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ORIGINAL RESEARCH

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Impact of diagnostic hysteroscopy on peritoneal washing status and survival rate of patients with endometrial cancer

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Abstract

The diagnostic technique of hysteroscopy can spread the malignant cells from the uterus into the abdominal cavity in endometrial cancer patients. The study was designed to evaluate the impact of diagnostic hysteroscopy on the status of peritoneal cytology and prognosis of endometrial cancer patients. Pathologically confirmed endometrial cancer patients participated in this study. A matched 1:2 ratio control group was created with patients without hysteroscopy matched per cancer stage and histology grade. The presence of cancer cell in peritoneal fluid, the overall survival rate and disease-free survival rate between the two groups were compared. A total of 66 patients (23 cases and 43 controls) were included in the final analysis. Regarding the endometrial cancer type, 75.8% were endometroid, 9.1% papillary serous and 6.1% carcinosarcoma. Of these pateints 50%, 4.6%, 36.4% and 9.1% had stage I, II, III and IV cancer respectively. A total of 6 patients (9.1%) had peritoneal cytology with malignant cells, 3 (13%) were from the cases and 3 (7%) from the control group. The median follow-up period was 42.3 months. The 5-year overall survival rate for both groups was 79.8% with a similar 5-year survival rate of 83.2%. Gea Gzz General Hospital. Diagnostic hysteroscopy does not increase the risk of positive peritoneal cytology or worsen the prognosis of patients with endometrial cancer.

Keywords

Endometrial cancer; Diagnostic hysteroscopy; Peritoneal cytology

1. Introduction

Endometrial carcinoma is one of the most common gynecologic malignancies in developed countries. It occupies the 6th place in incidence and 4th in mortality of all malignant neoplasms among women [1]. The most common symptom is abnormal uterine bleeding (AUB), reported in up to 91% of the patients [2]. Although AUB is a very common complaint, the prevalence of endometrial carcinoma in patients with AUB is 9% in postmenopausal and 4.9% in premenopausal patients [3].

In modern gynecology, the use of diagnostic hysteroscopy for the evaluation of AUB patients is increasing. According to Soucie *et al*. [4], the use of diagnostic hysteroscopy for the evaluation of AUB patients increased from 26% in 1996 to 40.9% in 2006. Potential to perform a biopsy under direct visualization makes hysteroscopy the ideal diagnostic approach in endometrial cancer patients [5], as it is 86.4% sensitive and 99.2% specific for the endometrial cancer detection [6, 7].

The fluid distension media requirement and increased intrauterine pressure allowing adequate hysteroscopic visualization of the endometrial cavity, it is suspected that hysteroscopy can disperse malignant cells from the uterus into the abdominal cavity in endometrial cancer patients. Various studies indicate that the frequency of positive peritoneal cytology increases in patients who underwent preoperative hysteroscopy, especially early staged (I and II) patients. However, it does not impact the recurrence, overall survival or disease-free survival rate [8, 9]. On the other hand, there are other studies where this correlation has not been observed [10, 11].

In the year 2009, the International Federation of Gynecology and Obstetrics (FIGO) eliminated "positive peritoneal cytology" as disease staging criteria. A systematic review published in 2009, reported that the prognosis of patients with positive cytology varies depending on multiple factors [12, 13]. Nonetheless, positive peritoneal cytology can be an independent adverse prognostic factor in early stage patients [14–18].

The current study was designed to explore the effect of diagnostic hysteroscopy for the prevalence of positive peritoneal cytology and survival rate in patients with endometrial cancer.

2. Materials and methods

Followed by approval from institutional review board (IRB), the medical records of the patients diagnosed with endometrial cancer from January 2005 to December 2018 at the Dr. Manuel Gea Gonzalez General Hospital and treated at the Instituto Nacional de Cancerología of Mexico City were identified. The medical records of patients treated with hysterectomy with bilateral salpingo-oophorectomy were selected. Patients having pathologically confirmed endometrial cancer were divided in 2 groups. Those who underwent diagnostic hysteroscopy before the hysterectomy were included in the case group. A 1:2 ratio matched control group was created with patients who had no hysteroscopy before the hysterectomy matched per cancer stage and histology grade.

Patients with double primary tumor or without complete medical records were excluded. The clinical course, pathology reports, surgical and adjuvant treatment were recorded. Overall survival was defined as the time period between diagnosis and death or last appointment during the study tenure. Disease-free survival was defined as the time period between surgery and recurrence of the disease or last appointment during the study tenure.

A central tendency measurement analysis was performed with medians and interquartile ranges (IQR) for continuous variables, and absolute and relative frequencies for qualitative variables. For comparative analysis between both groups, the Wilcoxon, Chi square or Fisher exact test were used as and when suitable. Logistic regression was used to find the odds ratio (OR) and identify the variables associated with the presence of peritoneal cytology with malignant cells. Survival curves were calculated by the Kaplan Meier method and compared with the log-rank test. A univariate analysis with Cox test was performed for overall survival and disease-free survival. A significant difference was defined when the p was < 0.05. The statistical analysis was performed using Stata (version 13.0, StataCorp, College Station, TX, USA).

3. Results

Overall 23 patients diagnosed with endometrial cancer who had diagnostic hysteroscopy before the hysterectomy were identified and included in the case group. A paired 1:2 ratio control group matched by cancer stage and histology type was created with patients without diagnostic hysteroscopy before the hysterectomy. Only one control case was detected for one patient on the case group with stage 3 endometroid histological subtype, and no controls cases were observed for one patient with stage 3 carcinosarcoma. A total of 66 patients (23 cases and 43 controls) were included in the final analysis.

Both groups had similar demographic characteristics, disease stage, histology type, treatment or recurrence rate. The median age was 50 (interquartile range (IQR) 55–68) years. The median weight was 67 kg (IQR 60–81), with a median body mass index (BMI) of 30 (IQR 26–35). Regarding the histological type, 50 (75.7%) were endometroid type, 6 (9.1%) papillary serous, 6 (9.1%) clear cells and 4 (6.1%) carcinosarcoma. Regarding the stage of cancer, 33 (50%) had stage I, 3 (4.5%) had stage II, 24 (36.4%) had stage III and 6 (9.1%) had stage IV. Overall 6 (9.1%) patients had peritoneal cytology with malignant cells (3 patients of the case group (13%) and 3 from the control group (7%); $p = 0.414$) (Table 1). A total of 24 patients (36.4%) received chemotherapy, while 40 (60.4%) received radiotherapy. Twenty-one patients (31.8%) had recurrence of the disease (Table 1). All patients underwent lymph node dissection.

The variables associated with positive malignant cells peritoneal cells were histology type carcinosarcoma (OR 49, 95% confidence interval (CI) 3.03–794.5; $p = 0.006$), clear cells type (OR 24.5, 95% CI 1.81–332; $p = 0.016$), presence of macroscopic peritoneal disease (OR 7.43; 95% CI 1.24–44.2) and histological grade 3 (OR 3.6, 95% CI 1.22–10.9; $p = 0.02$) (Table 2).

The median follow-up period was 42.3 months (IQR 23.6–67.2). The 5-year overall survival rate for both groups was 79.8% (95% CI 66.1–66.4) with a similar 5-year overall survival rate of 83.2% (95% CI 56.1–94.3) in the case group and 77.9% (95% CI 60.2–88.5) in the control group ($p = 0.611$) (Fig. 1). The 5-year disease-free survival rate of both groups was 65.9% (95% CI 51.5–76.9), with 63.9% (95% CI 37.9–81.4) in the case group and 66.6% (95% CI 48.5–79.6) in the control group, which was not statistically different ($p = 0.972$) (Fig. 2).

The variables associated with overall survival were histological grade 2 (Hazard ratio (HR) 18.33, 95% CI 2.2–152; $p \leq 0.001$), histological grade 3 (HR 11.0; $p < 0.001$), stage III (HR 6.21, 95% CI 1.24–30.91; $p = 0.026$), stage IV (HR 14.26, 95% CI 2.31–87.88; $p = 0.004$), papillary serous subtype (HR 7.58, 95% CI 1.9–30.29; $p = 0.004$), adnexal infiltration of malignant cells (HR 5.81, 95% CI 1.73–19.41; $p = 0.004$), parametrial infiltration of malignant cells (HR 8.35, 95% CI 1.97–35.53; $p = 0.004$), lymph node involvement (HR 3.74, 95% CI 1.17–12.03, $p = 0.027$), indication of macroscopic peritoneal disease (HR 4.17, 95% CI 1.21–14.4; $p = 0.024$) and recurrence of disease (HR 8.4, 95% CI 2.22–31.77; $p = 0.002$) (Table 3). The factors associated with disease-free survival were histological grade 2 (HR 14 95% CI 3.9–49.6; $p < 0.001$), histological grade 3 (HR 14.9; $p < 0.001$), disease stage III (HR 4.55, 95% CI 0.54–13.37; $p = 0.006$), disease stage IV (HR 14.25, 95% CI 4.9–67.99; $p = 0.001$), adnexal infiltration of malignant cells (HR 4.37, 95% CI 1.68–11.32; $p = 0.002$), parametrial infiltration of malignant cells (HR 4.89, 95% CI 1.37–17.43; $p = 0.014$), positive lymph nodes (HR 4.47, 95% CI 1.85–10.85; $p = 0.001$), macroscopic peritoneal disease (HR 6.08, 95% CI 2.3–16.07; $p \leq 0.001$), and chemotherapy recipients (HR 3.15, 1.30–7.63; $p = 0.011$) (Table 3). Hysteroscopy and positive peritoneal cytology had no impact on overall survival (HR 0.71, 95% CI 0.19–2.66; $p = 0.613$ and HR 1.17, 95% CI 0.15–9.08; $p = 0.883$, respectively), and on disease free survival rate (HR 1.01, 95% CI 0.40–2.56; $p = 0.972$ and HR 2.15, 95% CI 0.63–7.37; $p = 0.220$, respectively).

4. Discussion

The migration of malignant cells through the fallopian tubes during hysteroscopy in endometrial cancer patients and the potential risk of positive peritoneal cytology is unclear and so is the impact of the potential intracavitary spillage on the disease

TABLE 1. Demographic characteristics of patients with prior diagnostic hysteroscopy history (case group) and without diagnostic hysteroscopy history (control group) (n = 66).

Patient characteristics	Total 66 (100)	Case group 23 (34.9)	Control group 43 (65.2)	*p*
Age[Ψ]	60.5 (55–68)	64.0 (55–70)	60.0 (53–66)	0.306
Menopause	53 (80.3)	19 (82.6)	34 (79.1)	0.731
BMI[Ψ]	30 (26–35)	28 (26–34)	31 (25–36)	0.496
Histology grade[Ω]				
1	4 (6.1)	1 (4.4)	3 (7.0)	0.974
2	36 (54.6)	13 (56.5)	23 (53.5)	
3	11 (16.7)	3 (13.0)	7 (16.3)	
Histology type[Ω]				
Endometroid	50 (75.7)	17 (73.9)	33 (76.7)	0.933
Clear cells	6 (9.1)	2 (8.7)	4 (9.3)	
Papilary serous	6 (9.1)	2 (8.7)	4 (9.3)	
Carcinosarcoma	4 (6.1)	2 (8.7)	2 (4.7)	
Stage[Ω]				
I	33 (50.0)	11 (47.8)	22 (51.2)	0.990
II	3 (4.5)	1 (4.4)	2 (4.7)	
III	24 (36.4)	9 (39.1)	15 (34.9)	
IV	6 (9.1)	2 (8.7)	4 (9.3)	
Tumor size (mm)[Ψ]	40 (30–65.5)	45 (30–66)	40 (25–60)	0.597
Lymphovascular space invasion	32 (48.5)	12 (52.2)	20 (46.5)	0.661
Thickness >50%[Ω]	38 (57.6)	14 (60.9)	24 (55.8)	0.692
Spread to cervix[Ω]	14 (21.2)	5 (21.7)	9 (20.9)	0.939
Spread to anexa[Ω]	12 (18.2)	4 (17.4)	8 (18.6)	0.903
Spread to parametrium[Ω]	6 (9.1)	3 (13.0)	3 (7.0)	0.414
Positive lymph nodes[Ω]	17 (25.8)	6 (26.1)	11 (25.6)	0.964
Positive omentum[Ω]	10 (15.4)	4 (17.4)	6 (14.3)	0.740
Positive cell washings[Ω]	6 (9.1)	3 (13.0)	3 (7.0)	0.414
Chemotherapy[Ω]	24 (36.4)	11 (47.8)	13 (30.2)	0.157
Radiation[Ω]	40 (60.6)	15 (65.2)	25 (58.1)	0.579
Recurrence[Ω]	21 (31.8)	7 (30.4)	14 (32.6)	0.860

[Ψ] *Median (range).*
[Ω] *Absolute number (percentage).*
BMI: body mass index.

TABLE 2. Clinical features of patients with positive malignant cells in peritoneal washing.

	OR	95% CI	*p*
Age	1.03	0.94–1.12	0.540
Menopause	1.01	0.86–1.18	0.914
BMI	0.88	0.75–1.04	0.143
Grade 1–2 versus 3	3.66	1.22–10.95	0.020
Histology type			
Endometroid	1.00		
Clear cell	24.50	1.81–332.47	0.016
Papillary serous	9.80	0.52–181.8	0.126
Carcinosarcoma	49.00	3.02–794.5	0.006
Stage I–II versus III–IV	1.29	0.61–2.73	0.508
Tumor size	1.01	0.97–1.05	0.658
Lymphovascular space invasion	6.11	0.67–55.51	0.108
Thickness			
≤50%	1.00		
>50%	0.71	0.13–3.83	0.695
Spread to the cervix	2.00	0.32–12.24	0.453
Spread to the anexa	5.66	0.98–32.61	0.052
Spread to the parametrium	2.20	0.21–22.70	0.508
Positive lymph node	3.28	0.59–18.13	0.172
Positive omental disease	7.43	1.24–44.24	0.028
Diagnosed by hysteroscopy	2.00	0.37–10.82	0.421

Abbreviations: OR: odd ratio; CI: confidence interval; BMI: body mass index.

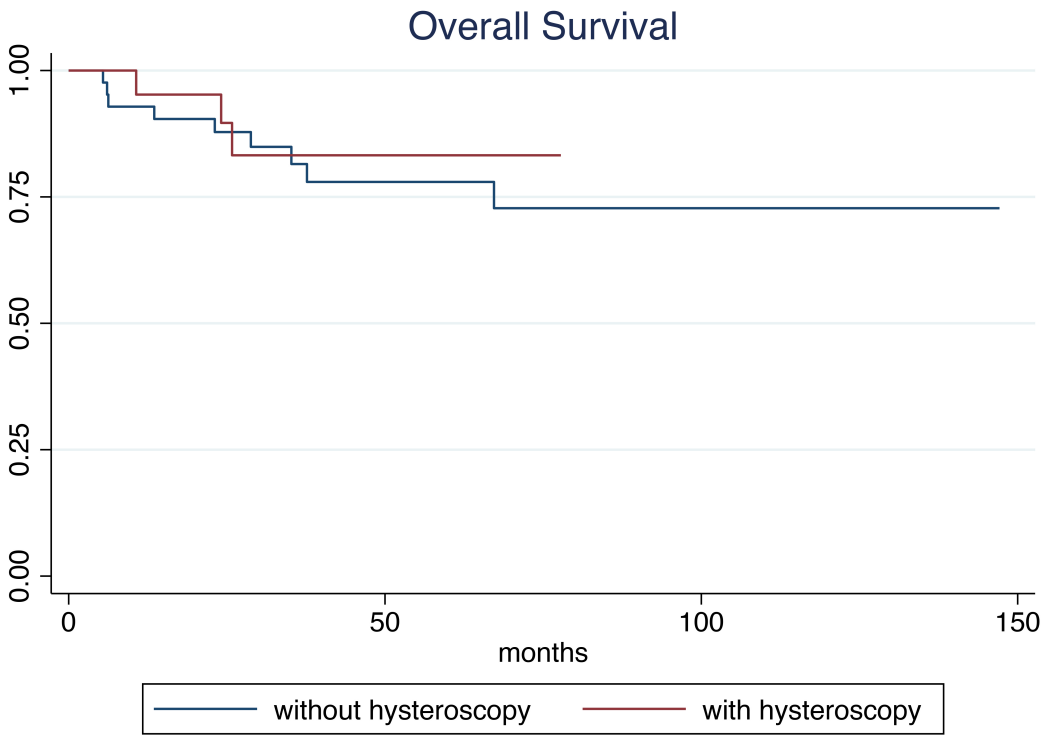

FIGURE 1. Overall Survival of patients.

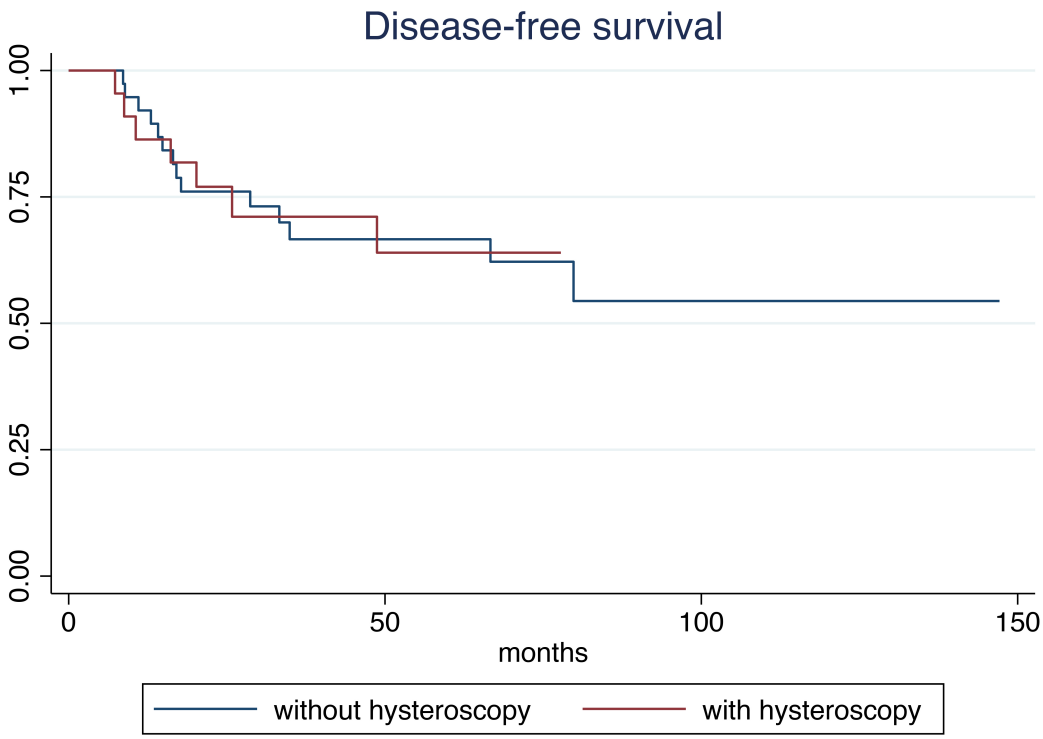

FIGURE 2. Disease-free survival of patients.

prognosis. Our results indicate that diagnostic hysteroscopy in endometrial cancer patients is not associated with the presence of positive peritoneal cytology, with no impact on cancer survival or disease-free survival rate. Similar results have been reported earlier. Aumiphin *et al.* [19] in a series of 29 endometrial cancer patients diagnosed with hysteroscopy revealed that 96.5% had negative peritoneal cytology and only one patient had positive peritoneal cytology, without worse prognosis or extrauterine disease. Similar results were also reported in two other studies [20, 21]. Liu *et al.* [10] detected 12 positive peritoneal cytology in 77 patients with endometrial cancer diagnosed with hysteroscopy had a 5-year recurrence-free survival rate and specific disease survival rate of 91.8% and 85.4% respectively. These results deserve special attention because the patients exhibited low-risk characteristics (71 patients were clinical stage I–II, 71 had no lymphovascular disease, and 44 had less than 50% of uterine wall involvement), demonstrating that hysteroscopy is not an independent risk factor for positive peritoneal cytology or worsening the prognosis of the disease. Soucie *et al.* [4], demonstrated that hysteroscopy in endometrial cancer patients impacted the stage and prognosis of the disease, increasing the incidence of stage III. However, this correlation was not verified and increased mortality rate among those who underwent non-hysteroscopic diagnosis 13.2% *vs.* 15.2% (OR = 0.87; 95% CI 0.69–1.10; p = 0.25) was not observed.

While comparing diagnostic hysteroscopy with dilation and curettage there is also contradictory information. Kudela *et al.* [22] reported that hysteroscopy does not increase the risk of positive peritoneal cytology when compared to dilation and curettage. Dovnik reported a statistically different frequency of positive peritoneal cytology between patients who underwent hysteroscopy during diagnosis and those diagnosed with dilation and curettage (12.8% *vs.* 3.4% respectively χ^2 = 0.062; p = 0.803), specifically in patients with FIGO stage I [9]. Some other studies demonstrate the correlation between diagnostic hysteroscopy before hysterectomy and positive peritoneal cytology. A meta-analysis reported an increased risk of positive peritoneal cytology in patients undergoing diagnostic hysteroscopy (relative risk (RR) 1.78; 95% CI 1.13–2.79; p = 0.013) [23]. The positive peritoneal cytology reported ranges from 4 to 22% in patients with previous hysteroscopy [12, 21, 24, 25]. The frequency of positive peritoneal cytology in current study was 13%, which is similar to previously reported frequency using normal saline as distention media during the diagnostic hysteroscopy [24]. Two key variables associated with an increased risk of having positive peritoneal cytology are type of distention media and intrauterine pressure above 50 mmHg during the procedure. The normal saline usage is frequently linked with positive peritoneal cytology (14%) when compared to carbon dioxine (1.4%) (OR = 11.2; 95% CI 1.3–94.5; p = 0.009) [24]. Similarly, hysteroscopic procedures performed with intrauterine pressures below 50 mmHg have no link with an increased frequency of positive peritoneal cytology [26, 27]. Unfortunately, in current study, the information on the intrauterine pressure was used during the diagnostic hysteroscopic procedures is missing.

The tubal cell migration during hysteroscopy was observed in endometrial cancer (FIGO stage I and II) patients after hysterectomy. In a study in which hysteroscopy was performed (pressure: 100 mmHg, infused volume: 150 mL for 3 minutes), the fluid expelled from the fallopian tubes was

TABLE 3. Clinical features associated with worse prognosis in patients diagnosed with endometrial cancer.

	Overall survival			Disease-free survival		
	HR	95% CI	*p*	HR	95% CI	*p*
Age	0.99	0.94–1.05	0.851	1.01	0.96–1.05	0.819
Menopause	1.28	0.28–5.88	0.744	2.69	0.62–11.58	0.183
BMI	1.04	0.96–1.11	0.343	0.98	0.92–1.05	0.613
Grade						
1	1.00			1.00		
2	18.33	2.20–152.0	<0.001	14.00	3.90–49.60	<0.001
3	11.00	NA	<0.001	14.90	NA	<0.001
Histology						
Endometroid	1.00			1.00		
Clear cells	1.75	0.21–14.4	0.601	1.48	0.33–6.65	0.604
Papillary serous	7.58	1.90–30.29	0.004	3.91	1.09–13.98	0.034
Carcinosarcoma	4.83	0.56–41.45	0.151	5.63	1.20–26.28	0.028
Stage						
I	1.00			1.00		
II	6.40	0.58–70.71	0.130	21.91	0.34–25.10	0.331
III	6.21	1.24–30.91	0.026	4.55	1.54–13.37	0.006
IV	14.26	2.31–87.88	0.004	14.25	4.90–67.99	<0.001
Tumor size	1.01	0.98–1.04	0.278	1.01	0.99–1.03	0.165
Lymphovascular space invasion	1.24	0.40–3.84	0.711	2.17	0.89–5.25	0.085
Thickness >50%	0.93	0.29–2.93	0.898	0.83	0.35–1.97	0.677
Spread to cervix	2.27	0.68–7.61	0.181	2.01	0.77–5.18	0.152
Spread to the adnexa	5.81	1.73–19.41	0.004	4.37	1.68–11.32	0.002
Spread to parametrium	8.35	1.97–35.53	0.004	4.89	1.37–17.43	0.014
Positive lymph nodes	3.74	1.17–12.03	0.027	4.47	1.85–10.83	0.001
Positive omental disease	4.17	1.21–14.44	0.024	6.08	2.30–16.07	<0.001
Diagnosis made by hysteroscopy	0.71	0.19–2.66	0.613	1.01	0.40–2.56	0.972
Positive peritoneal cytology	1.17	0.15–9.08	0.883	2.15	0.63–7.37	0.220
Chemotherapy	2.55	0.81–8.04	0.111	3.15	1.30–7.63	0.011
Radiotherapy	1.17	0.35–3.84	0.794	2.58	0.98–6.72	0.053
Recurrence	8.40	2.22–31.77	0.002	NA	NA	NA

HR: hazard ratio; CI: confidence interval; BMI: body mass index; NA: not applicable.

collected, obtaining 90% of viable cells which were later cultured. Transtubaric cell dissemination during hysteroscopy was observed in 83% of the patients. Of these, 71% were tumor cells and in 42% of them it was concluded that they were functional [28]. However, it has not been possible to demonstrate that the increased frequency of positive peritoneal cytology has an impact on the prognosis of endometrial cancer. A descriptive study of patients with endometrial cancer FIGO stage II reported a higher incidence of positive peritoneal cytology in patients who were diagnosed by hysteroscopy compared to those who had undergone blind endometrial curettage, presenting statistical difference in stages I and II. However, this statistical difference had no impact on the prognosis of the disease, reporting a specific 5-year survival rate of patients diagnosed by hysteroscopy of 60 months and of 71 months in those diagnosed by dilation and curettage ($p = 0.92$). The recurrence-free survival reported for those diagnosed by hysteroscopy was 60 months and 68 months for those who had blind endometrial curettage biopsy ($p = 0.99$). The reported recurrence rate was 33% *vs.* 32% in the hysteroscopy and curettage biopsy group respectively ($p = 0.92$) [8]. It is well accepted that the migration of malignant cells during hysteroscopy is possible, but further studies are needed to understand the consequences of the spillage on the prognosis of the disease. Several studies have shown the presence of an increased incidence of peritoneal tumor cells in patients undergoing hysteroscopy; however, the current evidence has not shown that hysteroscopy has an impact on the prognosis of

the disease [4, 21, 25–29].

Presence of high-grade histological types, carcinosarcomas, clear cells and the G3 histological grade were the variables associated with a positive peritoneal cytology. These results are consistent with previous study of Zerbe *et al.* [30] who reported higher frequency of positive peritoneal cytology in patients with high histological grade (33.3% *vs.* 19.4%; $p = 0.05$), lymphovascular space invasion (66.7% *vs.* 82.1%, $p = 0.005$) and invasion of tumor cells in the adnexa (19.1% *vs.* 5.5%, $p = 0.04$). Obermair *et al.* [25] reported different results while comparing hysteroscopy to dilation and blind curettage biopsy, reporting that positive peritoneal cytology was associated only with hysteroscopy ($p = 0.04$) but not with other pathological factors such as myometrial invasion ($p = 0.57$), pathology subtype ($p = 1.00$) or grade ($p = 0.10$).

Since 2009, positive peritoneal cytology is not included in the staging criteria for endometrial cancer [31]. The effect of positive peritoneal cytology for endometrial cancer prognosis has been extensively studied. A meta-analysis focusing the stage 1 and 2 of the disease, reported a higher incidence of grade 3, more than 50% uterine wall involvement, and decreased survival rate in patients with positive peritoneal cytology [15]. Brandon reported an increased frequency of advanced clinical stage, poor prognostic histology, worse differentiation, lymphovascular space invasion and greater tumor size ($p = 0.01$), with a decreased survival rate of 10% at 4 years (HR 1.85; 95% CI 1.54–2.21; $p = 0.001$) in patients with positive peritoneal cytology [17]. Numerous studies have reported positive peritoneal cytology as an independent prognostic factor impacting disease free survival and recurrence of the disease [13, 14, 17]. The current study suggested that the factors associated with positive peritoneal cytology were the histological subtypes of poor prognosis, omental involvement of the disease and the G3 histological grade. However, no correlation was observed between positive peritoneal cytology and the disease prognosis.

The factors associated with decreased overall survival rate and disease-free survival rate in current study are: histological grade G2 and grade G3, histology of poor prognosis, adnexal invasion and omental disease and clinical stages III and IV. These findings are consistent with previous studies [32, 33]. The reported overall survival rate in patients with clinical stage III and IV is 61.9% and 21%, as compared to 89.6% of FIGO stage I. Regarding histological grade, survival decreases from 92% for patients with G1 to 78% in histological grade G3 patients [33]. When the histological grade G3 is combined with other factors of poor prognosis, the survival rate decreases to 58% [34]. The clear cells subtype is a high-risk prognostic factor. Although they only represent 10% of all endometrial cancer, they represent 50% of recurrence and mortality rates with a 29–46% survival rate at 5 years, which is not associated with positive peritoneal cytology [35, 36].

Our study supports the safety of hysteroscopy as a diagnostic tool for endometrial cancer. The retrospective study design is a limitation of current study. However, it is a case-control study where it was possible to match cases to control at a 1:2 ratio, although it was not possible to find a control for the endometroid subtype and two for carcinosarcoma. Another limitation is the lack of information about intrauterine pressure. Prospective larger well-designed studies are needed to confirm the safety of hysteroscopy as a diagnostic approach for endometrial cancer patients with abnormal uterine bleeding.

5. Conclusions

These results suggest that diagnostic hysteroscopy neither increases the risk of positive peritoneal cytology nor affects the prognosis of patients with endometrial cancer.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author, (Barquet-Munõz SA), upon reasonable request.

AUTHOR CONTRIBUTIONS

CMV, SABM and DP—designed the research study. DCDL and JC—performed the research. JCGR and JAF—analyzed the data. CMV and SABM—wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics committee: Investigation Committee, National Institute of Cancer, Mexico City. Registry number: Rev/0006/20.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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