial cancer treated in two decades, medical records of patients with high-grade endometrial cancer were retrospectively investigated. *Results:* Of 447 endometrial cancers, 107 (24%) high-grade endometrial cancers were identified, with the increasing incidence in the last decade (28% vs 19%; $p = 0.026$). There were 24 SC, 14 CCC and 69 ECG3. Median age was 62, 68, and 61 years, respectively, with the CCC type showing an elder age than the ECG3 type ($p = 0.012$). The rates of patients with Stage IIIc-IV, lymph node assessment or complete resection at primary surgery, and post-operative chemotherapy were not significantly different; however, response rate to first-line chemotherapy in patients with measurable disease was lower in SC than ECG3 (3 / 11, 27% vs 14 / 19, 74%; $p = 0.037$), regardless of regimens. Five-year overall survival (OS) was 40%, 71%, and 71% respectively, and five-year progression-free survival (PFS) was 25%, 71%, and 61%, respectively, showing SC with worse prognosis than ECG3 on both OS ($p = 0.026$) and PFS ($p = 0.0028$). According to the multivariate analysis, age ≥ 70, Stage IIIc-IV and incomplete resection were independent prognostic factors on poor OS, whereas SC, Stage IIIc-IV and incomplete resection were on poor PFS. *Conclusions:* The increasing trend of high-grade endometrial cancer and different outcomes according to histological subtypes, especially poor PFS and chemotherapeutic response in SC, were suggested.

Key words: High-grade endometrial cancer; Endometrioid; Serous; Clear cell; Prognosis; Chemotherapy.

Introduction

Despite less frequencies among the endometrial carcinoma, International Federation of Gynecology and Obstetrics (FIGO) grade 3 endometrioid carcinomas (ECG3), along with serous carcinomas (SC) and clear cell carcinomas (CCC), relevant to type II endometrial cancers, are considered as high-risk endometrial carcinomas [1]. Most studies on endometrial carcinoma subtypes have compared SC, together with CCC [2-4], to endometrioid carcinoma including low-grade (grade 1 - 2) and grade 3 [5, 6] due to their rarity; thus there are relatively few data on the comparison of ECG3 with SC or CCC, respectively. Grade 1 - 2 endometrial carcinomas are associated with a favorable prognosis, but the effect of histological subtypes upon prognosis of high-grade endometrial carcinomas remains rather conflicting. Some studies reported no significant differences in outcomes between SC, CCC, and ECG3 [3, 7, 8]. In contrast, other studies have shown that SC or CCC are associated with an unfavorable prognosis compared with ECG3 [9-11]. A number of factors, such as a selection bias, criteria for pathologic diagnosis, and types of therapy including the extent of surgical procedure and the type of post-operative adjuvant therapy, could have differed between these studies, partly leading to the observed differences, together with their small number of cases. Moreover, although these type II endometrial carcinomas tend to have distant spread and recurrence, there is little information regarding responses to chemotherapy, as well as effective regimens in these subtypes. Controversy still remains whether these tumors should be treated differently, and there is no consensus regarding the most effective treatment for these subtypes without prospective data available to guide clinicians. The purpose of this study was to evaluate prognosis of high-grade endometrial carcinoma patients, comparing SC or CCC type to ECG3 carcinoma, respectively, and to explore the effective treatment strategy for these subtypes.

Materials and Methods

Among all patients who underwent primary surgery for endometrial carcinoma between 1990 and 2009 at the Institute, pathologic material and medical records of patients with high-grade endometrial carcinoma, including SC, CCC, and ECG3, were reviewed. Study protocol was approved by institutional ethics committee. Tumor cell type was assessed according to World Health Organization (WHO) criteria [12] and endometrial carcinomas were graded according to the FIGO grading system. Patients unsuitable for primary surgery due to advanced stage and poor medical conditions, precluding definitive pathologic diagnosis as primary endometrial carcinoma, were excluded from further analysis. Clinico-pathologic variables assessed included: patient age, histological subtype, FIGO stage, extent of primary surgery, and type of post-operative chemotherapy. Complete resection was defined as the surgical removal of all the visible tumors including primary and

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metastatic lesions regardless of the extent of lymphadenectomy. Chemotherapy after primary surgery was recommended for all high-grade endometrial carcinoma patients, except for those not suitable for chemotherapy due to their medical conditions or advanced age; however, different post-operative chemotherapies have been introduced during the study period: cyclophosphamide plus doxorubicin plus cisplatin in earlier years and later changed to taxan plus platinum, reflecting the changes in standard chemotherapy for ovarian cancers.

Overall survival (OS) was measured from the date of primary therapy to the date of death or last follow-up and PFS was measured from the date of primary therapy to the date of disease progression or last follow-up. Associations between variables were analysed using Chi-square or Fisher's exact test. Survival curves were estimated using Kaplan-Meier method and p values were generated using the log-rank test. Cox proportional hazards regression models were also used to examine OS and PFS for quantifying the relations between survival and covariates in univariate and multivariate models. Values of $p < 0.05$ were considered significant.

Results

Of 447 endometrial carcinomas during the study period, 340 (76%) low-grade and 107 (24%) high-grade endometrial carcinomas including SC, CCC, and ECG3 were identified. As shown in Table 1, there was a significant increase in the proportion of patients with high-grade endometrial carcinomas in the second decade (19% vs 28%; $p = 0.026$), despite the increasing number of patients both in low- and high-grade endometrial carcinomas. Median age of all endometrial carcinoma patients was also significantly higher in the second decade (59 vs 63 years; $p = 0.026$). The rate of patients with FIGO Stage IIIc-IV were not significantly different in the two periods of time.

There were 24 SC, 14 CCC, and 69 ECG3. Table 2 shows the comparative analysis of the characteristics of patients with SC type or those with CCC type to those with ECG3, respectively. Median age was 62, 68, and 61 years respectively, showing CCC with significant elder age compared to ECG3 ($p = 0.012$). The rates of patients with Stage IIIc-IV were not significant different, although there were only 3 Stage IIIc-IV cases among 14 patients with CCC. There were no significant differences in type of treatment and outcome, such as lymph node sampling or dissection at primary surgery, incomplete resection at primary surgery, and subsequent post-operative chemotherapy; however, response rate to first-line chemotherapy in patients with measurable disease was significantly lower in SC than that in ECG3 (27% vs 74%; $p = 0.037$). Responses to chemotherapy were poorer in SC than ECG3, either after taxan plus platinum (33% vs 80%), as well as after cyclophosphamide plus doxorubicin plus cisplatin (0% vs 67%). There were no data for CCC in regard to the chemotherapeutic response.

Kaplan-Meier test for OS (Figure 1) and PFS (Figure 2) showed significantly worse prognoses for SC than ECG3: five-year OS was 40% in SC ($p = 0.026$), 71% in CCC, and 70% in ECG3, and five-year PFS was 25% in SC ($p = 0.0028$), 71% in CCC, and 61% in ECG3. Table 3 demonstrates univariate and multivariate analysis of possible prognostic factors on OS and PFS. According to the multivariate analysis, age ≥ 70, Stage IIIc-IV, and incomplete resection were independent prognostic factors on poor OS, whereas SC type, Stage IIIc-IV, and incomplete resection were on poor PFS.

Table 1. — *Comparison of patients with low- and high-grade endometrial cancer between the first and the last term during the study period.*

	Number of patients (%)			
	Total	Year		
		1990 - 1999	2000 - 2009	
All grades	447 (100)	192 (100)	255 (100)	
Low-grade	340 (76)	156 (81)	184 (72)	$p = 0.026$
High-grade	107 (24)	36 (19)	71 (28)	
Serous	24	6	18	
Clear cell	14	5	9	
Endometrioid grade 3	69	25	44	
Median age (range)	61 (34-86)	59 (34-85)	63 (38-86)	$p = 0.026$
FIGO Stage I - IIIa	385 (86)	168 (88)	217 (85)	N.S.
IIIc - IV	62 (14)	24 (13)	38 (15)	

N.S. = not significant.

Table 2. — *Comparison of characteristics: serous (SC) or clear cell (CCC) type versus endometrioid grade 3 (ECG3).*

Characteristics	Histology	Number of patients (%)	
Median age (range in years)	SC	62 (38-80)	N.S.
	CCC	68 (54-86)	p 0.012
	ECG3	61 (44-84)	
FIGO Stage IIIc-IV	SC	16 (67%)	N.S.
	CCC	3 (21%)	N.S.
	ECG3	30 (43%)	
Lymph node sampling	SC	14 (58%)	N.S.
or dissection	CCC	8 (57%)	N.S.
at primary surgery	ECG3	50 (72%)	
Incomplete resection	SC	13 (54%)	N.S.
at primary surgery	CCC	2 (14%)	N.S.
	ECG3	23 (34%)	
Post-operative chemotherapy	SC	19 (79%)	N.S.
after primary surgery	CCC	8 (57%)	N.S.
	ECG3	46 (73%)	
Response rate to first-line	SC Total	3/11 (27%)	p 0.037
chemotherapy for measurable		CAP 0/2 (0%)	
disease (%)		TP 3/9 (33%)	
	CCC Total	0/0	
	ECG3 Total	14/19 (74%)	
		CAP 6/9 (67%)	
		TP 8/10 (80%)	

N.S. = not significant; CAP = Cyclophosphamide+doxorubicin+cisplatin; TP = taxan+platinum.

Discussion

The number of patients with endometrial carcinomas is rising, following the increasing life expectancy, as well as the prevalence of overweight and obesity especially in developed countries, such as North America and Europe [13]. Although the increase was observed in both low and high-grade endometrial carcinomas in the present study, the rate of high-grade endometrial carcinomas, which are typical of elderly women, significantly increased in the last decade. One of possible causes was the marked exten-

Fig. 1

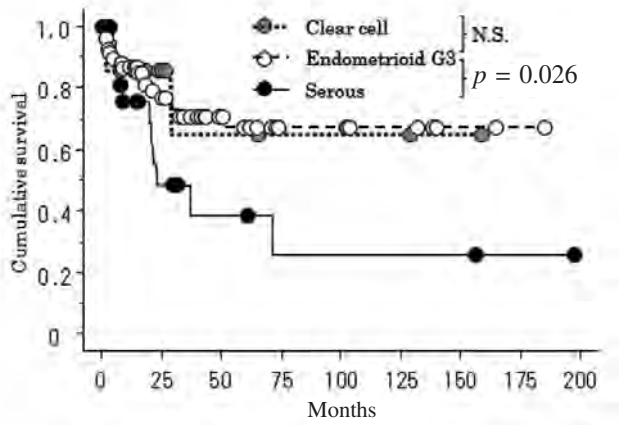

Fig. 2

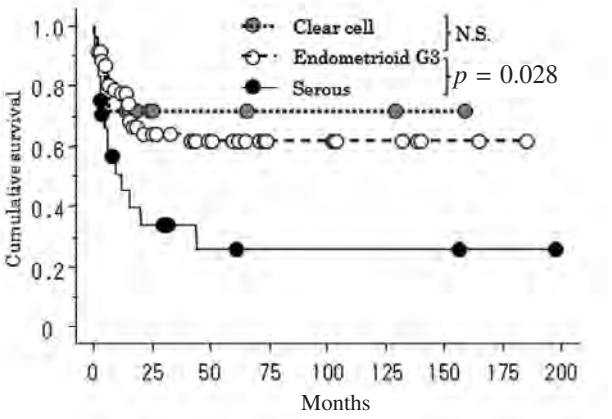

Figure 1. — Comparison of overall survival rates of the patients according to histological subtypes. Patients with serous-type had significant worse overall survival rate than those with endometrioid grade 3 ($p = 0.026$).
Figure 2. — Comparison of progression-free survivals of the patients according to histological subtypes. Patients with serous-type had significant worse progression free survival rates than those with endometrioid grade 3 ($p = 0.0028$).

Table 3. — *Univariate and multivariate analysis of prognostic significance on overall survival (OS) and progression-free survival (PFS).*

Variable		OS						PFS					
		HR	Univariate 95% CI	*p* value	HR	Multivariate 95% CI	*p* value	HR	Univariate 95% CI	*p* value	HR	Multivariate 95% CI	*p* value
Age	< 70	1.0	–	–	1.0	–	–	1.0	–	–	–	–	–
	≥ 70	2.3	1.1-4.6	0.022	2.5	1.2-5.2	0.018	1.4	0.7-2.8	0.279	–	–	–
FIGO Stage	I-IIIa	1.0	–	–	1.0	–	–	1.0	–	–	1.0	–	–
	IIIc-IV	14.3	5.0-41.1	< 0.001	4.8	1.2-19.4	0.027	12.8	5.3-30.6	< 0.001	5.3	1.7-16.4	0.003
Histology	Serous	2.3	1.1-4.9	0.033	1.5	0.7-3.2	0.341	2.5	1.3-4.9	0.005	2.0	1.1-3.9	0.041
	Clear cell	1.0	0.3-3.3	0.959	–	–	–	0.9	0.3-2.6	0.839	–	–	–
	Endometrioid G3	1.0	–	–	1.0	–	–	1.0	–	–	1.0	–	–
Primary	Complete	1.0	–	–	1.0	–	–	1.0	–	–	1.0	–	–
surgery	Incomplete	12.1	5.1-28.5	< 0.001	5.6	1.7-18.3	0.004	10.2	5.1-20.7	< 0.001	3.7	1.5-9.4	0.005
Post-operative	Yes	1.0	–	–	–	–	–	1.0	–	–	–	–	–
chemotherapy	No	1.2	0.6-2.6	0.574	–	–	–	0.9	0.4-1.7	0.671	–	–	–

HR = hazard ratio; CI = confidence interval; G3 = grade 3.

sion of female life expectancy in Japan from 74.7 years in 1970's, among the top 20 in the world, to 85.3 years in 2000's, the highest in the world [14]. In addition, the decreasing rate of obesity in perimenoposal women in Japan [15] may also contribute to rather lower incidence of low-grade endometrial carcinomas, as obesity is typically associated with type I endometrial carcinomas which usually peaks around the age of 50 [13]. Significant higher median age of endometrial carcinoma patients in the last decade from this study, together with other official statistics on trends in endometrial cancer patients across Japan [16, 17], could support these hypotheses indeed. Similar findings occurred in other countries, where an increase in the proportion of patients with grade 3 and serous-type endometrial cancers was reported [18].

As for prognosis in high-grade endometrial carcinomas, a study based on the largest cohort of patients including 2,316 ECG3, 1,473 SC, and 391 CCC by Hamilton *et al*. showed that patients with SC or CCC had a significantly poorer prognosis than those with ECG3, even after controlling for stages [10]. In this study, CCCs did not show worse prognosis compared with ECG3; however, statistical significance was not obtained due to the small number of cases with the higher rate of elderly patients, the low rate of advanced stage, and lack of cases with measureable disease unable to evaluate response to chemotherapy. Poorer outcomes were also reported by Boruta *et al*., with approximately 40% of five-year survival in SC compared to 75% in ECG3, showing close outcomes to the present study [9].

The impact of maximal cytoreductive surgery on the survival rate was explored, similarly to ovarian carcinoma and improved survival in advanced endometrial carcinomas was reported in several retrospective studies with the relatively small number of cases [19-21]. Bristow *et al*. reported 65 Stage IVb endometrial carcinomas treated with surgery as primary therapy and showed that patients with only microscopic residual disease had significantly better survival rate compared to those with optimal macroscopic (≤ 1 cm) residual disease [19]. In accordance with their study, the present study confirmed that complete resection with no gross residual tumors is an independent predictor for improved OS and PFS in

patients with high-grade endometrial carcinoma, after tumor stage, which is the most important prognostic factor recognized overall. Age was also considered a significant factor affecting disease-related outcome, as well as the treatment strategy including aggressive operative procedures and adjuvant therapies. In this study, age was actually the independent prognostic factor not on PFS but on OS; on the contrary, SC type was an independent prognostic factor not on OS but on PFS. The majority of patients with SC received post-operative chemotherapy, but their chemotherapeutic responses for measurable disease were considerably low compared to ECG3. This poor response to treatment could explain low PFS in patients with SC. In addition, to the knowledge of the authors, this is the first report with direct comparison of objective chemotherapeutic responses in ECG3 and SC according to regimens.

Despite frequent metastasis, as well as high risk for recurrence in high-grade endometrial carcinomas, there is little information regarding the responses of each histological subtypes to individual chemotherapeutic regimen [6, 22-26]. One of the largest analysis using pooled data of prospective studies, reported by McMeekin *et al*., showed 44% and 32% of response rates for doxorubicin, either alone, or in various combinations with doxorubicin and platinum and taxan in SC and CCC, respectively [6]. In that study, analyzing 1,203 patients with Stage III-IV or recurrent endometrial cancer, no significant difference occurred in the response to chemotherapy for SC or CCC when compared to all other histological types, including all grade endometrioid types and mixed types. In their separate analysis of 622 patients with endometrioid type, patients with ECG3 had an estimated odds of response 1.47 times that of those with grade 1 endometrioid carcinoma, showing rather better response rate in ECG3 like the present study. Goldberg *et al*. and Price *et al*. reported that response rate of 37% to first-line platinum-based chemotherapy in SC [22]. Levenback *et al*. and Price *et al*. reported that 2 / 11 and 3 / 11 of response rate to chemotherapy with cisplatin, doxorubicin, and cyclophosphamide in SC, showing poor response rates similar to the present study [23, 24]. These response rates in SC are considerably lower than those reported in ovarian serous adenocarcinoma. Although Zanotti *et al*. and Ramondetta *et al*. reported better response rates of 7 / 11 and 10 / 13 to chemotherapy using paclitaxel for SC, respectively [25, 26], the present results showed rather poorer chemotherapeutic responses of 3 / 9 with taxan plus platinum as well in SC compared to 8 / 10 in ECG3 patients. Different chemotherapeutic response rates observed in all these studies including the present study are probably due to the small number of patients [22-26] or various chemotherapeutic regimens [6, 22, 25].

With relatively little evidence compared to ovarian carcinoma, patients with advanced endometrial carcinoma are treated with similar chemotherapeutic regimens following cytoreductive surgery, yet showing poorer outcomes. Landrum *et al*. reported that OS for endometrial carcinoma patients with intraperitoneal metastasis does not approach with that of patients with advanced ovarian cancer [27]. Although SCs of endometrium is considered to share similar tumor characteristics to ovarian cancer in terms of histological appearance and tendency of intra-abdominal dissemination, differences may exist, particularly in respect to the low chemotherapeutic responses. The reported gene profile analysis in the comparison of serous or endometrioid tumors across endometrial and ovarian cancers by Zorn *et al*. showed unique gene expression patterns reflecting their organ of origin [28]. They suggested that these tumors have important gene expression differences, which makes it less likely that they can be clinically managed in an identical fashion. It is understandable that response rates in serous-type endometrial cancer are considerably lower than those reported in ovarian serous adenocarcinoma and that seems to mainly contribute to the poorer prognosis in serous-type endometrial cancer.

In addition to considering the introduction of highly intensive regimens, there is a need to identify novel agents to improve survival. Attention has turned to drugs that target molecular pathways. Over the past years, a considerable number of studies have been made in this field. In the recent report of phase II study of temsirolimus, response was seen in patients with all grades of disease, as well as in patients with serous histology [29]. In a phase II trial of bevacizumab, targeting VEGF, clinical responses were reported in serous-type and clear cell type as well [30]. Although patient numbers are still too small to formally evaluate the role of histologic subtype and response in these studies, it seems worthy of further studies. Targeting differential molecular characteristics of high-grade endometrial carcinomas could contribute to developing effective therapeutic strategies and multi-institutional prospective trials are needed to establish individual guidelines for these relatively infrequent types of tumors. In conclusion, the increasing trend of high-grade endometrial carcinoma and different outcomes among their histological subtypes suggested the necessity to explore differential approaches including surgery and chemotherapy for the management of these tumors.

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Address reprint requests to:
T. GOTO, M.D.
Department of Obstetrics and Gynecology
National Defense Medical College
3-2 Namiki, Tokorozawa
Saitama 359-8513 (Japan)
e-mail: tgoto@ndmc.ac