

Diabetes mellitus indicate poor prognosis in uterine serous cancer patients

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Abstract

Purpose. We aimed to find prognostic factors for uterine serous cancer(USC) patients in a retrospective study.

Methods. 51 USC patients between 2010-2020 were enrolled. All pathological specimens were reviewed. The research protocol was approved by Institutional Review Board and all patients were informed consent before the study began. Statistics were done using SPSS 25.0, T test and chi-square analyses were used to compare differences, the overall survival(OS) was estimated with Kaplan-Meier(KM) analysis, univariate and multivariate Cox regression analyses were utilized to find prognostic factors.

Results. The median overall survival(OS) and progressive free survival(PFS) were 75.94 and 63.49 months, respectively. Diagnosed with diabetes mellitus($P=0.006$, HR=6.792, 95%CI=1.726-26.722) and CA125 \geq 28U/ml($P=0.006$, HR=7.136, 95%CI=1.780-28.607) before surgery were independent risk factors for OS, advanced FIGO stage($P=0.001$, HR=10.628, 95%CI=2.894-39.026) and DM($P=0.003$, HR=6.327, 95%CI=1.875-21.354) were independent factors for PFS. Age \leq 52, , tumor size \geq 2.5cm and cervical mucosal infiltration may indicate poor prognosis but were not independent risk factors. Hypertension patients with routine medical treatment tend to survive longer, but there was no statistical differences in OS and PFS compared to patients with normal blood pressure.

Conclusion. In addition to surgical and adjuvant treatments, gynecologists should focus more on the comorbid conditions of USC patients, especially for DM.

Introduction

Endometrial cancer(EC) is the 7th most common cancer and the 14th most common cause of cancer death in women, globally[1]. Most EC presented as early-stage disease, with a favorable 5-year overall survival(OS) of greater than 85%[1]. However, uterine serous carcinoma(USC), which is classified into type 2 EC, is an aggressive and rare subtype of EC with an estimated 5 year OS of 18-27%[2]. USC patients usually suffered from recurrence even in early stage. According to the FIGO guideline, the standard system treatment strategies are surgical staging(for patients with early stage) or debulking surgery(for advanced stage) followed by radiochemotherapy[3]. Improved systemic treatment protocols have prolonged the disease-free survival but have had little effect on long- term overall survival. We aim to find risk factors of disease prognosis in USC patients, which would benefit survivors in providing consulting and management after primary treatment.

Co-morbidities may affect patients' pathological state and prognosis to some extent. Roy showed, cancer survivors had a higher prevalence of hypertension, diabetes mellitus(DM) compared to health people, and among all the cancer type, uterine cancer had the highest prevalence of DM(42.9%)[4]. Recent evidence suggested, DM may perform a more important biologic link in terms of uterine cancer[5, 6]. Uterine cancer can be classified into type 1 and 2, the former was associated with high estrogen status and insulin-resistance, including metabolic syndrome and DM[7]. In 2013, Zanders et al. showed a lower five-year OS

rate of 68% compared to 84% in patients with diabetes and EC[8]. Additional meta-analysis by Liao et al. in 2014 showed a similar pooled relative risk of disease specific mortality of 1.32[6]. USC is type 2 uterine cancer which had a significantly poorer prognosis than type 1 uterine cancer, there were no studies on DM and USC.

Materials And Methods

A total of 51 patients diagnosed with USC between 2010-2020 were enrolled in this retrospective study, which was approved by hospital institutional review board. Inclusion criteria were as follows: (1) all patients' pathological specimens were re-reviewed and reconfirmed, (2) received primary operation and first-line adjuvant therapy.

Clinical informations were obtained from medical records. Patients were restage according to the 2018 FIGO stage. All patients were initially diagnosed and operated in the Memorial Hospital of Sun Yat-sen, Sun Yat-sen University, followed by adjuvant therapy. Information of recurrence or death were obtained from the follow-up department. In this study, all death was caused by USC, so overall survival was equal to cancer-specific survival(CSS).

Statistics were done using SPSS 25.0(IBM, Armonk, NY, USA). The best cut off value of CA125, tumor size and age were estimated with ROC curve. T test and chi-square analyses were used to compare clinical variables between groups. Significance level is 0.05. The OS and PFS was calculated using Kaplan-Meier(KM) analysis and compared using the log-rank test. Univariate and multivariate Cox regression analyses were utilized to find prognostic factors.

The Kaplan-Meier(KM) curves and forest plots were visualized via R 3.6.1, 'survival' and 'survminer' packages were used.

Results

Of the enrolled 51 patients, 16 had DM. Cut-off values for age, menopause time, CA125, and number of resected lymph nodes were calculated via SPSS using ROC curve.

Most patients(42/51) were diagnosed with USC over 52 years old. About 2/3 patients were at early stage. 16 patients didn't receive lymphadenectomy, so we couldn't confirm their pathological status of lymph nodes.

The baselines of patients with or without DM are listed in Table 1. The differences between all the listed factors including stages, BMI, age, and etc were not statistically significant in the 2 group of patients.

The median PFS and OS of all patients were 63.49 months and 75.95 months, respectively(Table 1). The 2-year-OS rate was 85.4% and 2-year-PFS rate was 77.3%. The OS and PFS rate of patients with DM were significantly lower than those without DM($P=0.002$ and 0.029 , respectively, Fig 1a and Table 1).

To analyze pathological parameters and co-morbidities in USC patients, univariate and multivariate cox regressions were run. As shown in Table 2, DM was related to a poorer OS. DM and higher stage, BMI, CA125 were unfavourate factors for USC patients' PFS, small tumor size, higher number of resected lymph nodes, and negative lymph nodes were favourate factors for PFS.

In order to find more potential risk factors for OS in multivariate regression analysis, we also include factors with P value ≤ 0.10 and stage in multivariate analyses. We found that diagnosed with diabetes mellitus ($P=0.006$, HR=6.792, 95%CI=1.726-26.722) and CA125 ≥ 28 U/ml ($P=0.006$, HR=7.136, 95%CI=1.780-28.607) before surgery were independent risk factors for OS, the survival curve of these risk factors were shown in Fig 2. Advanced FIGO stage ($P=0.001$, HR=10.628, 95%CI=2.894-39.026) and DM ($P=0.003$, HR=6.327, 95%CI=1.875-21.354) were independent factors for PFS. Unlike type 1 endometrium cancer, BMI was not related to prognosis of USC.

Interestingly, it indicated that hypertension may be a protect factor for USC patients, which contradicts with mainstream view, but the result was not statistically significant (Fig 1).

Discussion

USC is a rare but deadly subtype of EC, we conducted a single center retrospective study of 51 patients and found that DM was the independent risk factor of both OS and PFS, the HR were 6.792 and 6.327, respectively.

In our data, about 60% patients were early stage, which differed from previous study[9]. Almost all patients' complaints were vaginal bleeding or abnormal discharge, which may be the reason for the higher early stage rates of diagnosis.

Only 62.7%(32/51) patients had an accurate pathologic diagnosis before surgery, the rest of patients were mis-diagnosed with endometrioid adenocarcinoma by pre-operation biopsy. According to the famous 'Mayo Criterion', for patients of grade 1-2 stage I EC, with tumor size ≤ 2 cm and myometrial invasion depth $\leq 1/2$ regional lymphadenectomy could be avoided[10]. But for early stage USC, lymphadenectomy is debatable. In our study, Cox regression showed that although the number of lymph nodes removed was not an independent factor, patients with more lymph nodes resected had a better PFS. As for OS (Figure 2), K-M analysis showed patients without lymph node metastasis had a significantly better prognosis, and the OS of patients whose lymph nodes were not removed was poorer, patients with lymph nodes metastasis had the poorest end. Li's study enrolled 2853 patients registered in SEER, the result suggested that patients with ≥ 12 pelvic lymph nodes (PLNs) removed had significantly better OS than those without (both $P < 0.001$)[11]. Our results showed the number of lymph nodes removed was not associated with prognosis, we speculated that the small sample size was the reason.

Hence, we think systemic lymph node resection may be recommended to USC patients. Accordingly, the accuracy of pathologic diagnosis before operation was important, cause it directly impacted the decision

to resect lymph nodes or not. If we mis-diagnosed an early stage USC as an endometrioid adenocarcinoma, we may make a wrong surgical decision.

DM has reached epidemic proportions worldwide, its rate shockingly doubled over the last 3 decades[12]. From a gynecologic cancer prospective, the rise in DM impacts patients' medical condition across their lifespan. A direct link between DM and type 1 EC is now well appreciated[13, 14]. Hyperglycemia promoted the development of type 1 endometrial cancer and led to poor prognosis. High blood glucose facilitated EC tumor growth by providing carbon sources for diverse metabolic pathways[13]. In vitro experiments exhibited, the proliferation, adhesion and chemo-resistance of tumor cells were promoted when cultured with high glucose condition[15-17]. There are significant differences in molecular phenotypes and hormone receptor expression between type 1 and type 2 EC, thus the prognostic risk factors of the two types may be different. So did DM affect USC patients' survive time? The answer was positive. Our study revealed for the first time that DM was an independent risk factor for OS and PFS in USC patients. Shou did a retrospective analysis in 139 Chinese non-endometrioid adenocarcinoma patients(including 45 USC), he found that metabolic syndrome(MS), stage and age were independent risk factors for OS of USC patients[18]. MS was a group of diseases including DM, hypertension and hyperlipidemia, while our study was focus on DM only.

Surgery and radiochemotherapy are important in USC, but before or after these oncology treatments, we should pay more attention to the control of co-morbidities to improve outcomes. Metformin is commonly used to treat type 2 DM, it may benefit outcomes of EC in an indirect manner[19]. Perez found among postmenopausal women with EC, taking metformin could decrease overall mortality[20]. Sarfstein's study showed that metformin decreased expressions of IGF pathway molecules via inhibition of IGF-IR promotor activities in USC cells, finally promoted cell apoptosis, attenuated cell migration and proliferation[21]. On the contrary, Lilia reported that merformin shortened lifespan of C.elegans and human primary cells when provided in late life[22]. But this research studied individuals with healthy metabolic status. As we know, the peak age of USC is later than type 1 EC, therefore, the use of metformin may require more careful selection. Future prospective trials are needed to explore its impact on USC.

Our present study also found that, contrary to previous findings, the prognosis of hypertensive patients seemed to be slightly better than that with normal blood pressure, although the difference was not statistically significant. By increasing the sample size, the differences may be weakened or enlarged.

Limitations of this study are as follows: 1. Single-center retrospective study with low level of evidence, 2. The sample size is small, but USC is a rare disease, and Gynecologic Cancer InterGroup(GCIG) appeals that it should be separately managed and studied[23], 3. For some patients, the follow-up time is less than 2 years, which may lead to bias.

The advantages of this study is that the operation quality is guaranteed in the famous gynecological tumor center in China. It is the first time that medical comorbidities have been found to influence the prognosis of USC, which will guide the treatment of these patients.

Abbreviations

KM:Kaplan Meier, DM: Diabetes mellitus, OS: overall survival time.

Declarations

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Conflicts of interest : All the authors declare no conflicts of interest.

Ethics approval: the study was approved by the institutional review board of Sun Yat-sen Memorial Hospital.

Consent to participate and publication: all the patients enrolled in the study are consent informed, and we reconfirmed for publication when we did phone call follow-up.

Availability of data and material: all data and R codes comply with field standard and are available to all the readers.

Author contribution

YY Liu: Manuscript writing, Data analysis

J Li: Manuscript editing

ZB Cheng: Data collection

GC Xu: Data analysis

YP Peng: Project development

HW Lu: Project development, Data collection

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Tables

Table 1. Baseline features of uterine serous carcinoma patients with or without DM.

Characteristics	Total n=51	Without DM n=35	DM n=16	Pvalue
Age				0.588
≤52	9[17.6%]	6[17.1%]	3[18.8%]	
≥52	42[82.4%]	29[82.9%]	13[81.3%]	
Menopause time (year)				0.519
≤6.5	21[41.2%]	14[40.0%]	7[43.8%]	
≥6.5	30[58.8%]	21[60.0%]	9[56.3%]	
Tumor size (cm)				0.159
≤2.5	26[51%]	20[57.1%]	6[37.5%]	
>2.5	25[49%]	15[42.9%]	10[62.5%]	
FIGO stage				0.140
Early[I-II]	31[60.7%]	20[57.1%]	11[68.8%]	
Late[III-IV]	20[39.2%]	15[42.9%]	5[31.2%]	
BMI				0.481
≤24	30[58.8%]	20[57.1%]	10[62.5%]	
>24	21[41.2%]	15[42.9%]	6[37.5%]	
CA125(U/mL)				0.548
≤28	34[66.7%]	23[65.7%]	11[68.8%]	
>28	17[33.3%]	12[34.3%]	5[31.3%]	
LVSI				0.159
Positive	21[41.2%]	15[42.9%]	10[62.5%]	
Negative	30[56.9%]	20[57.1%]	6[37.5%]	
LN status				0.787
Unknown	16[31.4%]	11[31.4%]	5[31.3%]	
Negative	25[49.0%]	18[51.4%]	7[43.8%]	
Positive	10[19.6%]	6[17.1%]	4[25.0%]	
Cervical mucosal invasion				0.224
Negative	31[60.8%]	23[65.7%]	8[50%]	
Positive	20[39.2%]	12[34.3%]	8[50%]	
Myometrial invasion				0.224
≤1/2	31[60.8%]	23[65.7%]	8[50%]	
≥1/2	20[39.2%]	12[34.3%]	8[50%]	
Num of LN				0.305
None	16[31.4%]	12[34.3%]	4[25.0%]	
≤20	11[21.6%]	9[25.7%]	2[12.5%]	
≥20	24[47.1%]	14[40.0%]	10[62.5%]	
Median PFS	63.49%±7.32%	73.75%±8.78%	47.08%±12.57%	0.016*
Median OS	75.94%±7.75%	94.59%±7.68%	47.67%±10.91%	0.030*
2-years-PFS	77.3%±6.8%	88.4%±6.4%	41%±15.9%	0.029*
2-years-OS	85.4%±6.1%	90.2%±6.6%	67.1%±13.8%	0.002*

Legends: chi-square analysis was used to compare differences. Of all the features listed, there were no statistical differences between patients with or without DM. Thus baseline characteristics were well balanced between the two arms. Logrank analysis showed that the PFS and OS were significantly poorer in DM arm. *:P<0.05.

Abbreviations:

DM: Diabetes Mellitus, FIGO: International Federation of Gynecology and Obstetrics, BMI: body mass index, LVSI: lymph-vascular space invasion, LN status: lymph node metastasis status, Num of LN: numbers of resected lymph nodes, OS: overall survival time, PFS:progressive free survival time.

Table 2. Univariate cox regression for OS and PFS

	PFS			OS		
	HR	95%CI	P	HR	95%CI	P
	0.13	0.00-5.15	0.28	0.30	0.00-31.06	0.61
	8.39	1.45-48.53	0.02	9.55	0.62-147.01	0.11
ause time	23.72	0.24-2375.84	0.18	1.88	0.00-1200.07	0.85
	4.25	0.85-21.14	0.08	2.30	0.13-39.20	0.57
al mucosal invasion	1.00	0.15-6.78	1.00	0.19	0.01-6.20	0.35
size	0.06	0.01-0.52	0.01	0.96	0.04-23.47	0.98
tus	0.15	0.033-0.73	0.02	0.59	0.06-5.71	0.65
f LN	0.19	0.04-0.90	0.04	1.28	0.17-9.84	0.81
	212.54	8.15-5544.01	0.001	8.47	0.30-237.73	0.21
(U/ml)	12.43	1.65-93.82	0.02	11.13	0.72-171.02	0.08
	94.83	7.94-1132.20	0.001	34.09	1.70-684.91	0.02

Legends: Univariate cox regressions showed that DM and advanced stage, higher BMI, CA125 were unfavourate factors for USC patients' PFS, small tumor size, higher number of resected lymph nodes, and negative lymph nodes were favourate factors for PFS. DM was the only risk factor for OS.

Abbreviations:

DM: Diabetes Mellitus, BMI: body mass index, LN status: lymph node metastasis status, Num of LN: numbers of resected lymph nodes, OS: overall survial time, PFS:progressive free survival time, HR: hazard rate, CI: confidence interval.

Figures

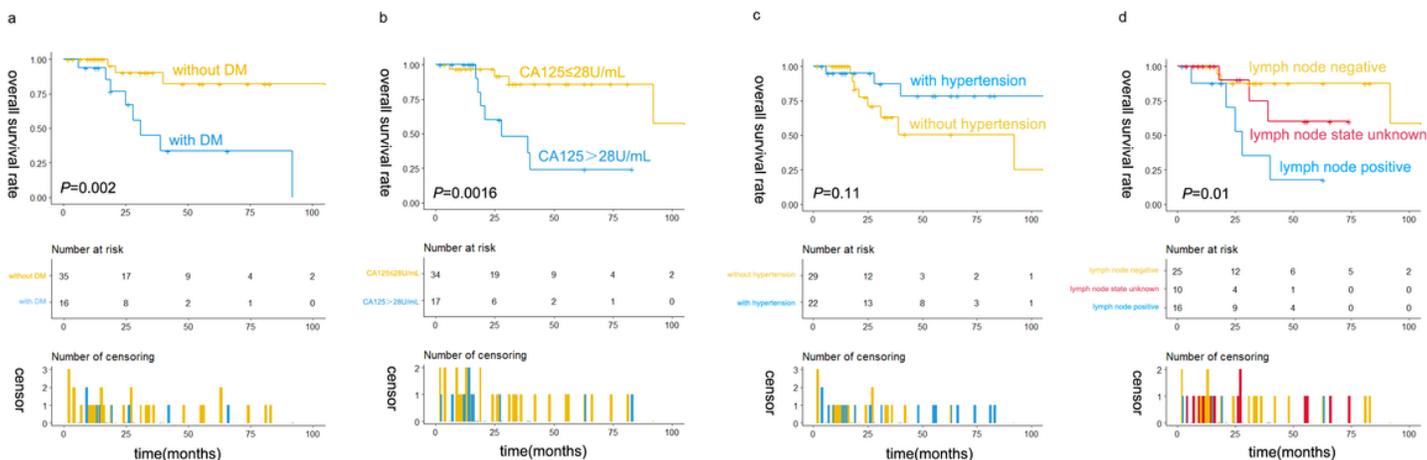


Figure 1

Kaplan-Meier survival curves of USC patients a) The KM curve for patients with (blue curve) of without DM (yellow curve) ($P=0.002$). b) The KM curve for USC patients with $CA125 \leq 28U/L$ (yellow curve) and $CA125 > 28U/L$ (blue curve) ($P=0.0016$). c) The KM curve for USC patients with hypertension (blue curve) was higher compared with patients without hypertension (yellow curve), but the difference did not reach statistical significance ($P = 0.11$). d) The KM curve of lymph node status for USC patients ($P=0.01$), the prognosis of patients without lymph nodes metastasis were better than the group of patients whose lymph nodes were not resected, patients with lymph nodes invasion suffered the worst prognosis