

# Hysteroscopy combined dilatation and curettage, serum CA125 and CA19-9 play an important role in preserving fertility or endocrine function for early-stage endometrial cancer patients

T. Ni<sup>1</sup>, Y. Liu<sup>1</sup>, Y. Huang<sup>1</sup>, X. Sun<sup>2</sup>, J. Wang<sup>1</sup>, Y.D. Wang<sup>1</sup>

<sup>1</sup> Department of Gynecology and <sup>2</sup> Laboratory for Gynecologic Oncology, International Peace Maternity and Child Health Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai (China)

## Summary

**Objective:** The aim of the study was to evaluate the role of hysteroscopy combined dilatation and curettage (D&C), serum CA125 and CA19-9 in endometrial cancer (EC) patients who desire to preserve fertility or endocrine function. **Materials and Methods:** This retrospective study included a total of 622 patients with EC between January 2006 and December 2014. The consistency of preoperative and postoperative histopathological findings were compared in patients who underwent D&C with or without hysteroscopy. The incidence of positive peritoneal cytology was also compared to assess the safety of hysteroscopy. Receiver operating characteristic (ROC) curve was used to evaluate the role of preoperative serum CA125 and CA19-9 in predicting extrauterine metastasis. **Results:** In 151 patients who underwent hysteroscopy combined D&C, the consistency of pre- and postoperative pathology was higher than the remaining 447 patients who underwent classical D&C alone (83.44% vs. 74.94%,  $p < 0.05$ ) and there was no significant difference in the incidence of positive peritoneal cytology between the two groups (2.64% vs. 2.73%,  $p > 0.05$ ). ROC curve analysis results showed the CA125 serum level of 31.75 U/ml and CA19-9 serum level of 35.40 U/ml were the best cutoff to predict extrauterine metastasis in endometrial cancer, with 66.7% sensitivity, 83% specificity, and 61.9% sensitivity and 84.9% of specificity, respectively. **Conclusions:** Hysteroscopy combined D&C should be recommended for early-stage EC patients who desire to preserve fertility or endocrine function, and the preoperative serum levels of CA125 and CA19-9 were powerful in predicting tumor stage in these patients.

**Key words:** Endometrial carcinoma; Hysteroscopy; CA125; CA19-9.

## Introduction

Endometrial cancer (EC) is one of the most common malignancies of female reproductive organs. In the United States, ~54,870 cases of EC will be newly diagnosed and 10,170 deaths are projected in 2015 [1]. Usually the standard surgical strategy for EC patient is hysterectomy with bilateral salpingo-oophorectomy, peritoneal lavages, and pelvic and para-aortical lymphadenectomies regardless of age. However, previous studies suggest that 2-14% of patients will be under the age of 40 years [2] and up to 55% of premenopausal patients were nulliparous [3]. Surgical castration may affect the quality of life for the nulliparous and the young women without coexisting ovarian cancer. However, the complexity of patient selection has stunted the development of conservative treatment without compromising survival. Thus, early-stage diagnoses and metastases assessment method were vital for these patients.

Although classical dilatation and curettage (D&C) has long been established as a widely accepted procedure for obtaining diagnostic endometrial tissue, however, due to blind curettage,

some of the small lesions in the uterine cavity may be missed by this procedure. Differently, hysteroscopy proves to be powerful in malignant endometrial pathology, in that it makes direct biopsies possible [4]. Comparison of the biopsy results from conventional curettage and hysteroscopy combined direct biopsy suggest that hysteroscopy guided endometrial biopsy to be the golden standard for postmenopausal women with abnormal uterine bleeding (AUB) [5]. However, few studies were conducted to compare the consistency of preoperative and postoperative histopathological findings in patients who underwent D&C with or without hysteroscopy. Furthermore, although hysteroscopy is a common practice, no definitive guidelines have been issued for the exact population and time to perform this procedure.

At the time of initial diagnosis of EC, surgical decisions rely on the recognition of remote metastases. Many studies have confirmed that the concentration of serum cancer antigen 125 (CA125) in patients with EC was associated with extrauterine metastases, and with especially high sensitivity in lymph node metastasis prediction [6-8]. CA19-9 as asso-

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Table 1. — Patient clinicopathological characteristics.

Characteristics	N (%)
Total	622 (100)
Age (years)	
≤ 40	23 (3.70)
> 40	599 (96.30)
Vaginal bleeding	
Yes	541 (86.98)
No	81 (13.02)
Vaginal fluid	
Yes	49 (7.88)
No	573 (92.12)
Menopause	
Yes	436 (70.10)
No	186 (29.90)
FIGO Stage	
I	541 (86.98)
II	39 (6.27)
III	37 (5.95)
IV	5 (0.80)
Grade	
G1	351 (56.43)
G2	171 (27.49)
G3	100 (16.08)
Histological type	
Endometrioid cancer	567 (91.16)
Non endometrioid cancer	55 (8.84)
Myometrial invasion	
None	128 (20.58)
< 1/2	402 (64.63)
≥ 1/2	92 (14.79)
Lymph node metastasis	
Yes	20 (3.21)
No	355 (57.07)
Not removed	247 (39.71)
Methods of preoperative diagnosis	
Classical D&C	447 (71.86)
Hysteroscopy + D&C	151 (24.28)
Neither <sup>a</sup>	24 (3.86)

FIGO: Federation of International Gynecology and Obstetrics, 2009.

D&C: dilatation and curettage.

<sup>a</sup>Endometrial cancer was found occasionally during other hysterectomy surgery.

ciated with epithelial cell-derived carcinoma is also detectable in EC. It could predict deep myometrial invasion, cervical involvement, and adjuvant treatment requirement [9], and the combined use of CA125 and CA19-9 had permitted a high sensitivity in relapsed cases in the monitoring of surgically treated EC patients [10]. However, these studies have limited clinical utility due to small number of patients or inconsistent cutoff values of serum CA125 or CA19-9.

Thus, the present authors conducted this retrospective study to discover the most appropriate diagnostic method and valuable metastases-assessment markers for premenopausal women with EC who were eager to have fertility or endocrine function preserving surgery.

## Materials and Methods

Data for this retrospective analysis was collected from a total of 622 patients with EC operated at International Peace Maternity and Child Health Hospital, Shanghai Jiao Tong University

Table 2. — Clinical features of the two groups (low-risk vs. high-risk group).

Group	Low risk <sup>a</sup> N (%)	High risk <sup>b</sup> N (%)	<i>p</i> value
Total	296 (100)	326 (100)	
Vaginal bleeding	254 (85.81)	287 (88.04)	> 0.05
Vaginal fluid	18 (6.08)	31 (9.51)	> 0.05
Menopausal	190 (64.19)	246 (75.46)	0.030
Under age of 40 years	16 (5.41)	7 (2.15)	0.035
Hypertension	108 (36.48)	1221 (37.12)	> 0.05
Diabetes mellitus	38 (12.84)	48 (14.2)	> 0.05
Family history of cancer	5 (1.69)	15 (4.6)	0.043
Breast cancer history	9 (3.04)	8 (2.45)	> 0.05
Nulliparous	14 (5.2)	15 (6)	> 0.05

<sup>a</sup>Low-risk group: grade I, FIGO Stage IA and endometrial cancer patients were assigned in the low-risk group. <sup>b</sup>High-risk group: patients had at least one of the following risk factors: tumor grades 2-3, FIGO Stage IB-IV and non-endometrioid cancer of histological type were placed in high-risk group.

School of Medicine, China between January 2006 and December 2014. Patients with incomplete clinical data were excluded from the study. Surgical staging of the disease was established in accordance with the criteria of Federation International of Gynecology and Obstetrics (FIGO, 2009) staging system. Patients had at least one of the following risk factors: tumor grade 2-3, FIGO Stage IB-IV and non endometrioid cancer of histological type were considered as high-risk group, while grade I, FIGO Stage IA and endometrioid cancer patients belonged to the low-risk group. General clinical characteristics were compared between the two groups. Preoperative D&C, with or without hysteroscopy, was routinely performed at the decision of the surgeons' and patients' preference. The histological results (D&C) from other institutions were reconfirmed by the experienced pathologist in the present hospital. Peritoneal cytology was obtained at the time of hysterectomy. Histopathological diagnoses of patients who underwent both D&C (with or without hysteroscopy) and hysterectomy were examined. Blood samples for the analysis of serum CA125 and CA19-9 were obtained preoperatively.

## Statistical analysis

Data were analyzed by SPSS statistical software. The chi-square test was applied to compare categorical data. Receiver operating characteristic (ROC) curve analysis was employed to find a cutoff level of CA125 and CA19-9 in serum with predictive sensitivity and specificity. Statistical significance was set at values of  $p < 0.05$ .

## Results

### Patient characteristics

During the study period, a total of 622 EC patients treated primarily by surgery were eligible for the study (Table 1). The mean age was  $56.96 \pm 8.93$  (range 27-91) years. Three hundred and twenty-six women were assigned to the high-risk group according to the grouping criteria, while the other 296 patients were placed in the low-risk group. Comparison of the two groups was summarized in (Table 2). No significant difference was found in vaginal bleeding/fluid,

Table 3. — Comparison of the consistency between the two groups (hysteroscopy + D&C vs. classical D&C group).

Group	Total	Consistency <sup>a</sup> N (%)	Positive peritoneal cytology N (%)
Hysteroscopy + D&C <sup>b</sup>	151	126 (83.44)	4 (2.64)
Classical D&C	447	335 (74.94)	11 (2.73)
<i>p</i> value		0.003	> 0.05

<sup>a</sup>Consistency: consistency of preoperative and postoperative histopathological findings in patients between the two groups. <sup>b</sup>D&C: dilatation and curettage.

Table 4. — Comparison of preoperative serum level of CA125 and CA19-9 in groups A and B.

	CA125		CA19-9	
	Mean U/ml	Median U/ml	Mean U/ml	Median U/ml
Group A	24.54±29.66	16.55	25.29±73.92	12.1
Group B	119.83±197.25	54.4	112.74±220.54	44.7

<sup>a</sup>Group A: patients without extrauterine metastases (FIGO Stage I and II patients). <sup>b</sup>Group B: patients with extrauterine metastases (FIGO Stage III and IV patients).

hypertension, diabetes mellitus, breast cancer history, and reproductive history between the two groups. When compared to the low-risk group, the proportion of women postmenopausal (75.46% vs. 64.19%, *p* = 0.03), and with family history of tumor (4.60% vs. 1.69%, *p* = 0.043) was significantly greater in the high-risk group while the proportion of women under age of 40 were more likely to be in the low-risk group (Table 2).

*Dilatation and curettage with or without hysteroscopy*

A total of 598 patients who underwent D&C procedure with or without hysteroscopy were divided into hysteroscopy group (151 patients) and D&C group (447 patients). Of the 151 cases in hysteroscopy group, hysteroscopy findings were at variance with the surgical pathology in only 25 cases (13 surgically confirmed EC patients were diagnosed as complex atypical hyperplasia, three grade 3 patients were diagnosed as grade 2, nine grade 2 patients were diagnosed as grade 1 by curettage combined with hysteroscopy). However, in 447 patients undergoing traditional D&C alone, 112 curettage findings did not match the surgical pathology (47 surgically confirmed EC patients were diagnosed as complex atypical hyperplasia, seven grade 3 patients were diagnosed as grade 2, and 58 grade 2 patients were diagnosed as grade 1 preoperatively by classical D&C). Peritoneal cytology was positive in four of 151 patients (2.64%) in the hysteroscopy group and positive in 11 of the 447 patients (2.73%) in the D&C group. Compared to classical D&C group, the hysteroscopy group showed more accurate diagnosis of endometrial pathology (the consistency of pre- and postoperative diagnosis: 83.44% vs. 74.94%, *p* = 0.033), but did not increase the risk of peritoneal spread (the incidence of positive peritoneal cytology: 2.64% vs. 2.73%, *p* > 0.05)

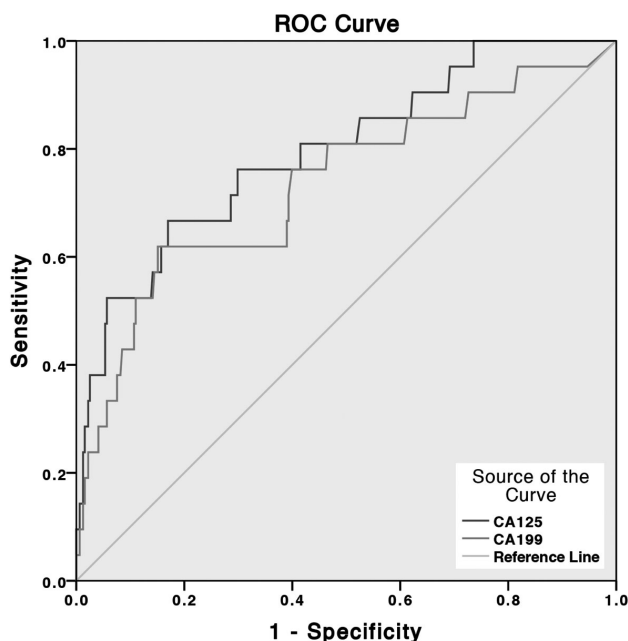


Figure 1. — Receiver operating characteristic (ROC) curve of preoperative serum. CA125 (area under ROC curve (AUC) = 0.796) and CA199 (AUC = 0.734) for predicting extrauterine metastases in endometrial cancer patients.

(Table 3).

*Preoperative CA125 and CA19-9*

In this part of the present study, 580 patients without extrauterine metastases (FIGO Stage I and II patients) were placed in group A, while a total of 42 patients with extrauterine metastases (FIGO Stage III and IV patients) were placed in group B. There were 348 patients undergoing preoperative CA125 measurement and 327 patients undergoing CA19-9 measurement in group A. As in group B, the number of patients undergoing CA125 and CA19-9 measurement were both 21. Comparison of the two groups is listed in Table 4. To evaluate the best cutoff level of extrauterine metastases prediction, a ROC curve analysis was used (Figure 1). The preoperative serum CA125 level of 31.75 U/ml was found to be the best, with 66.7% sensitivity and 83% specificity, while the CA19-9 level of 35.40 U/ml was the best cutoff, with 61.9% sensitivity and 84.9% specificity.

**Discussion**

An accurate assessment of histological grade and tumor extent may enable optimization of the surgical treatment, especially for the early-stage patients. In the present study, hysteroscopy combined D&C along with preoperative serum levels of CA125 and CA19-9 were applicable examinations in guiding the surgical management.

As clinical characteristics were compared in the low- and high-risk groups in the present study, the results showed that the cases of women postmenopausal (75.46% vs. 64.19%,  $p = 0.03$ ), or with family history of cancer (4.60% vs. 1.69%,  $p = 0.043$ ) was significantly greater in the high-risk group while the proportion of women under age of 40 years were more likely to be in the low-risk group (5.41% vs. 2.15%,  $p = 0.035$ ). The major reason may be that the tumors in young patients are usually well-differentiated endometrioid adenocarcinoma, at low-stage and with a favorable outcome [11, 12]. Of the patients with family history of cancer, 65% (13/20) were with a first-degree family history of EC or colorectal cancer in this study, and it is reported in other studies that family history of EC or colorectal cancer are important risk factors for EC [13, 14]. Some previous studies suggested that conservative therapy should be taken into consideration in premenopausal patients under age of 40 with low risk of metastases [15, 11], which was similar to the present authors' opinion. However, the study of Penner *et al.* [16] had shown no significant correlation with age or family history of malignancy in the success of conservative treatment with progestin in premenopausal women. However, Simpson *et al.* [17] found that older age of diagnosis was associated with a lower incidence of complete response after progestin treatment. Unfortunately, many of the previous studies are based on small sample sizes and with inconsistent results, which limited its clinical utility. According to the present study, premenopausal women under age of 40 years with EC are more likely to be in the low-risk group, which made uterus or ovary saving surgery possible.

Hysteroscopy is widely used in the assessment of uterine pathology and directed biopsies can be taken if needed. Studies were found comparing the hysteroscopic impression with directed biopsies through the hysteroscope [4] and with traditional D&C [18]. Diagnostic accuracy of hysteroscopic biopsy and D&C were also compared [5, 19]. In the present study, when compared to surgical pathologic results, the accuracy rate of preoperative diagnosis made by D&C with hysteroscopy was significantly higher than that in the classic D&C group (83.44% vs. 72.94%), while there was no statistical difference in the previous study [20]. The incidence of positive peritoneal cytology was not much higher for patients who underwent D&C with hysteroscopy before surgical staging than for patients who underwent D&C alone, and the result is consistent with those reported by several other investigators [21-23]. The present study has demonstrated the superiority of hysteroscopy combined D&C over classical D&C in the detection of EC and the authors recommend this procedure in young patients who are eager to keep fertility or endocrine function for it has improved prediction of tumor grade.

Serum CA125 measurement was first described by Niloff *et al.* [24] in patients with EC, and they demonstrated that CA125 levels were elevated in recurrent or disseminated disease but not with tumors confined to the uterus. Since

then, many studies were established to investigate the clinical value of CA125. Kim *et al.* [25] found that adnexal involvement was predicted with the highest accuracy (83.0%) at  $\geq 40.8$  U/ml while Jiang *et al.* [26] demonstrated the best cutoff level of adnexal involvement was 30 U/ml. The preoperative serum CA125 levels also facilitated the prediction of lymph node metastases [7, 26, 27]. The present authors' efforts of tumor markers demonstrated that the serum CA125 level of 31.75 U/ml was the best cutoff level to predict extrauterine metastases, with 66.7% sensitivity and 83% specificity, which are within the range reported by previous investigators. Tumor associated antigen CA19-9 was frequently detected in gastrointestinal tumors. However, it could also predict deep myometrial invasion, cervical involvement, and adjuvant treatment requirement in EC [9]. Cherchi *et al.* [10] reported that the combined use of CA125 and CA199 permitted a high sensitivity in predicting relapsed disease during follow-up. Thus in the present study, the authors confirmed the value of preoperative serum CA19-9 in predicting extrauterine metastases, which was similar to the previous study [6]. The best cutoff level was 35.40 U/ml, with 61.9% sensitivity and 84.9% specificity in the current study. Serum CA125 and CA19-9 along with MRI scan [28] were valuable predictors for preoperative tumor stage in patients with EC. However, the present study has some limitations such as a retrospective design and due to a single center study; the sample size of patients who underwent serum CA19-9 measurement in the high risk group was small. Meanwhile, long-term postoperative follow-up is lacking as well. Therefore, to confirm the present results, a prospective, large-scale, multicenter study is needed.

In conclusion, the present study demonstrated that among the premenopausal low risk endometrial cancer patients with preoperative diagnoses made by hysteroscopy combined D&C, and with low serum level of CA125 and CA19-9, fertility or endocrine function saving surgery can be taken into consideration.

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The first two authors contributed equally to this work.

Corresponding Author:

Y.D. WANG, M.D.

Department of Gynecology

International Peace Maternity and

Child Health Hospital

Shanghai Jiao Tong University School of Medicine

No. 910 Hengshan Road

Shanghai 200030 (China)

e-mail: owangyudong@126.com