

## **Risk factors of cytologic positive rate of ascites in early endometrial cancer patients and its influences on prognosis.**

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### **Abstract**

**Objective:** To explore risk factors of cytologic positive rate of ascites in early endometrial cancer patients and its influences on prognosis.

**Methods:** 3415 endometrial cancer patients in I and II stage in endometrial cancer prevention and treatment of Ankang project in Guangdong Women and Children hospital from 2000 to 2010 were given ascites cytologic examination. Then this study analyzed the relations between ascites cytologic positive examination and clinical pathological conditions, the relations between ascites cytologic positive and patients' prognosis.

**Results:** First, scites cytologic positive rate of early endometrial cancer patients was 3.7%. Second, single analysis show that the onset age more than 60 years old ( $P=0.008$ ), deep muscle infiltration ( $P=0.001$ ), cervical interstitial invasion ( $P=0.007$ ), which were the influencing factors of ascites cytologic positive of early endometrial cancer patients. Multiple factors analysis show that onset age ( $OR=1.797$ , 95% CI 1.064~3.036,  $P=0.028$ ), deep muscle infiltration ( $R=1.724$ , 95% CI 1.025~2.900,  $P=0.040$ ), cervical interstitial invasion ( $OR=2.051$ , 95% CI 1.083~3.886,  $P=0.027$ ) were independent risk factors of ascites cytologic positive of early endometrial cancer patients. Third, recurrence rate of positive and negative patients with ascites cytologic examination (14.2% vs. 7.2%,  $P=0.005$ ), remote recurrence rate (11.0% vs. 4.5%,  $P=0.001$ ), there were statistical differences, local recurrence rate (3.1% vs. 2.9%,  $P>0.05$ ), there were no statistical differences. Fourth, survival time of ascites cytologic positive and negative patients compared with progress-free survival time, there were statistical differences ( $P<0.001$ ,  $P=0.001$ ). Multiple factors analysis showed that ascites cytologic positive had no obvious influences on survival time ( $OR=0.620$ , 95% CI 0.194~1.986,  $P=0.421$ ) and progress-free survival time ( $OR=0.496$ , 95% CI 0.182~1.348,  $P=0.169$ ).

**Conclusion:** Ascites cytologic positive has close relations with independent factors of old age, deep muscle infiltration, cervical interstitial invasion. The prognosis of scites cytologic positive patients poorer than negative patients, but scites cytologic positive isn't independent prognostic influencing factors of early endometrial cancer.

**Keywords:** Endometrial cancer, Ascites cytology, Prognosis.

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### **Introduction**

Endometrial cancer (EC) is a kind of epithelial malignant tumor occurs in endometrium, is one of common malignant tumor in female reproductive organs [1]. EC is the most common gynecologic cancer in developed countries [2], and its incidence is increasing [3]. Over 50% of women with endometrial carcinoma present with early-stage, low-risk disease, and are treated by surgery alone [4]. Although the outcome is favorable for many cases diagnosed at an early stage with a five-year survival rate of 75%~86% [5]. The majority of women with endometrial cancer are diagnosed at

an early stage and have a favorable cancer-related prognosis [6]. According to the staging system developed in 1988, peritoneal cytology was considered as an important variable, and positive peritoneal cytology, adnexal metastasis, and serosal invasion were defined as stage IIIA [7]. Various studies showed that peritoneal cytology has important implications for prognosis [8,9]. International Federation of Gynecology and Obstetrics (FIGO) excluded ascites examination from IIIA diagnostic criteria by stages in 2009 [10]. There are still great arguments on the influences of cytologic positive on prognosis in clinic. This study gives retrospective analysis on data collected by endometrial cancer prevention and treatment of

Ankang project in Guangdong Women and Children hospital, to evaluate the prognostic value of peritoneal cytology in 1988 FIGO stage IIIA for endometrial malignancy and to determine factors that affect survival in this stage and its influences on prognosis, which will provide references for clinic.

## Materials and Methods

### *Clinical data collection*

This study collected 5816 endometrial cancer cases with follow-up, complete case data and diagnosed by pathological examination after surgery in endometrial cancer prevention and treatment of Ankang project in Guangdong Women and Children hospital from January 1<sup>st</sup>, 2000 to December 31<sup>st</sup>, 2010, of which, there were 3476 cases in FIGO 2009 I~II stage, who were given ascites cytologic examination during surgery. 61 cases that have been excluded from assistant treatment before surgery carried out subtotal hysterectomy, adnexal preservation surgery. All 3415 were included into this study.

### *Methods*

This study analyzed the relations between ascites cytologic positive and clinical pathological conditions, the relations between ascites cytologic positive and patients' prognosis.

### *Follow-up*

This study used phone follow-up, letter follow-up and out-patient follow-up. The end of follow-up was December 31<sup>th</sup>, 2012. Losing follow-up number were 372 cases. Losing follow-up rate was 10.9%. Follow-up time were from 3 months to 155 months. Median follow-up time were 57 months.

### *Statistical methods*

This study used SPSS 16.0 software to do statistical analysis. Measurement data used t test. Enumeration data used  $\chi^2$  test. Survival curve used Kaplan-Meier to do analysis. Multiple factor analysis used Log-rank test. Multiple factors analysis used Cox ratio risk ratio model to do analysis.  $P < 0.05$ , there were statistical differences.

## Results

### *General conditions*

Onset age of 3415 endometrial cancer cases were from 22 to 93 years old. Median onset age was 53 years old. There were 127 ascites cytologic positive cases (3.7%), 3288 negative cases (96.3%). There were 3088 cases in I stage (90.4%), 327 cases in II stage. There were 3323 endometrial adenocarcinoma (97.3%), 92 non-endometrial adenocarcinoma (2.7%). According to histological grade of endometrial adenocarcinoma, there were 1034 G1 cases (31.1%), G2 1561 cases (47.0%), G3 368 cases (11.1%), 360 uncertain cases (10%). There were 2258 cases (66.1%) whose muscle

infiltration depth less than 1/2, 518 cases whose muscle infiltration depth equal to or more than 1/2, 639 uncertain cases (18.7%). There were 1456 patients who were given total hysterectomy (42.6%), 598 cases who given subradical hysterectomy (17.5%), 1361 cases who given radical hysterectomy (39.9%). There were 1696 cases who given lymphadenectomy (49.7%), 1719 cases who not given lymphadenectomy (50.3%). 2629 cases not received assistant treatment after surgery (77.0%), 161 cases (4.7%) received assistant radiotherapy after surgery, 538 cases had assistant chemotherapy after surgery (15.8%), 87 cases (2.5%) had combination chemotherapy after surgery.

### *The relations between ascites cytologic positive and various clinical pathological factors*

Clinical pathological data of ascites cytologic positive and negative endometrial cancer in I and II stages, seen in table 1. Single factor analysis showed that onset age more than 60 years old ( $P=0.008$ ), deep muscle infiltration ( $P=0.001$ ), cervical interstitial invasion ( $P=0.007$ ) were influencing factors of endometrial ascites cytologic positive in I and II stages. Multiple factors analysis showed that onset age (OR=1.797, 95% CI 1.064~3.036,  $P=0.028$ ), deep muscle infiltration (OR=1.724, 95% CI 1.025~2.900,  $P=0.040$ ), cervical interstitial invasion (OR=2.051, 95% CI 1.083~3.886,  $P=0.027$ ) were independent risk factors of endometrial ascites cytologic positive in I and II stages.

### *Recurrence conditions*

Recurrence rate of ascites cytologic positive patients were 14.2%. Recurrence rate of ascites cytologic negative patients were 7.4%, there were statistical differences ( $\chi^2=7.970$ ,  $P=0.005$ ). Local recurrence rate in ascites cytologic positive and negative patients were 3.1% and 2.9% respectively, there were statistical differences ( $\chi^2=1.000$ ,  $P>0.05$ ). Remote recurrence rate were 11.0% and 4.5% respectively, there were statistical differences ( $\chi^2=11.688$ ,  $P=0.001$ ) (Table 2).

### *Analysis of prognosis and influencing factors of prognosis*

Total survival rate of ascites cytologic positive and negative patients in five years were 90.5%, 95.5% respectively. Progress free survival rate in five years were 82.8%, 92.3% respectively. Through Log-rank analysis, there were statistical differences in survival time ( $\chi^2=14.183$ ,  $P<0.001$ ) and progress free survival time ( $\chi^2=10.347$ ,  $P=0.001$ ) of patients in two groups. Through single factor analysis found that onset age ( $\chi^2=40.307$ ,  $P<0.001$ ;  $\chi^2=47.997$ ,  $P<0.001$ ), histological type ( $\chi^2=9.755$ ,  $P=0.002$ ;  $\chi^2=9.893$ ,  $P=0.002$ ), histological grade ( $\chi^2=87.401$ ,  $P<0.001$ ;  $\chi^2=89.290$ ,  $P<0.001$ ), muscle infiltration depth ( $\chi^2=98.050$ ,  $P<0.001$ ;  $\chi^2=100.154$ ,  $P<0.001$ ), cervical interstitial invasion ( $\chi^2=14.951$ ,  $P<0.001$ ;  $\chi^2=18.392$ ,  $P<0.001$ ), LVSI ( $\chi^2=14.951$ ,  $P<0.001$ ;  $\chi^2=18.392$ ,  $P<0.001$ ) were influencing factors of survival time and progress survival time of endometrial cancer. Whether ascites cytologic examination was positive, onset age, histological type, histological grade,

muscle infiltration depth, cervical interstitial invasion, LVSI all were included into Cox multiple factors analysis, the results showed that ascites cytologic positive had no obvious influences on survival time (OR=0.620, 95% CI 0.194~1.986, P=0.421) and progress survival time (OR=0.496, 95% CI 0.182~1.348, P=0.169). Onset age (OR=2.438, 95% CI 1.544~3.850, P<0.001; OR=1.934, 95%CI 1.361~2.774, P<0.001), histological grade (OR=1.645, 95% CI 1.162~2.330, P=0.005; OR=1.505, 95% CI 1.164~1.947, P=0.002), muscle infiltration depth (OR=3.349, 95% CI 2.089~5.370, P<0.001; OR=2.553, 95% CI 1.801~3.619, P<0.001) were independent prognostic influencing factors of survival time and progress free survival time of endometrial cancer in I and II stages.

**Table 1.** Clinicopathological data of patients with stage I-II endometrial cancer between positive and negative peritoneal cytology n (%).

		Ascites examination		$\chi^2$	P
		Negative (n=3288)	positive (n=127)		
Onset age	≤ 60 years old	2774 (84.4)	96 (75.6)	7.023	0.008
	>60 years old	514 (15.6)	31 (24.4)		
Histological type	Endometrial adenocarcinoma	3202 (97.4)	121 (95.3)	1.348	0.246
	Non-Endometrial adenocarcinoma	86 (2.6)	6 (4.7)		
Histological grade	G1	1001 (30.4)	33 (26.0)	4.214	0.239
	G2	1503 (45.7)	58 (45.7)		
	G3	356 (10.8)	12 (9.4)		
	uncertain	428 (13.0)	24 (18.9)		
muscle infiltration depth	<1/2	2193 (66.7)	65 (51.2)	14.898	0.001
	≥ 1/2	486 (14.8)	32 (25.2)		
	uncertain	609 (18.5)	30 (23.6)		
cervical interstitial invasion	no	2982 (90.7)	106 (83.5)	7.380	0.007
	yes	306 (9.3)	21 (16.5)		
LVSI	no	3222 (98.0)	121 (95.3)	3.156	0.076
	yes	66 (2.0)	6 (4.7)		

**Table 2.** Comparison of relapse of patients with stage I- II endometrial cancer between positive and negative cytology n (%).

	Ascites cytologic examination		P
	positive (n=127)	negative (n=3288)	
Recurrence	18 (14.2)	243 (7.4)	0.005

Local recurrence	4 (3.1)	96 (2.9)	>0.05
Remote recurrence	14 (11.0)	147 (4.5)	0.001

Histological type, cervical interstitial invasion, LVSI had no obvious influences on survival time and progress free survival time of endometrial cancer in I and II stages (all P>0.05).

## Discussion

### Ascites cytologic positive influencing factors of early endometrial cancer

Reports show that ascites cytologic positive rate of early endometrial cancer are from 3.3% to 10.6% [11-13]. These data show that ascites cytologic positive rate of early endometrial cancer patients is 3.7%, which is similar to documents reports. At present, the specific mechanism of ascites cytologic positive rate of early endometrial cancer is still unclear. In general, it is think that ascites cytologic positive rate of early endometrial cancer without metastasis beyond uterus first caused by bilateral fallopian entering into abdominal cavity; second by deep muscle infiltrating into muscle layer and serosa; third by lymphatic drainage; fourth by primary focus in peritoneal skin. Results of this paper show that deep muscle infiltration rate of ascites cytologic positive rate of early endometrial cancer is 25.2%, higher than negative patients obviously. Multiple factors analysis show that deep muscle infiltration is an independent risk factors of ascites cytologic positive. In pelvic cavity of women, Douglas depression is the lowest point. Deciduous cell easily gather in this place. Cancerous cell in deep muscle infiltration easily migrates through serous surface of peritoneal viscera. The possibility of cancerous cells in douglas depression is high. There are scholars think that plentiful lymphatic network and migrated cancerous cells in pelvic and abdominal cavity can enter into abdominal cavity accompanies with lymphatic tube network, such as lymphatic obstruction. The number of cancerous cells will increase [14]. Results of this study not show that LVSI has correlations with ascites cytologic positive. Whether ascites cytologic positive has correlations with lymphatic drainage still needs to be verified. Results of this study show that onset age more than 60 years old is an independent risk factor of ascites cytologic positive, which has correlations with high poor prognostic factors of deep muscle infiltration, specific pathological type and histological G3 in elderly patients.

### The influences of ascites cytologic positive on early endometrial cancer prognosis

Ascites cytologic positive in FIGO 2009 has been excluded from FIGO 2009 stage. But in recent years, the influences of ascites cytologic positive on endometrial cancer prognosis still has relatively great argument. Some scholars think that prognosis of ascites cytologic positive patients of early endometrial cancer poorer than ascites cytologic negative patients of early endometrial cancer. Ascites cytologic positive

is an independent prognostic factors of early endometrial cancer patients. There are data show [15] that total survival rate of ascites cytologic negative patients of early endometrial cancer and negative patients in five years are 80.8% and 95.1% respectively. Serous adenocarcinoma patients are 50.4% and 70.8% respectively. There are also documents report that [11] Focus locates of endometrial adenocarcinoma in uterus, survival rate of ascites cytologic positive patients in five years lower than negative patients (83% vs. 97%,  $P=0.011$ ).

There are also people think that cytologic examination has a certain false positive. Positive result may be caused by uterus squeeze during surgery and hysteroscopy before surgery. Ascites cytologic positive of high risk factors of migration beyond uterus cannot influence prognosis of endometrial cancer patients [13,16]. Kasamatsu et al. [17] analyze 280 endometrial cancer patients without migration beyond uterus retrospectively, it finds that ascites cytologic positive has no significant differences in prognosis of patients. Ascites cytologic positive isn't the independent prognostic factors of early endometrial cancer. The significance of positive patients with assistant treatment after surgery is little. Results of this study show that recurrence rate of ascites cytologic positive patients of early endometrial cancer is twice as high as negative patients. Remote recurrence rate of positive patients higher than negative patients (11.0% vs. 4.5%). Survival analysis show that total survival rate and progress free survival rate in five years of ascites cytologic positive patients also lower than negative patients, it shows prognosis of ascites cytologic positive patients of early endometrial cancer in I and II stage poorer than negative patients, which shows that ascites cytologic positive of early endometrial cancer patients is the poor prognostic factors of endometrial cancer. After confounding factors of multiple factors, it shows that whether ascites cytologic examination is positive has no significant influences on survival time (OR=0.620, 95% CI 0.194~1.986,  $P=0.421$ ) and progress free survival time (OR=0.496, 95% CI 0.182~1.348,  $P=0.169$ ). Ascites cytologic positive isn't the independent prognosis influencing factors of endometrial cancer. It shows that ascites cytologic positive itself cannot increase death rate, which needs to combine with other high risk factors, such as onset age, histological grade, muscle infiltration depth, thus influencing prognosis of patients, which is in accordance with document reports [18-20].

In conclusion, ascites cytologic positive isn't the independent prognosis influencing factors of endometrial cancer. But the prognosis of ascites cytologic positive patients poorer than negative patients, which may has relations with ascites cytologic positive combined with risk factors of deep muscle infiltration, cervical invasion and so on. Therefore, ascites cytologic positive has been excluded from IIIA diagnostic criteria of FIGO 2009 stage. But clinical experts suggest that it is still needs ascites cytologic examination during surgery. During ascites cytologic examination, clinic should give attention, especially combining with positive management of deep muscle infiltration and cervical invasion. In addition, these data show that recurrence rate of ascites cytologic positive patients higher than negative patients. Remote

recurrence rate is more high. During follow-up, we should pay more attention to whether has recurrence, especially remote recurrence.

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