RISK FACTORS FOR THE POOR OUTCOME FOLLOWING SURGICAL TREATMENT OF PATIENTS WITH USC

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ABSTRACT

Objective: *To explore the risk factors of poor prognosis in patients with endometrial serous carcinoma (USC) undergoing surgery.*

Methods: *The clinical data of 142 patients with USC who underwent surgical treatment in our hospital from January 2008 to December 2020 were retrospectively analyzed. The general data, surgical data, postoperative adjuvant treatment data and follow-up prognosis data were analyzed. Cox re-gression model was used to evaluate the independent risk factors of poor prognosis.*

Results: *univariate analysis showed that age, lymph node resection, intraoperative peritoneal cytology, depth of myometrial invasion, staged operation, adnexal/uterine serosal invasion and omental metastasis were associated with the 5-year cumulative disease-free survival rate (P<0.05); Lymph node resection, staging operation, intraoperative peritoneal cytology, adnexal/uterine serosal invasion and postoperative adjuvant treatment were associated with 5-year cumulative overall survival rate (P<0.05); Multivariate analysis of Cox regression model showed that incomplete staged surgery and combined adnexa / uterine serosa invasion were independent risk factors for the decrease of 5-year cumulative disease-free survival rate (P<0.05); Unresected lymph nodes and positive intraoperative peritoneal cytology were independent risk factors for 5-year cumulative overall survival (P<0.05).*

Conclusion: *the poor prognosis of patients with USC undergoing surgery is independently as-sociated with incomplete staging surgery, adnexal / uterine serosal invasion, unresected lymph nodes and positive intraoperative peritoneal cytology.*

Keywords: *Surgery, endometrial serous carcinoma, prognosis, risk factors.*

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Introduction

USC is a special histopathological type of endometrial carcinoma which accounts for less than 10% of all endo-metrial carcinoma, but the proportion of recurrences and deaths often exceeds 50%[1]; Currently, it is considered that USC has strong biological invasiveness, and its clinicopathological characteristics and prognosis are similar to high-grade ovarian serous carcinoma, but are quite different from endometrioid adenocarcinoma[2-3]. Relatively few studies have been reported for the poor prognosis risk factors for USC patients, but the conclusions among studies are still controversial[4].

Based on the above evidence, the present study retrospectively analyzed the clinical data of a total of 142 cases of USC patients admitted to our hospital from January 2008 to December 2018, and analyzed general data, surgical data, postoperative adjuvant treatment data, and follow-up prognostic data, so as to explore the risk factors for a poor outcome following surgical treatment of patients with USC. The details were reported as follows.

Materials and methods

General information

A total of 142 cases of USC admitted to our hospital from January 2008 to December 2018 were studied.

Inclusion criteria:

- USC was diagnosed by surgical histopathological examination;
- The diagnosis of mixed USC was based on WHO (2014) criteria[5];
- Complete clinical pathology and follow-up data.

Exclusion criteria:

- Other types of en-dometrial carcinoma;
- Surgery Contraindications;
- Other types of malignant tumors.

The study complied with the Declaration of Helsinki, all patients and their family members gave written informed consent.

Methods

The patient's age, height, weight, laboratory examination index, complicated basic diseases, operation and postoperative adjuvant treatment were obtained and recorded[5]. The operative methods included total hysterectomy + bilateral adnexectomy, subtotal hyster-ectomy + bilateral adnexectomy and ex-tensive hysterectomy + bilateral adnexectomy. For patients with suspected cervical stromal invasion or pathological biopsy-confirmed cervical involvement, subextensive/extensive hysterectomy was performed when necessary. The paclitaxel + platinum regimen was used as postoperative adjuvant chemotherapy. Postoperative adjuvant radiotherapy in-cluded two-dimensional external radio-therapy, three-dimensional conformal radiotherapy, two-dimensional external radiotherapy + intracavitary brachytherapy and intracavitary brachytherapy; Among them, the isocenter dose of external radiotherapy was 4500cGy, and the 95% planned target dose of three-dimensional conformal radiotherapy was 4500~5040 cGy; The dose of vaginal mucosa surface in brachytherapy was 2200~2400cGy. The patients were followed up by telephone, outpatient or in-patient medical records. The patients were reexamined every three months in the first two years, and then every six months; The deadline of follow-up was March 2020 or death. The disease-free survival time and overall survival time were recorded.

Statistical analysis

SPSS21.0 software was used for the data statistical analysis. Survival analysis were evaluated with the Kaplan-Meier method, and the intergroup comparison was performed using the Log-rank test. The Cox proportional hazard regression model was used in multivariate analysis. $P<0.05$ was determined as statistically significant.

Results

Analysis of general data, surgical data and postoperative adjuvant treatment data

Among the 142 patients, simple and mixed USC were 52 cases and 90 cases respectively; mixed USC included 64 cases of mixed endometrioid adenocarcinoma, 6 cases of mixed clear cell carcinoma, 2 cases of mixed transitional cell carcinoma and 18 cases of coexisting endometrioid adenocarcinoma and clear cell carcinoma. 50 cases underwent comprehensive staged operation, namely, total hysterectomy + bilateral appendec-tomy + pelvic and abdominal paraaortic lymph node resection + omentum resection; After operation, 94 cases received adjuvant chemotherapy alone, 4 cases received adjuvant radiotherapy alone, 24 cases received adjuvant chemotherapy plus radiotherapy, and the other 20 cases did not receive adjuvant treatment after operation.

Analysis of follow-up survival data

During the follow-up process, 36 cases of 142 patients relapsed, including 4 cases of local recurrence, 6 cases of distant metastasis, 26 cases of local recurrence + distant metastasis; A total of 24 patients died, of which 22 cases died of USC, 1 died of primary colorectal cancer and 1 case died of heart disease. The cumulative disease-free survival rate and overall survival rate were 77.1% and 80.9%, respectively.

Univariate analysis of risk factors for poor prognosis

The results of the univariate analyses revealed that age, lymph node resection, intraoperative peritoneal cytology, depth of myometrial infiltration, staged operation, adnexal/uterine serosa invasion and omentum metastasis were related to the 5-year follow-up cumulative disease-free survival ($P<0.05$). Lymph node resection, staged operation, intraoperative peritoneal cytology, adnexal/uterine serosa invasion and postoperative adjuvant treatment plan are related to the 5-year follow-up cumulative overall disease-free survival ($P<0.05$). Details were presented in Table 1.

Indicators	Cases	5-year cumulative DFS rate (%)	*P*	5-year cumulative overall survival rate	*P*
Age			0.03		0.24
<60yrs	70	89.0		84.3	
≥60yrs	72	65.5		70.1	
BMI			0.85		0.32
<25kg/m^2	50	69.5		70.7	
≥25kg/m^2	92	80.0		81.5	
Complicated with basic diseases			0.93		0.68
None	92	72.7		70.5	
Hypertension	36	81.0		84.7	
Diabetes	2	100.0		100.0	
Both	12	84.5		82.2	
Baseline serum CA125 level			0.20		0.29
Normal	92	85.5		83.5	
Elevated	50	68.0		70.7	
Hysterectomy scope			0.23		0.43
Fully automatic resection	58	62.0		72.9	
Extensive resection	56	72.1		84.3	
Extensive resection	28	94.5		95.6	
Scope of lymph node resection			0.02		0.02
Pelvic lymph node resection	80	90.2		94.0	
Pelvic + para-aortic lymph node resection	52	61.3		64.7	
Not excised	10	34.0		20.0	
Omentum resection			0.50		0.40
Yes	68	87.0		87.3	
No	74	72.5		72.5	
Scope of staging surgery			0.25		
Comprehensive	50	98.5		94.0	
Incomplete	92	69.5		79.5	0.01
Intraoperative abdominal cavity cytology			0.01		
Negative	102	80.0		87.0	
Positive	40	51.0		55.0	
Histopathological type			0.41		0.00
Simple	52	68.5		70.2	
Mixed	90	85.0		83.5	
Histopathological grade			0.26		0.59
Level 1	8	100.0		100.0	
level 2	40	78.5		73.0	
Level 3	68	73.3		86.9	
Unclear	26	-		-	
Lymphatic vascular infiltration			0.29		0.30
Negative	108	75.5		84.0	
Positive	34	68.0		74.0	
Depth of muscular layer infiltration			0.02		0.51
<1/2	84	81.5		89.8	
≥1/2	58	52.5		60.23	
Cervical stromal invasion			0.20		0.20
No	92	80.5		88.0	
Yes	50	51.0		72.5	
Annex/Uterine serosal invasion			0.02		0.82
No	96	82.5		82.5	
Yes	46	51.5		52.4	
Lymph node metastasis			0.44		0.90
No	90	81.0		87.7	
Yes	42	73.0		82.5	
Omentum transfer			0.01		0.14
No	56	81.5		94.0	
Yes	12	69.2		69.5	
Postoperative adjuvant treatment			0.47		0.00
No	20	83.5		87.9	
Chemotherapy	94	72.9		75.0	
Radiotherapy	4	52.4		52.4	
Chemotherapy	24	76.9		80.6	

Table 1: Univariate analysis of influencing factors of DIE in pelvic endometriosis.

Multivariate analysis of risk factors for poor prognosis

Multivariate Cox regression analysis showed that incomplete staging surgery and combined adnexal/uterine serous invasion were independent risk factors for the decrease of the 5-year follow-up overall disease-free survival (P<0.05); Unresected lymph nodes and positive abdominal cytology during operation were independent risk factors for the decrease of the 5-year follow-up overall disease-free survival (P<0.05). Details were presented in Table 2.

Indicators	*P*	*HR*	95%CI
5 years follow-up cumulative disease-free survival rate			
Incomplete staging	0.03	6.31	2.04~28.67
Complicated with adnexa/ uterine serosal invasion	0.00	2.94	1.47~84.90
5-year cumulative overall survival rate			
Unremoved lymph nodes	0.04	17.14	1.83~76.80
Positive intraoperative abdominal cavity cytology	0.03	6.37	1.36~19.57

Table 1: Multivariate analysis of influencing factors of DIE in pelvic endometriosis.

Discussion

Analysis of influencing factors of 5-year cumulative disease-free survival rate

The results of this study showed that incomplete staging surgery is an inde-pendent risk factor for the decrease of the 5-year follow-up cumulative disease-free survival (P<0.05), which is consistent with the NCCN guidelines[6]; In view of the strong biological invasiveness of USC, patients with early disease still have a high risk of occult metastasis outside the uterus. Previous studies have demon-strated that[7] the preoperative evaluation of lesions in USC patients is limited to the uterus without myometrial infiltration, and more than 37% of patients underwent full staging surgery may progress into extra-uterine metastases, which further indicated that comprehensive staging operation is of great value for improving radical resection effect and long-term prognosis of USC patients. Hence, we considered that the use of a comprehen-sive staging operation contributes to ac-curately assess the clinical staging of USC patients and guide the choice of postop-erative adjuvant treatment.

The results of this study showed that combined adnexal/uterine serous inva-sion is an independent risk factor for the decrease of the 5-year follow-up cumu-lative disease-free survival (P<0.05). According to the FIGO staging, the presence of uterine serosal/adnexa inva-sion is classified as stage IIIa, and the 5-year disease-free survival rate of such patients is only 30%, which is lower than stage IIIc and closer to stage IVb[8-9].

All the above-mentioned results suggested that patients with USC who have lesions invading the adnexa or retroperitoneum often have a poor prognosis, and should be given more active and reasonable postoperative adjuvant treatment. A number of studies have demonstrated that[10-11] the long-term survival rate of pa-tients with stage III-IV USC who received adjuvant chemotherapy and radiotherapy after surgery was higher than that of chemotherapy alone; Meanwhile, the prognosis of patients with advanced USC who received postoperative chemother-apy + radiotherapy + chemotherapy was also improved significantly; both the 3-year disease-free survival rate and overall survival rate exceeded 50% with good safety. Based on the evidence above, we proposed that postoperative adjuvant chemotherapy and radiotherapy may increase long-term survival benefits for patients with tumors confined to the pelvic adnexa/uterine serosal invasion of USC.

Analysis of influencing factors of 5-year cumulative overall survival rate

The results of this study showed that unresected lymph nodes is an independent risk factor for the decrease of the 5-year follow-up overall disease-free survival (P<0.05); Namely, the prognosis of patients undergoing intraoperative resection of pelvic and abdominal paraaortic lymph nodes is more advantageous; The NCCN guidelines recommend that USC patients need to remove the lymph nodes from the pelvic cavity to the abdominal aorta. However, due to preoperative misdiagnosis and differences in doctors' understanding of USC, the scope of intraoperative lymph node resection in some patients does not meet the above requirements[12]; A retrospective study showed that[13], the metastasis rate of pelvic and paraaortic lymph nodes in USC patients could reach 13%~52%; while the above-mentioned lymph node metastasis rate in patients with type I endometrial carcinoma is less than 10%; Therefore, the importance of systematic retroperitoneal lymphadenectomy should be emphasized for pa-tients with USC. Relevant research has found that for USC patients with the le-sion being confined to the endometrium and stage Ia of clinical-stage, pelvic

and para-aortic lymphadenectomy can increase the long-term survival benefit to a certain extent[14], which indirectly indicated the importance of full lymphade-nectomy for USC patients.

The results of this study showed that positive intraoperative abdominal cavity cytology is an independent risk factor for the decrease in the cumulative overall survival rate of patients during the 5-year follow-up ($P<0.05$). Previous research has revealed that the results of in-traoperative peritoneal lavage fluid cell blood test in patients with stage I endometrial carcinoma have no obvious im-pression on the survival prognosis, and thus the FIGO staging standard of endometrial carcinoma has not been in-cluded in this test[15]. However, it should be noted that the patients included in the study were mainly type I endometrial carcinoma patients, and the proportion of USC was relatively small. Some scholars have reported that patients with stage Ia USC who have positive intraoperative peritoneal lavage fluid cytology test have a 3-4-fold increased risk of death, and may also increase the risk of distant metastasis[16-17]. The results of our study further confirmed the above view. In line with the above evidence, we suggested that for USC patients, hysteroscopy should be avoided as much as possible before surgery to cause tumor cells to enter the abdominal cavity, meanwhile, attention should be paid to the cytological examination results of intraoperative peritoneal lavage fluid to guide the formulation of postoperative adjuvant treatment plan. In addition, chemotherapy could be used as the main postoperative adjuvant treatment to maximize the clin-ical prognosis of positive patients.

There are certain limitations to this investigation, including:

• The included sample size was small and difficult to carry out more detailed stratification;

• This study was a single-center retro-spective report, and the influence of confounding factors on the conclusions obtained cannot be ruled out, which needs to be confirmed by further expanding the sample size and multi-center study.

Taken together, the poor prognosis of USC patients undergoing surgical treatment is independently related to in-complete staging surgery, combined ad-nexal/uterine serosal invasion, unre-sected lymph nodes, and positive in-traoperative abdominal cavity cytology.

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