

Does duration of hysteroscopy increase the risk of disease recurrence in patients with endometrial cancer? A multi-centre trial

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Abstract. Women with endometrial cancer often undergo hysteroscopy during their diagnostic work-up. Whether or not the duration of hysteroscopy affects the rate of positive peritoneal cells and the duration of recurrence-free survival is unknown. In a retrospective multi-centre study, the records of 552 patients with endometrial cancer were investigated. Duration of hysteroscopy was correlated with clinicopathological parameters and patient survival data. The mean [standard deviation (SD)] duration of hysteroscopy was 18.2 (10.5) min in the study population and 17.9 (10.1) min and 17.9 (10.2) min in patients with positive ($n=109$) and negative peritoneal cytology ($n=443$), respectively ($p=0.9$). There were no statistically significant correlations between duration of hysteroscopy and positive peritoneal cytology ($p=0.6$; $\rho=-0.028$), FIGO stage ($p=0.2$; $\rho=-0.080$), lymph node involvement ($p=0.2$; $\rho=0.106$) and patient age ($p=0.5$; $\rho=0.033$). Longer duration of hysteroscopy (>15 min) was not associated with positive peritoneal cytology (yes vs. no, $p=0.8$), advanced tumour stage (FIGO I vs. II, III and IV, $p=0.3$), lymph node involvement (yes vs. no, $p=0.1$) and patient age (≤ 65 vs. >65 years, $p=0.4$). In a multivariate analysis, FIGO stage [$p<0.0001$; hazard ratio (HR)=5.1, 95% confidence interval (CI) 2.5-10.2], lymph node involvement ($p=0.02$; HR=3.2, 95% CI 1.2-8.8) and patient age ($p=0.003$; HR=2.4, 95% CI 1.3-4.2), but not duration of hysteroscopy ($p=0.4$; HR=1.2, 95% CI 0.7-2.2), were associated with recurrence-free survival. We conclude that longer duration of hysteroscopy does not increase the risk of positive peri-

toneal cytology and it is not an adverse prognostic factor for recurrence-free survival in patients with endometrial cancer.

Introduction

Endometrial cancer accounts for approximately 4% of all cancers in women and occurs predominantly after menopause. Some of the highest incidence rates worldwide are found in the US and European populations (1). Clinical signs and symptoms associated with endometrial cancer include postmenopausal bleeding and perimenopausal meno-metrorrhagia (2). Women presenting with these conditions undergo histological evaluation of the endometrium. Typically, endometrial tissue sampling is combined with hysteroscopy, i.e., the optical visualization of the endometrial cavity via an endoscope (2-5). Hysteroscopy is a highly accurate method and is useful in diagnosing, rather than excluding endometrial cancer in women with abnormal uterine bleeding (6). This technique, however, flushes fluid and endometrial cells into the abdomen via the fallopian tubes, thus potentially spreading malignant cells. For example, in a prospective randomized study, Nagle et al examined 30 women undergoing hysteroscopy and concomitant laparoscopy for infertility. Endometrial cells were present in the peritoneal fluid in 6% of patients before hysteroscopy and in 25% after hysteroscopy (7). A number of studies have associated hysteroscopy with an increased risk of positive peritoneal cytology in women with endometrial cancer (8,9), while certain studies have raised the possibility of an adverse impact of hysteroscopy on prognosis in women with endometrial cancer (10-13).

Despite these concerns, however, hysteroscopy is considered a safe and acceptable procedure and is used extensively for the evaluation of women with postmenopausal bleeding or perimenopausal meno-metrorrhagia (14,15). Whether or not the duration of hysteroscopy is a matter of concern in women with suspected endometrial cancer is yet unknown. If prolonged hysteroscopy increased the risk of positive peritoneal cytology and disease recurrence, this would have

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clinical implications regarding time restriction or avoidance of hysteroscopy in women with suspected endometrial cancer.

To investigate this issue, we performed a retrospective multi-centre study in a large series of women with endometrial cancer who underwent pre-operative hysteroscopy. The aim of our study was to investigate whether the duration of hysteroscopy is associated with positive peritoneal cytology at surgery and adverse prognosis in patients with endometrial cancer.

Materials and methods

Five hundred and fifty-two patients with endometrial cancer, treated at the Departments of Obstetrics and Gynecology of the Medical University of Vienna, Austria ($n=220$), the Medical University of Innsbruck, Austria ($n=204$), the Landeskrankenhaus Klagenfurt, Austria ($n=87$), the Landeskrankenhaus Wiener Neustadt, Austria ($n=39$) and the Department of Gynecologic Oncology, Royal Adelaide Hospital, Adelaide, Australia ($n=2$), between February 1996 and July 2009, were included in the present study. Clinical and laboratory data were extracted retrospectively from patient files.

Diagnosis of endometrial cancer was established by diagnostic hysteroscopy and dilation and curettage. Hysteroscopy was performed with saline as the distension medium. Duration of hysteroscopy was defined as the time between the start and the end of the surgical procedure. The duration of hysteroscopy was noted by the nursing staff on a surgical procedure documentation sheet. Patients were surgically staged according to the International Federation of Gynaecology and Obstetrics (FIGO)/American Joint Committee on Cancer (AJCC) classification system. Hysterectomy, bilateral salpingo-oophorectomy, cytological examination of peritoneal fluid and biopsy of any suspicious intraperitoneal or retroperitoneal lesions were performed. Pelvic and paraaortic lymphadenectomy were performed, except for tumour stages FIGO Ia and Ib (using the 1989 FIGO classification for endometrial cancer) with histological grades 1 and 2 and endometrioid histology. In patients with intermediate- or high-risk disease, adjuvant radiotherapy was provided according to standardized treatment protocols (16). A regimen of adjuvant chemotherapy using carboplatin/paclitaxel was used in selected patients with advanced disease.

Three months after completion of primary therapy, the first follow-up visit was scheduled. Patients had follow-up visits at 3-month intervals for the following 2 years, including inspection and vaginal-rectal palpation. In the third and fourth year, visits were scheduled bi-annually and once a year from the fifth year on. When patients did not present for the scheduled follow-up visits, they were contacted by administrative personnel. In the event of any clinically suspicious symptoms and/or elevation of tumour markers, computed tomography was performed.

Values represent the means [standard deviation (SD)] in the case of a normal distribution, or the medians (range) in the case of a skewed distribution. T-tests and one-way ANOVA were used to compare the duration of hysteroscopy and clinicopathological parameters. Correlations are described by Spearman's correlation coefficient. Survival probabilities were calculated by the product limit method of Kaplan and Meier. Differences between groups were tested using the log-rank test. The results were analyzed for the endpoint of

Table I. Patient characteristics.

Parameter	
Total no. of patients enrolled	552
Age at diagnosis in years, mean (SD)	66.7 (10.9)
Histological type, n (%)	
Type I	520 (94.2)
Type II	32 (5.8)
Tumour stage, n (%)	
FIGO IA	78 (14.1)
FIGO IB	259 (46.9)
FIGO IC	91 (16.5)
FIGO IIA	24 (4.3)
FIGO IIB	27 (4.9)
FIGO III	59 (10.8)
FIGO IV	14 (2.5)
Histological grade, n (%)	
G1	236 (42.8)
G2	214 (38.8)
G3	102 (18.4)
Peritoneal cytology, n (%)	
No. of patients with positive peritoneal cytology	109 (19.7)
Recurrence status, n (%)	
No. of patients with recurrent disease	61 (11.1)
Time to recurrent disease in months (SD)	35.5 (28.9)
Status at last observation, n (%)	
Alive with no evidence of disease	439 (79.5)
Progressive disease	23 (4.2)
Tumour-related death	38 (6.9)
Death due to other causes	52 (9.4)

FIGO, International Federation of Gynaecologists and Obstetricians; SD, standard deviation.

disease-free survival. Events were defined as recurrence, death or progression at the time of last follow-up. Survival times of disease-free patients or patients with stable disease were censored with the last follow-up date. Survival times of patients who died due to other causes were censored with the date of death. Univariate analysis and a multivariate Cox regression model for disease-free survival were performed using duration of hysteroscopy (≤ 15 vs. > 15 min), FIGO tumour stage (FIGO I vs. FIGO II-IV), histological grade (G1+G2 vs. G3) and histological subtype (type I vs. type II). p -values < 0.05 were considered statistically significant. The statistical software SPSS 16.0 for Mac (SPSS 16.0.1; SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

The present study was approved by the Ethics Committee of the Medical University of Vienna and the General Hospital of Vienna.

Results

Patient characteristics are provided in Table I. Lymph node status was available in 147/552 (27%) patients. Lymph node

Table II. Relationship between clinicopathological parameters and duration of hysteroscopy in 552 patients with endometrial cancer.

	HSC ≤15 min (n=312)	HSC >15 min (n=240)	p-value ^a
Tumour stage			
FIGO I	234 (75%)	194 (81%)	0.3
FIGO II-IV	78 (25%)	46 (19%)	
Age at first diagnosis			
≤65 years	154 (49%)	107 (45%)	0.4
>65 years	158 (51%)	133 (55%)	
Peritoneal cytology			
Yes	62 (20%)	47 (20%)	0.8
No	208 ^b (67%)	170 ^b (71%)	
Histological grade			
G1+2	249 (80%)	201 (84%)	0.5
G3	63 (20%)	39 (16%)	
Histological type			
Type I	297 (95%)	223 (93%)	0.5
Type II	15 (5%)	17 (7%)	
Lymph node involvement			
Yes	11 (4%)	16 (7%)	0.1
No	301 ^c (96%)	224 ^c (93%)	

HSC, hysteroscopy; FIGO, International Federation of Gynaecologists and Obstetricians. ^aChi-square test; ^bexcluding missing values (n=65); ^cincluding women with and without lymph node sampling.

Table III. Univariate Kaplan Meier analysis and multivariate Cox regression model of prognostic covariates and recurrence-free survival in 552 patients with endometrial cancer.

	Univariate ^a	Multivariate ^b	
	p-value	HR (95% CI)	p-value
FIGO stage (I vs. II-IV)	<0.00001	5.1 (2.5-10.2)	<0.0001
Tumour grading (G1+2 vs. G3)	0.05000	1.7 (0.9-3.3)	0.0800
Age (>65 vs. ≤65 years)	0.00200	2.4 (1.3-4.2)	0.0030
Lymph node involvement (yes vs. no)	0.01000	3.2 (1.2-8.8)	0.0200
Histological type (type I vs. II)	0.10000	1.2 (0.8-1.8)	0.3000
Duration of HSC (≤15 vs. >15 min)	0.40000	1.2 (0.7-2.2)	0.4000

HR, hazard ratio; 95% CI, 95% confidence interval; HSC, hysteroscopy. ^aLog-rank test; ^bmultivariate Cox regression analysis.

involvement was noted in 27/552 (5%) patients. Adjuvant radiotherapy was administered to 298/552 (54%) patients and 45/552 (8%) patients received adjuvant chemotherapy.

The mean (SD) duration of hysteroscopy in all patients was 18.2 (10.5) min. The mean (SD) duration of hysteroscopy in patients with positive (n=109) and negative peritoneal cytology (n=443) was not statistically different [17.9 (10.1) min vs. 17.9 (10.2) min, respectively; p=0.9]. There were no statistically significant correlations between duration of hysteroscopy (as a continuous variable) and positive peritoneal cytology (p=0.6; rho=-0.028), FIGO stage (p=0.2; rho=-0.080), lymph node involvement (p=0.2; rho=0.106) and patient age (p=0.5; rho=0.033). The associations between duration of hysteroscopy

and clinicopathological parameters are provided in Table II. Longer duration of hysteroscopy was not associated with positive peritoneal cytology, advanced tumour stage, histological grade, histological type, lymph node involvement or advanced patient age.

In a univariate analysis, tumour stage (FIGO I vs. II-IV), histological grade (G1+G2 vs. G3), histological type (type I vs. II), lymph node involvement (yes vs. no) and patient age (as a continuous variable), but not duration of hysteroscopy (as a continuous variable), were associated with disease-free survival. In a multivariate analysis, tumour stage, histological grade, histological subtype and lymph node involvement were associated with disease-free survival. Results of the univariate

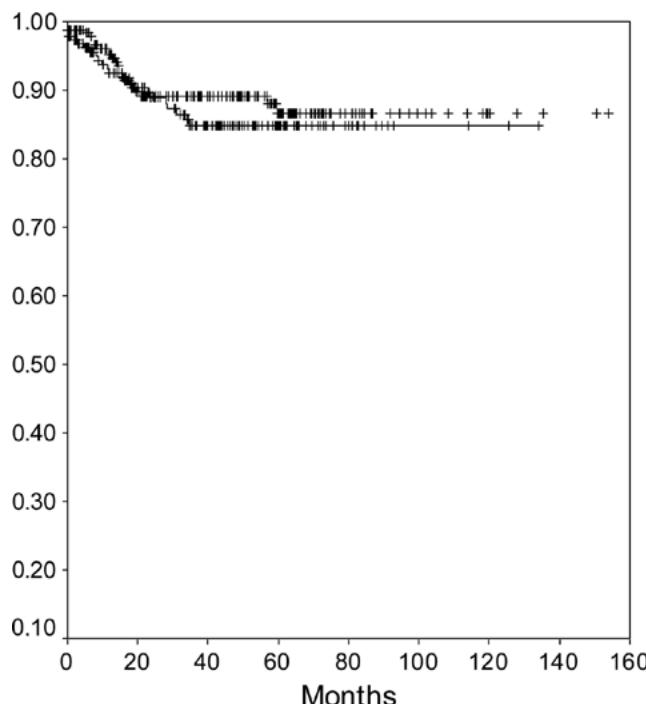


Figure 1. Recurrence-free survival analysis of 552 women with endometrial cancer according to duration of hysteroscopy ≤ 15 min (upper line) and >15 min (lower line).

and multivariate Cox-regression models and log-rank tests with respect to disease-free survival are shown in Table III. When patients were grouped according to the duration of hysteroscopy, patients with a duration of hysteroscopy ≤ 15 and >15 min had a 5-year recurrence-free survival rate of 87 and 85%, respectively [$p=0.4$; hazard ratio (HR)=1.2, 95% confidence interval (CI) 0.7-2.2] (Fig. 1).

Discussion

In the present study, we investigated whether a prolonged duration of hysteroscopy leads to a higher risk of positive peritoneal cytology and an increased risk of recurrence in women with endometrial cancer. We found that the duration of hysteroscopy was not associated with positive peritoneal cytology nor was it a prognostic parameter for recurrence-free survival. We conclude from these data that longer duration of hysteroscopy in patients with endometrial cancer is oncologically safe. It does not increase the risk of positive peritoneal cytology and does not adversely impact prognosis.

A number of studies have demonstrated that hysteroscopy increases the risk of positive peritoneal cytology and upstaging among women with endometrial cancer. For example, in a recent meta-analysis of 9 studies and 1,015 patients, Polyzos *et al* reported a significantly higher rate of malignant peritoneal cytology after hysteroscopy with an odds ratio of 1.78 (9). Thus, even though there is no clear evidence of an adverse prognostic effect of hysteroscopy and positive peritoneal cytology is no longer part of the FIGO staging system (9-13), concerns remain. Since endometrial cancer in general is associated with a favorable prognosis, subtle effects may be difficult to detect. Also, relevant confounders, such as the histological type of endometrial cancer or the duration of hysteroscopy, may influ-

ence the effect of this procedure on cancer cell spread and prognosis. These issues are of clinical relevance, since the duration of hysteroscopy is a potential risk factor under the control of the treating physician. Therefore, we investigated the influence of the duration of hysteroscopy on the risk of positive peritoneal cytology and recurrence-free survival in a large retrospective cohort study using a multi-centre study approach. We found that duration of hysteroscopy, both as a continuous variable and as a dichotomous variable with an arbitrary cutoff point of 15 min, was not associated with the rate of positive peritoneal cytology at the time of surgery or with the duration of disease-free survival. The results of our study have clinical implications, since they demonstrate that hysteroscopy can be used safely in women with suspected endometrial cancer even when a prolonged procedure is necessary to obtain an optimal diagnostic result. Also, these data support the new 2009 FIGO staging revision which omits stage IIIA based on positive peritoneal cytology only.

Our study has limitations which include the retrospective study design and the inclusion of multiple surgeons and centers. Thus, we cannot exclude selection and ascertainment bias. For example, technical expertise and equipment standards may vary among surgeons and centers as well as over time, and specific patient populations may or may not preferentially choose the centers included in this study. Also, hydrostatic pressure during hysteroscopy was not assessed. On the other hand, hysteroscopy is a relatively simple and well-standardized procedure, thus minimizing these effects. The strength of our study is the large number of patients allowing for an accurate estimate of the association between duration of hysteroscopy and clinicopathological parameters and prognosis.

In summary, our results demonstrate that prolonged duration of hysteroscopy is not associated with an increased risk of positive peritoneal cytology and it does not adversely affect the extent of recurrence-free survival. Therefore, hysteroscopy may be used safely in women with suspected endometrial cancer, even when the procedure requires an extended duration due to technical or other circumstances.

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