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Full length article

The oncological safety of hysteroscopy in the diagnosis of early-stage endometrial cancer: An Israel gynecologic oncology group study

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ABSTRACT

Objective: To compare survival measures of women with early-stage endometrial cancer who underwent either hysteroscopy or a non-hysteroscopic procedure as a diagnostic procedure.
Study design: An Israel Gynecologic Oncology Group multicenter study of 1324 patients with stage I endometrial cancer who underwent surgery between 2002 and 2014. Patients were divided into two groups: hysteroscopy and non-hysteroscopy (curettage or office endometrial biopsy). Clinical, pathological, and survival measures were compared between the groups.
Results: There were 355 patients in the hysteroscopy group and 969 patients in the non-hysteroscopy group. The median follow-up was 52 months (range 12–120 months). There were no differences between the groups in the 5-year recurrence-free survival (90.2% vs. 88.2%; p = 0.53), disease-specific survival (93.4% vs. 91.7%; p = 0.5), and overall survival (86.2% vs. 80.6%; p = 0.22).
Conclusion: Our findings affirm that hysteroscopy does not compromise the survival of patients with early-stage endometrial cancer.

Introduction

Endometrial cancer is the most common gynecologic cancer in developed countries [1]. In the majority of patients, the disease is confined to the uterus at diagnosis, and 5-year survival rates are as high as 80–90% in these patients [2,3]. Abnormal uterine bleeding is the most common symptom at presentation and is observed in up to 90% of patients [4,5]. The diagnosis of endometrial cancer is based on histologic results of endometrial sampling by office endometrial biopsy, uterine curettage, or hysteroscopy and directed endometrial biopsy.

Hysteroscopy provides direct visualization of the endometrial cavity; hysteroscopy-guided biopsy has a high accuracy for the diagnosis of endometrial cancer and is considered the gold standard for evaluation of abnormal uterine bleeding [6]. However, a concern regarding the possible intraperitoneal spread of cancer cells during the procedure, and thereby a potentially deleterious effect on staging and prognosis in cases of endometrial cancer, has been voiced. Although some publications have reported a higher frequency of positive peritoneal washings in women having surgery for endometrial cancer following a hysteroscopic procedure, the prognostic significance of isolated malignant cells in the peritoneal cavity in these cases is unclear [7,8]. Our purpose is to compare survival measures of women with stage I endometrial

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cancer who underwent either hysteroscopy or a non-hysteroscopic procedure as a diagnostic procedure. One can expect that the effect of hysteroscopic dissemination of tumor cells on survival would be small. The study was therefore designed as a study aiming to determine whether there was less than a 5% fall in overall survival in the hysteroscopy group.

Materials and methods

In this Israel Gynecologic Oncology Group study, the records of 1816 consecutive women with endometrial cancer who underwent surgery in one of 11 medical centers between January 2002 and December 2014 were reviewed. The study was approved by the respective institutional review boards. We included only 1324 patients with stage I endometrial cancer based on the International Federation of Gynecology and Obstetrics (FIGO) 2009 staging system [9]. The data, which included the clinical, surgical, and pathological reports, and follow-up information (for patients both censored and with an event), was combined into a single dataset for analysis. Our cohort of patients was followed from the date of surgery until an event (recurrence, death from disease, or death) or last follow-up up to 10 years or December 2014.

Patients were divided into two groups according to the preoperative diagnostic procedure: hysteroscopy versus endometrial office biopsy/endometrial curettage. Hysteroscopy with endometrial biopsy was performed either under general anesthesia or as an office procedure, with medium normal saline. Patients with endometrial cancer diagnosed postoperatively, without a preoperative diagnostic procedure, were excluded.

All patients underwent washings for cytology and total abdominal or laparoscopic hysterectomy with bilateral salpingo-oophorectomy. Pelvic lymph node assessment was performed in patients with tumors of moderate–high-grade histology or deep myometrial invasion. Para-aortic sampling was performed at the surgeon's discretion. We classified and grouped tumors as low grade (endometroid grade 1–2, and villoglandular) and high grade (endometroid grade -3, uterine serous papillary carcinoma, clear cell carcinoma, and carcinosarcoma). Therapeutic and adjuvant therapy including brachytherapy, external beam radiotherapy, and/or chemotherapy were generally administered according to National Comprehensive Cancer Network (NCCN) guidelines [10].

We calculated the number of patients needed based on previous data showing the proportion of hysteroscopically diagnosed endometrial patients to nonhysteroscopically to be 1:3. The overall endometrial cancer 5-year survival in the Israel National Cancer Registry is 80%. We assumed 5% decrease in overal survival in hysteroscopy group. With a power of 0.8 and an alpha of 0.05, 283 hysteroscopic and 849 non-hysteroscopic patients were needed.

The patients were divided into two groups according to the diagnostic method. The comparison of continuous variables was performed using Student's t-test. For the categorical variables, Chi-Square Test and Fisher's Exact Test comparisons between percent differences were performed as appropriate; $p < 0.05$ was considered significant. Patients were followed from the date of surgery until either death, death from endometrial cancer, or last follow-up up to 10 years. The primary endpoints of study included: overal survival, recurrence-free survival and disease-specific survival. We conducted a series of survival analyses using Kaplan-Meier statistics. The significance of the difference in the unadjusted survival curves was assessed using the log-rank test.

Results

The study included 1324 women with stage I endometrial cancer who underwent surgery. According to the preoperative diagnostic procedure, patients were divided into two groups: hysteroscopy (n = 355) and non-hysteroscopy (n = 969). Clinical, surgical, and pathological features of cases in the hysteroscopy and non-hysteroscopy groups are shown in Table 1. Pelvic lymph node dissection was performed in 57.1% of patients in the non-hysteroscopy group, compared to 50.1% in the hysteroscopy group (p = 0.024). Positive peritoneal cytology was 2.3% and 2.1%, respectively; there was no significant difference between the two groups (p = 0.832). The rate of adjuvant radiotherapy and chemotherapy rates were comparable in the two groups (9.7% vs 11.1%, p = 0.49; and 32.7% vs 33.7%, p = 0.84; respectively).

The median follow-up was 52 months (range 12–120 months). There was no difference between the hysteroscopic and non-hysteroscopic groups in 5-year recurrence-free survival (90.2% vs. 88.2%, p = 0.53) (Fig. 1), 5-year disease-specific survival (93.4% vs. 91.7%, p = 0.5) (Fig. 2), or in overall survival (86.2% vs. 80.6%, p = 0.22) (Fig. 3).

Discussion

Abnormal uterine bleeding is the clinical hallmark of endometrial cancer. Office endometrial sampling is generally a well-tolerated procedure that could be considered as a first step in the endometrial evaluation. The sensitivity to detect endometrial cancer was previously reported as 99% [11,12]. In a recent

Table 1
Pre and postoperative clinicopathological characteristics.

	Hysteroscopy (n = 355)	Non-hysteroscopy (n = 969)	*p* value
Age, mean ± SD	64.7 ± 10.3	65.6 ± 10.8	0.19
Pre-operative histology, n (%)			0.08
Low grade*	256 (73.4)	723 (75.3)	
High grade	83 (23.8)	189 (19.7)	
Others	10 (2.9)	48 (5%)	
Postoperative histology, n (%)			0.08
Low grade*	261 (74.4)	722 (74.7)	
High grade	71 (20.2)	227 (23.5)	
Others	19 (5.4)	17 (1.8)	
Lymphovascular space invasion, n (%)	31 (8.7)	83 (8.6)	0.92
Low uterine space involvement, n (%)	50 (14.1)	181 (18.7)	0.05
Pelvic lymph node dissection, n (%)	176 (50.10)	552 (57.1)	0.02
Para-aortic lymph node dissection, n (%)	27 (9.5)	80 (9.1)	0.85
Positive peritoneal cytology, n (%)	8 (2.3)	20 (2.1)	0.83
Adjuvant chemotherapy, n (%)	116 (32.7)	327 (33.7)	0.84
Adjuvant radiotherapy, n (%)	32 (9.7)	101 (11.1)	0.49

* Endometroid grade 1–2, villoglandular.

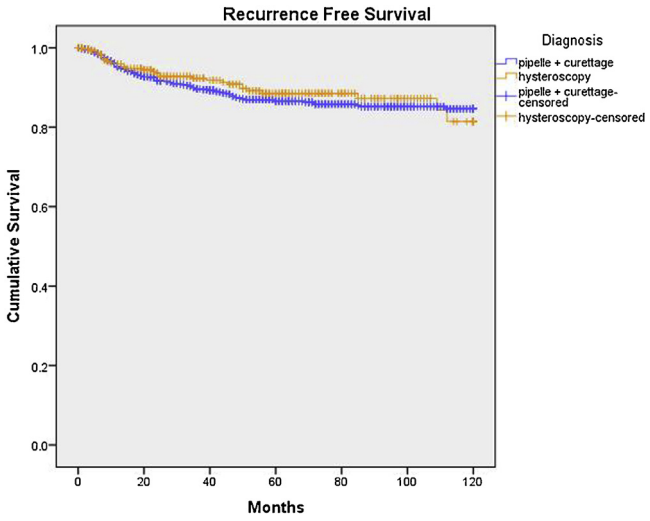

Fig. 1. Recurrence-free survival grouped by diagnostic procedure.

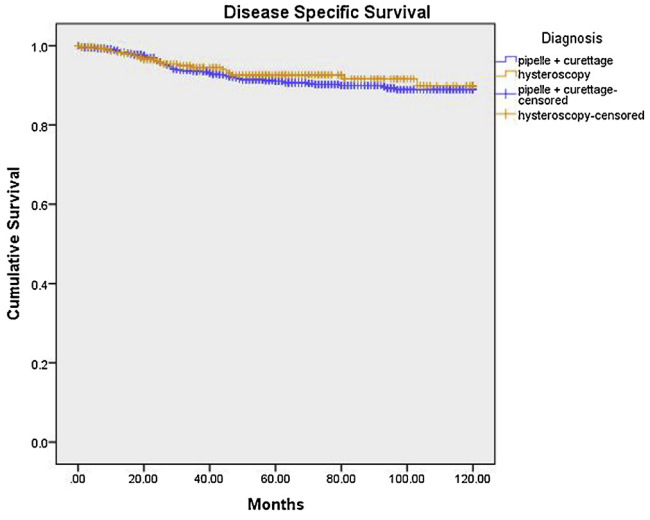

Fig. 2. Disease-specific survival grouped by diagnostic procedure.

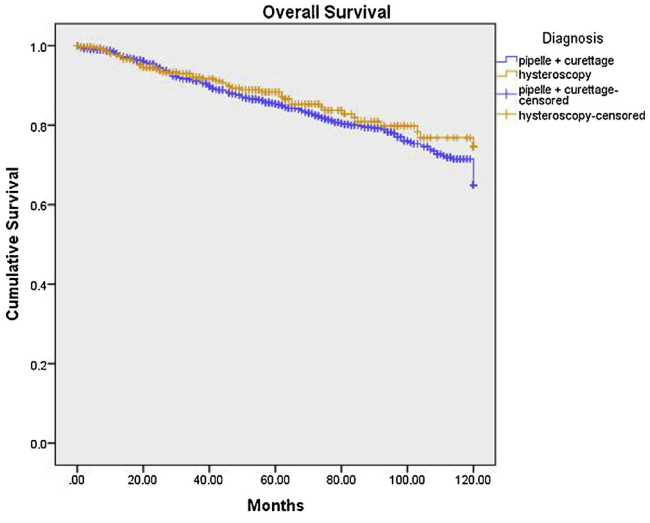

Fig. 3. Overall survival grouped by diagnostic procedure.

meta-analysis, the reported sensitivity was 90% [13]. In cases of intolerance to office endometrial sampling, failed endometrial sampling due to stenosis of the cervix or persistent bleeding, uterine curettage or hysteroscopy is appropriate. Hysteroscopy is considered the gold standard for evaluation of the uterine cavity in cases of abnormal uterine bleeding. Hysteroscopy has been reported to have high sensitivity, specificity, negative predictive value, and positive predictive values of 94.2%, 88.8%, 96.3%, and 83.1%, respectively, in predicting normal or abnormal endometrial histopathology [14]. Moreover, as the incidence of focal lesions in patients with is as high as 74%, and as it has recently been shown that hysteroscopy can accurately diagnose cancer in cases of atypical endometrial hyperplasia, hysteroscopy followed by a guided endometrial biopsy is highly recommended in the assessment of abnormal uterine bleeding [14,15]. Due to its accuracy, hysteroscopy has become one of the most common techniques for investigating suspected pathology of the uterine cavity [16].

To allow complete visualization of the uterine cavity, the hysteroscopic technique involves flushing the uterine cavity with a distension media under pressure, with the potential for retrograde dissemination of cells through the tubes into the peritoneal cavity. As the risk of endometrial cancer being the cause of AUB in either premenopausal or postmenopausal patients, this raises concern that during hysteroscopy in patients who are ultimately diagnosed with endometrial cancer, cancer cells may disseminate into the peritoneal cavity and potentially worsen prognosis. Positive peritoneal cytology is an important prognostic factor in multiple gynecologic cancers [17]. Because it's not considered as an independent prognostic risk factor by some authors [18], positive peritoneal cytology no longer alters endometrial cancer FIGO staging [9]. However, FIGO still recommends obtaining peritoneal washings during surgery, because of the potential for positive peritoneal cytology to compound the effects of other risk factors in early stage endometrial cancer [8]. Some recent studies still affirm that positive cytology is an independent prognostic risk factor in either early or advanced-stage endometrial cancer [19–21].

There are some reports that compare the rate of positive cytology after two diagnostic procedures, hysteroscopic and non-hysteroscopic. A meta-analysis of 756 patients with endometrial cancer revealed no increased risk after hysteroscopy [22]. However, a later meta-analysis of 1015 women with endometrial cancer reported a significant increase in the rate of malignant cells in peritoneal washings in patients who underwent hysteroscopy as a diagnostic procedure [23]. Also, in another meta-analysis of 2944 women, the overall rate of positive peritoneal cytology was found to be significantly higher in the hysteroscopy group, but a subgroup analysis of patients with stage I—II endometrial cancer revealed no difference between the two groups in early stage disease [24].

One possible explanation for the variation in the reported rate of positive peritoneal cytology may be attributed to the different time intervals between the diagnostic procedure and definitive surgery allowing tumor cells to dissipate. The peritoneal cavity consists of an immune cell population including T lymphocytes, B lymphocytes, and natural killer cells. These cell populations play an important role in initiating peritoneal inflammation and host immune protection [25]. A longer interval from hysteroscopy to surgery may allow time for tumor cells to be destroyed. In a meta-analysis by Polyzos et al. that found hysteroscopy as a risk factor for positive cytology [23], 6 of 9 studies reported time interval between hysteroscopy and surgical staging [26–31]. In these 6 studies, the average interval time was 24.4 days (12–32.7 days). However, Biewenga et al. reported negligible rates of positive peritoneal cytology with relatively longer interval period, 33.5 days [32]. In the current study of 1324 women with stage I endometrial cancer, the rate of positive cytology was similar between two

Table 2
Baseline characteristics of previous trials.

Author	Year	Number of patients	Stages included	Follow-up	Outcome*
Obermair et al. [26]	2000	Hysteroscopy: 135 No hysteroscopy: 127	Stage I	Up to 60 months	Similar RFS
De La Cuesta et al. [35]	2004	Hysteroscopy: 30 No hysteroscopy:20	Stage I	Up to 71 months	Similar OS, RFS
Ben-Arie et al. [31]	2008	Hysteroscopy:100 No hysteroscopy: 292	Stage I	Up to 121 months	Similar OS, RFS
Li et al. [36]	2009	Hysteroscopy: 37 No hysteroscopy: 68	All Stages	Up to 36 months	Similar RFS
Zhu et al. [37]	2010	Hysteroscopy: 90 No hysteroscopy: 197	All Stages	Up to 60 months	Similar OS
Cicinelli et al. [38]	2010	Hysteroscopy: 70 No hysteroscopy: 70	Stage I-II	Up to 123 months	Similar OS, RFS
Soucie et al. [34]	2012	Hysteroscopy: 672 No hysteroscopy: 1300	Stage I-IIIc	Up to 120 months	Similar OS
Chen et al. [39]	2017	Hysteroscopy: 54 No hysteroscopy: 86	All stages	Up to 140 months	Similar DSS
Current study		Hysteroscopy: 355 No Hysteroscopy: 969	Stage I	Up to 120 months	Similar OS, RFS, DSS

* DSS = disease-specific survival, OS = overall survival, RFS = recurrence-free survival.

groups, hysteroscopy and non-hysteroscopy (2.1% vs. 2.3%). In our study, the average interval period was 34.6 days (7–43 days).

Another theoretical explanation for a variation in the rates of positive cytology could be differences in the pressure of the distension medium used at hysteroscopy. Achieving appropriate intrauterine pressure for optimal visualization is essential in hysteroscopy, usually ranging from 70 to 80 mmHg. In procedures with intrauterine bleeding, sometimes high pressures (120–150 mmHg) could be required. In a study using Tc-99 and blue dye, Solima et al. reported that with higher intrauterine pressures, hysteroscopy could increase the risk of transtubal leakage [33]. However, previous meta-analyses showed no significant association between positive peritoneal cytology and higher (>100 mmHg) intrauterine pressures [23,24]. In our study, there are no exact data about the intrauterine pressure during hysteroscopy, but most of the centers participating in the study commonly used a medium pressure of 100 mmHg.

These are both plausible discussion points as explanations for variations in rates of positive peritoneal cytology reported after hysteroscopy in observational studies.

Histologic type, grade, and stage of the disease are the main prognostic factors in endometrial cancer. In the current study histologic type and grade were evenly distributed in both patient groups of hysteroscopy and non-hysteroscopy, and we have included only stage I endometrial cancer patients to evaluate the assumed isolated effect of hysteroscopy on prognosis. In our study, we found similar 5-year recurrence-free, disease-specific, and overall survival rates between patients undergoing hysteroscopy and non-hysteroscopic diagnostic procedures.

A meta-analysis of 2944 patients (range 50–392 patients per study) found that the prognosis of endometrial cancer was not impaired with preoperative hysteroscopy [24]. This meta-analysis included 19 studies; however, only 6 of them reported survival rates. However within the meta-analysis there is not any data about these 6 studies. Also in this meta-analysis, most of the studies were extracted from Chinese database searches. Unfortunately, abstracts are not available in some of these studies.

In a previously published retrospective study of 1973 women with endometrial cancer (stages I-III) by Soucie et al., with follow-up ranging from 1 to 10 years, the overall survival was found to be similar for patients undergoing hysteroscopy and non-hysteroscopic diagnostic procedures [34]. The mean follow-up period was 4 and 4.4 years in the two groups. However, in Soucie et al.'s study, there was no subgroup analysis for early stage endometrial cancer, whereas, in our study, we included only stage I to exclude the adverse effect of advanced stage on survival, thus evaluating the assumed isolated effect of hysteroscopy on survival. Furthermore, important information on disease-free and disease-specific analyses was missing in Soucie et al.'s study [34].

Table 2 summarizes the previous studies and current study that compare prognosis of endometrial cancer between two diagnostic methods.

This study was designed as retrospective study, therefore it could cause several biases. Ideally, prospective randomized studies with enough statistical power could give a definite answer concerning the safety of hysteroscopy. We currently can only rely on retrospective studies. The current study, by design, allows sufficient power and extended follow-up to identify small differences in outcome between patients undergoing hysteroscopy and those undergoing non-hysteroscopy procedures. Our findings affirm that hysteroscopy as a diagnostic procedure is not associated with a worse prognosis and may probably be safely used in patients at a high risk for endometrial cancer.

Declaration of Competing Interest

The authors report no conflict of interest.

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