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Hysteroscopic view with targeted biopsy in the assessment of endometrial carcinoma. What is the rate of underestimatated diagnosis? The results of a multicenter Italian trial

Giancarlo Garuti[1], Stefano Angioni[2]* , Liliana Mereu[3], Stefano Calzolari[4], Luca Mannini[5], Federica Scrimin[6], Paolo Casadio[7], Davide De Alberti[8], Luigi Nappi[9], Enrico Busato[10], Francesco P. G. Leone[11], Gaetano Perrini[12], Vito Cela[13] and Massimo Luerti[14]

Abstract

Objective: In the last two decades, many reports demonstrated the unreliability of endometrial biopsy pathology showing an AH (atypical hyperplasia) to exclude a synchronous EEC (endometrioid endometrial carcinoma), with an underestimation of EEC in up to 50% of women. Hysteroscopy is now considered the standard diagnostic tool for endometrial pathology. However, a recent meta-analysis showed that hysteroscopically guided biopsy provides a high rate of failure with respect to dilatation and curettage (D&C) and endometrial resection, in underestimating AH instead of concurrent EC. The aim of this study was to assess the sensitivity of hysteroscopy view and hysteroscopic sampling in diagnosing EEC.

Materials and methods: A multicenter, retrospective, observational trial was conducted between January 2012 and December 2018 in 14 Italian gynecological units (university-affiliated or public hospitals). Eligible patients were identified as those women in whom either a pathologic report of EEC was found on hysterectomy specimen and a preoperative hysteroscopy assessment with endometrial biopsy targeted under vision had been performed. As primary outcome, we calculated the sensitivity of hysteroscopy view and biopsy pathology on hysteroscopically driven sampling in the diagnostic workup of EC.

Results: Nine hundred forty-eight patients (age 65.83 ± 10.43) resulted eligible for analysis. Hysteroscopy view showed a sensitivity of 54.2%, a specificity of 47.2%, and an accuracy of 54% in the diagnosis of EC. Moreover, hysteroscopic view was significantly able to distinguish carcinoma from hyperplasia ($p < 0.001$). We evidenced an important difference of the results comparing the centers involved. Hysteroscopy-driven biopsy presented a sensitivity of 76.2%, a specificity of 52.8%, and an accuracy of 75.3%. AH pathology was reported in 19% of the cases.

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* Correspondence: sangioni@yahoo.it
[2]Department of Surgical Sciences, Division of Gynecology and Obstetrics,
Univeristy of Cagliari, Monserrato, Italy
Full list of author information is available at the end of the article

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Conclusion: Our study showed that EEC diagnosis via hysteroscopy diagnosis could be improved through the implementation of operator training. Hysteroscopy-driven biopsies have excellent sensitivity and accuracy in the diagnosis of EEC, and the advantages of using hysteroscopy for making a diagnosis can improve the management of the patients with EEC. While it seems reasonable that hysteroscopy is the preferred technique for diagnosing and treating a benign pathology of the uterus, it could play a major role even in the diagnosis of a malignancy.

Keywords: Hysteroscopy, Endometrial carcinoma, Atypical hyperplasia, Biopsy

Introduction

Endometrioid endometrial carcinoma (EEC) is the most common gynecological malignancy occurring in western countries, and atypical hyperplasia (AH) is considered its biological precursor [1, 2]. The differential diagnosis between AH and EEC on endometrial biopsy is clinically significant. Depending from clinical background, simple hysterectomy or fertility-sparing management such as endometrial resection and/or medical treatments may be considered in women with ascertained AH, whereas in patients with EEC, an oncological surgical staging is recommended even if in very selected cases a conservative approach could be considered [3–7]. In the last two decades, many reports demonstrated the unreliability of endometrial biopsy pathology showing an AH to exclude a synchronous EEC, with an underestimation of EEC in up to 50% of women [8–11]. Current data suggest that with respect to the other biopsy techniques, dilatation and curettage (D&C) yields the better sensitivity in distinguishing preoperatively AH from EEC, by lowering to about 30% the rate of unexpected EEC [12, 13]. Nevertheless, allowing the direct visual assessment of endometrium, hysteroscopy is now considered the golden standard for the diagnosis of endometrial pathology, overcoming the limits of procedures based on blind tissue sampling and allowing targeted biopsies [14, 15]. Despite this assumption, a recent meta-analysis showed that hysteroscopically guided biopsy provides a high rate of failure with respect to D&C and endometrial resection, in underestimating AH instead of concurrent EEC [16]. The aim of this study was to assess the sensitivity of hysteroscopy view and hysteroscopic sampling in diagnosing or excluding EEC. Furthermore, we evaluated whether hysteroscopy imaging, operative setting, and hysteroscopy technique can contribute to decrease the rate of missed EEC.

Materials and methods
Study design and outcomes

A multicenter, retrospective, observational trial was conducted between January 2012 and December 2018 in 14 Italian gynecological departments (university-affiliated or public hospitals). All centers involved in the study were selected by the Italian School of Minimally Invasive Gynecologic Surgery (SICMIG). All participating institutions routinely shared the same technique of endometrial biopsy to study endometrial abnormalities, based on hysteroscopically driven tissue sampling. After obtaining the approval from the resident Institutional Ethical Committee, we performed a retrospective search from each institutional pathology database. Eligible patients were identified as those women in whom either a pathologic report of endometrial carcinoma of endometrioid histology was found on hysterectomy specimen and a preoperative hysteroscopy assessment with endometrial biopsy targeted under vision was available. As primary outcome, we calculated the sensitivity of hysteroscopy view and biopsy pathology on hysteroscopically driven sampling in the diagnostic workup of EC. In addition, we established the prevalence of hysteroscopy biopsies yielding a diagnosis of AH instead of a true one of EC. In this group of patients, the secondary endpoints were the following: (1) to evaluate whether hysteroscopy view diagnosis, based on current pathomorphology knowledge and consistent with an overt neoplastic growth, could be of diagnostic support to decrease the rate of missed EEC; (2) to assess whether surgical variables such as the hysteroscopy sampling technique and hysteroscopy operative settings could affect the diagnosis of EEC; (3) We highlighted on pathological grade and surgical stage of missed EECs to suggest if an underestimated diagnosis of AH could lead to a surgical under-treatment of poor prognosis EECs.

Patient selection

Either premenopausal and postmenopausal women were recruited. In postmenopausal patients, diagnostic hysteroscopy was indicated because of abnormal uterine bleeding; afterward, a transvaginal sonographic assessment showed an endometrial thickness measuring 3 mm or more in the longitudinal plane of uterine scan. In asymptomatic menopausal women, hysteroscopy was carried out when a routinely accomplished transvaginal sonography showed an endometrial stripe of more than 4 to 6 mm, accordingly with the single institutional custom. In premenopausal women, hysteroscopy examination was indicated because of abnormal uterine bleeding refractory to medical therapy and/or a non-

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homogeneous endometrial lining estimated by transvaginal ultrasonography in middle-late proliferative phase of menstrual cycle. From the search on pathology databases, we retrieved the medical record of all patients with a diagnosis of endometrial carcinoma obtained from hysterectomy specimens during the study period. Hysteroscopy imaging reports, hysteroscopy technique of tissue collection, and results of biopsy pathology were recorded and compared to hysterectomy histologic findings. The pathological assessment of either biopsies and hysterectomy specimens were accomplished by resident pathologists, and each report was adapted to the current WHO guidelines [17]. Surgical management of hysterectomy was at the discretion of the primary surgeon and surgical approaches included vaginal, open, and laparoscopic techniques. The addition of lymphadenectomy was also at the surgeon's discretion. EEC surgical stage and grade were classified according to the 2009 International Federation of Obstetrics and Gynecology guidelines [18]. Patients suffering from endometrial carcinoma of clear cells and serous histology, such as those affected by uterine sarcomas were excluded from the study.

Hysteroscopy imaging

The hysteroscopy view diagnosis was made according to pathomorphologic correlations reported in the previous trials [19–22], but it was based on the subjective impression and expertise of the responsible surgeon. All participating centers shared the following definitions of hysteroscopy view pictures.

Normal endometrium: An evenly lined atrophic or functional mucosa showing a regular distribution of gland openings without any architectural distortion of endometrial shape.

Endometrial polyp: Focal, single or multiple, sessile or pedunculated luminal projections fluttering under the distending medium flow, showing from soft to mild fibrous consistence, covered by an evenly lined functional or atrophic mucosa, frequently showing cyst-gland formation and supplied by a thin vascular network.

Endometrial hyperplasia: One or more of the following features suggested a diagnosis of hyperplasia: (1) focal or diffuse polypoid or papillary mucosal endometrial thickening without obvious necrosis; (2) abnormalities of the endometrial gland architecture such as gland cyst detection sometimes with button-like whitish appearance, gland crowding, and irregularly spaced gland openings; and (3) a concurrent enhanced and irregular but not overtly atypical, vascular network.

Endometrial cancer: An endometrial cavity showing focal or extended polypoid, papillary, nodular, or mixed patterns of mucosal overgrowth showing friable/cerebroid consistence, surface necrosis appearing as avascular whitish-grayish tissue, and an overt atypical vascular network.

Biopsy surgical techniques

Based on the custom of each participating center, hysteroscopy was carried out either as outpatient office intervention with or without anesthetic local support and as inpatient procedure accomplished in a surgical room under general anesthesia or conscious sedation. All procedures were assisted by a video camera and were conducted by using a fluid distending medium delivered by a pressure bag or a peristaltic pump. Normal saline or hypotonic solutions were used according to the use of bipolar or monopolar technology, respectively. Endometrial biopsies were carried out by using one of the following hysteroscopes: (1) 12–16 Fr rigid hysteroscopes with a 5-Fr operative channel; (2) 16 Fr mini-resectoscopes armed with a mini-loop electrode; and (3) 26–27 Fr resectoscopes armed with a loop electrode. The vaginoscopic technique was routinely used to gain uterine entering [23] with the exception of patients treated under general anesthesia by 26–27 Fr resectoscopes, in whom cervical dilatation was done before hysteroscopy assessment. The cutting devices used for endometrial sampling included (1) mechanical tools such as sharp scissors and grasping forceps and (2) electrosurgical tools such as 5 Fr co-axial or angled bipolar electrodes, bipolar or monopolar loops, and bipolar or monopolar mini-loops. After a hysteroscopy inspection suggestive for EC, based on the responsible hysteroscopist's judgement, one or more endometrial biopsies under vison were accomplished, addressing the tissue sampling to the viable tissue showing the most predictive features of malignancy. When hysteroscopy view was consistent with hyperplasia or polyp, biopsies targeted to the most significant mucosal abnormality or a full polypectomy were carried out, respectively.

Data collection

The directory board of SICMIG addressed to single certified physicians of each institution a xlsx database containing the clinical parameters of interest. These latter included (1) patient age, (2) menopausal status, (3) bleeding symptoms, (4) hysteroscopy operative setting, (5) hysteroscopy view diagnosis, (6) hysteroscopy technique of biopsy, (7) pathologic findings on biopsy, (8) grade of EEC on biopsy, (9) Pathologic findings on hysterectomy specimens, (10) grade of EEC on hysterectomy specimens, and (11) surgical stage of EEC. The written reports describing either the hysteroscopy imaging and the surgical technique of tissue sampling were used to draw the data about hysteroscopy assessment. We recorded but excluded from the analysis all patients in whom a primary hysteroscopy tissue sampling yielded

to the pathologist a too scant amount of tissue to provide any diagnosis.

Study outcomes

As primary outcome, we calculated the sensitivity of hysteroscopy view and biopsy pathology on hysteroscopically driven sampling in the diagnostic workup of EEC. In addition, we established the prevalence of hysteroscopy biopsies yielding a diagnosis of AH instead of a true one of EC. In this group of patients, the secondary endpoints were the following: (1) to evaluate whether hysteroscopy view diagnosis, based on current pathomorphology knowledge and consistent with an overt neoplastic growth, could be of diagnostic support to decrease the rate of missed EEC; (2) to assess whether surgical variables such as the hysteroscopy sampling technique and hysteroscopy operative settings could affect the diagnosis of EEC; (3) We highlighted on pathological grade and surgical stage of missed EECs to suggest if an underestimated diagnosis of AH could lead to a surgical under-treatment of poor-prognosis EECs.

Statistical analysis

Data analyses were carried out by the Jamovi software (version 1.2; https://www.jamovi.org). Sensitivity considered the probability that a test outcome will be positive when the illness is present and specificity referring to the probability that a test outcome will be negative when the illness is not present. To verify the hypotheses, binary logistic regressions were applied to assess which

Table 1 Clinical characteristics of 984 patients who underwent hysterectomy confirming an endometrial carcinoma after a selective endometrial biopsy accomplished under hysteroscopy guidance was carried out

Clinical variables	Number of patients	(%)
Age (years) mean ± SD (range)	65.83 ± 10.43	
Menopausal status		
Premenopausal	122	12.39
Postmenopausal	862	87.60
Abnormal uterine bleeding (AUB)		
Yes	770	78.25
No	214	21.74
Hysteroscopy setting		
Outpatient	663	67.37
Inpatient	321	32.62
Biopsy hysteroscopy technique		
Mechanical 5 Fr	804	81.70
Electrosurgical 5 Fr	31	3.15
Mini-resectoscope or resectoscope	149	15.14

variables independently supported the correct classification of the patients having EEC. The estimated weights were given for each predictor to represent the change in probability and thus identify the target modality in the dependent variable. The odds ratios measures the strength of the association between each independent and dependent (outcome) variable. The odds ratios measured the strength of the association between each independent and dependent (outcome) variable, with $p \leq .05$ considered statistically significant.
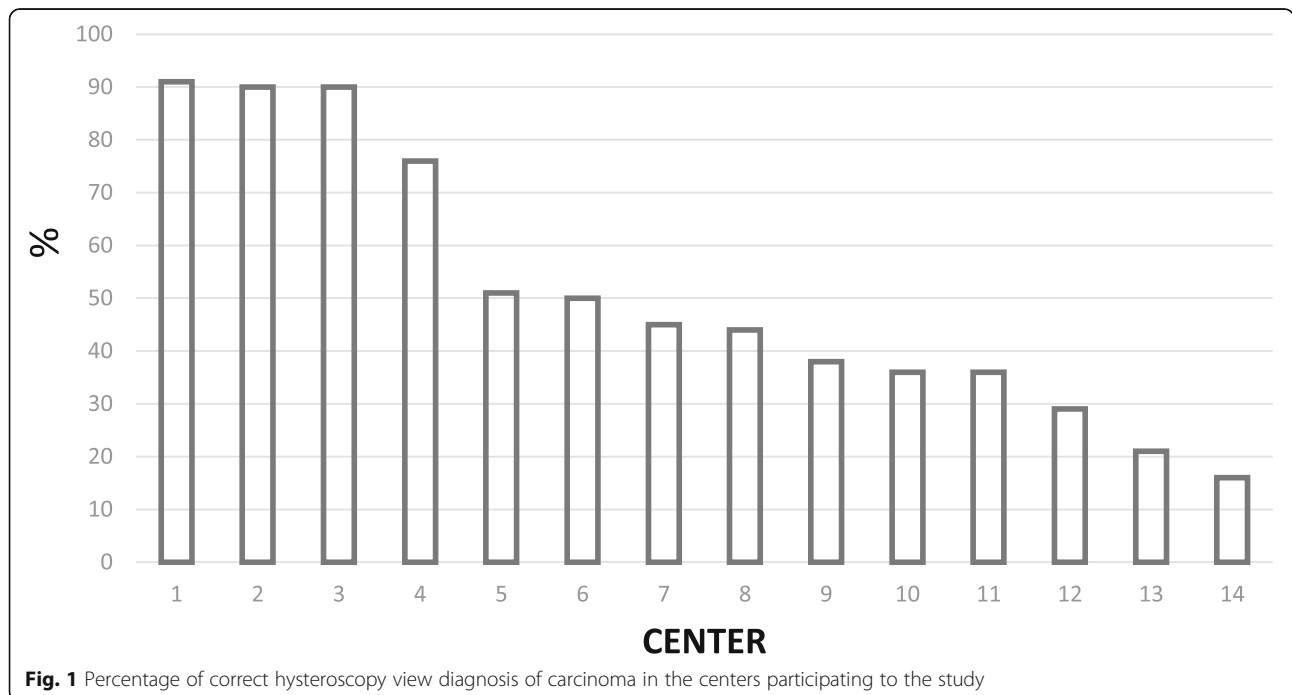
Fig. 1 Percentage of correct hysteroscopy view diagnosis of carcinoma in the centers participating to the study

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Results

The clinical data of 984 patients who underwent hysteroscopy-targeted biopsy followed by hysterectomy with a pathologic diagnosis of endometrial carcinoma were collected. Among these patients, 36 were excluded from the study because of a non-endometrioid histology. Finally, 948 patients resulted eligible for analysis. Clinical variables, operative hysteroscopy setting, and technique of hysteroscopy biopsy are reported in Table 1.

As shown in Table 2 in 514 (54.2%) cases hysteroscopy imaging and in 722 (76.2%) cases eye-driven biopsy pathology consented a correct diagnosis of EEC. Hysteroscopy view underestimated EEC as normal endometrium, polyp, hyperplasia, or other in 471 cases, accounting for a sensitivity of 54.2%, a specificity of 47.2%, and an accuracy of 54%. The percentage of correct hysteroscopy view diagnosis was greatly different in centers participating to the study varying from 91 to 16% (Fig. 1). Hysteroscopy-driven biopsy yielded a diagnosis of normal endometrium or non-atypical hyperplasia in 9 (0.9%) and AH 185 cases (19.5%). It accounted for a sensitivity of 76.2%, a specificity of 52.8%, and an accuracy of 75.3% in the correct diagnosis of EEC. Nevertheless, in 40 cases of pathology diagnosis of AH at biopsy, the hysteroscopy view suggested an endometrial carcinoma C (Table 3). Inpatient versus outpatient procedures of endometrial sampling were significantly associated to the identification of the cases with EEC (*p* < 0.001), while we did not show a statistical difference comparing different types of device used to perform biopsy (resectoscopic or hysteroscopic techniques) (*p* = 0.594) (Table 4). Interestingly, hysteroscopic view was statistically significantly able to differentiate hyperplasia and EC (*p* < 0.001). Pathological grade and surgical stage according to FIGO 2009 in the 185 patients with a

Table 2 Hysteroscopy view diagnosis and biopsy pathology results obtained by hysteroscopy-guided sampling in 948 eligible women undergoing hysterectomy due to endometrioid EC

Factor	Number of patients	(%)
Hysteroscopy view	11	1.16
Normal	172	18.14
Polyp	219	23.10
Hyperplasia	514	54.21
Carcinoma	32	3.37
Other		
Biopsy pathology	3	0.31
Normal endometrium	6	0.63
Non-atypical hyperplasia	185	19.51
Atypical Hyperplasia	722	76.16
Endometrioid carcinoma	10	1.05
Serous	3	0.31
Clear cell carcinoma	15	1.58
Insufficient tissue		

Table 3 Hysteroscopy view diagnosis, surgical operative setting, and hysteroscopy technique of tissue collection in 185 patients with a pathological diagnosis of atypical hyperplasia on biopsy specimens

Factor	Number of patients	(%)	*p* value
Hysteroscopy view	1	0.5	
Normal	26	14.1	
Polyp	109	58.9	
Hyperplasia	40	21.6	
Carcinoma	9	4.9	
Other			
Hysteroscopy surgical setting	160	86.5	
Outpatient	25	13.5	
Inpatient			
Hysteroscopy biopsy technique	170	91.9	
Mini-hysteroscope techniques	15	8.1	
Resectoscopic techniques			

pathological diagnosis of AH on biopsy specimens are reported in Table 5.

Discussion

Endometrial cancer is the most common gynecologic malignancy in the USA, accounting for 3.6% of all cancers (incidence rate of 26.1/100,000 women) and generally affecting postmenopausal women, with a median age at diagnosis of 62 years [24]. Diagnostic hysteroscopy is an accurate and less invasive method for the evaluation of common gynecological disorders, such as premenopausal or postmenopausal abnormal uterine bleeding (AUB), endometrial hyperplasia, endometrial cancer, and infertility [22]. A systematic quantitative review by Clark showed that the overall sensitivity and specificity of hysteroscopy for endometrial cancer were 86.4 and 99.2%, respectively [25]. We performed a retrospective study on 948 patients who underwent hysterectomy and had ECC confirmed after a selective endometrial biopsy was accomplished under hysteroscopic guidance in 14 public hospitals. We showed that the hysteroscopy view had good sensitivity and an accuracy of around 54% in the diagnosis of EEC (Table 2). Moreover, the hysteroscopic view was able to significantly differentiate EEC and endometrial hyperplasia (Table 4). Interestingly, the operator opinion regarding the hysteroscopic findings had great variability in the different centers (correct diagnosis range, 91-14%), which could explain the results (Fig. 1). These data emphasize the need for continuous training in referral centers to optimize and improve the ability to correctly define the diagnosis related to the vision [26]. The second aim of our study was to evaluate hysteroscopic sampling in either diagnosing or excluding EEC. Many reports have debated the unreliability of endometrial biopsy pathology. In cases showing an AH, the possibility of underestimating an EEC is as high as 50% [8–11]. This high rate of unrecognized endometrial cancers is firstly due to the difficulty in distinguishing

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Table 4 Binomial logistic regression analysis of different variables in cases with AH at biopsy

| | Estimate | 95% confidence interval | | SE | *Z* | *p* |
		Lower	Upper			
Biopsy						
Resector 16–26 Fr vs. hysteroscope	0.186	− 0.4993	0.872	0.350	0.533	**0.594**
Setting						
Office vs. operating room	− 1.167	− 1.6968	− 0.637	0.270	− 4.317	**< .001**
Hysteroscopic view						
Negative vs. hyperplasia	2.296	0.1924	4.399	1.073	2.139	**0.032**
Carcinoma vs. hyperplasia	2.514	2.0923	2.936	0.215	11.679	**< .001**
Other vs. hyperplasia	0.885	0.0680	1.702	0.417	2.123	**0.034**
Polyp vs. hyperplasia	1.291	0.8046	1.777	0.248	5.205	**< .001**

between AH and EEC on endometrial biopsy specimens. The pathologic criteria defined by the World Health Organization (WHO) classification system are highly subject to individual interpretation, resulting in poor interobserver reproducibility [27]. Secondly, various techniques for endometrial biopsy, such as blind office-based procedures, hysteroscopy sampling, and dilatation and curettage (D&C), showed varied accuracy at differentiating between AH and EEC [28, 29]. Hysteroscopy can provide direct visualization of the endometrial cavity, thereby allowing a targeted biopsy or excision of the lesions identified during the procedure [18]. The progress of techniques and technology, when combined with improvements in understanding endometrial endoscopic imaging, have enabled hysteroscopy to supply the pathologist with biopsies that are reliably fashioned under the targeted vision [19, 20, 29]. Nevertheless, a recent meta-analysis has shown different results, evidencing poor diagnostic performance of the targeted biopsy with hysteroscopy compared to endometrial resection in the diagnosis of EEC [16]. By contrast, in our series, we showed that a hysteroscopic-driven histology had good sensitivity and accuracy of > 75% in correctly diagnosing EEC. The use of hysteroscopy-driven biopsy underestimated the disease in only 194 cases (a diagnosis of normal endometrium or non-atypical hyperplasia in 9 cases [0.9%] and AH in 185 cases [19.5%]) (Table 2). Notably, in 40 cases in which the biopsy pathology underestimated EEC with a diagnosis of AH,

hysterscopic diagnosis identified the cancer. We did not find a significant difference between hysteroscopic (microscissors or electrodes) and resectoscopic techniques in obtaining samples for histology, confirming that the key factor is likely not the chosen biopsy technique but rather hysteroscopic guidance in terms of target selection (Table 4). Moreover, in accordance with previous results, we evidenced that the operating room setting was significantly more associated with a correct diagnosis compared to an office setting. This finding is likely related to the possibility of obtaining more material for the pathologist, which may be limited in an office setting due to the time required and possible pain for the patient. Staging at surgery evidenced a good prognosis in most cases with a biopsy diagnosis of AH (stage I Figo in 97%) (Table 5).

In conclusion, our study supports the choice of diagnostic hysteroscopy and hysteroscopic-driven biopsy in the diagnosis of EEC. This approach can result in excellent performance when hysteroscopy and pathology diagnoses are combined to limit the possibility of undertreating patients with endometrioid carcinoma.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
This retrospective study received an exemption from the Institutional Review Board of each recruiting center.

Table 5 Surgical stage of the 185 patients with a pathological diagnosis of atypical hyperplasia on biopsy specimens

FIGO stage 2009	Number of patients	(%)
IA	145	78.4
IB	32	17.3
II	3	1.6
III	5	2.7

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Author details
[1]Department of Obstetrics and Gynecology, Lodi Hospital, Lodi, Italy.
[2]Department of Surgical Sciences, Division of Gynecology and Obstetrics, Univeristy of Cagliari, Monserrato, Italy. [3]Department of Obstetrics and Gynecology, Santa Chiara Hospital, Trento, Italy. [4]Department of Day Surgery, Palagi Hospital, Florence, Italy. [5]Department of Day Surgery, S. Jacopo Hospital, Pistoia, Italy. [6]Institute for Maternal and Child Health – IRCCS "Burlo Garofolo", Trieste, Italy. [7]Department of Obstetrics and Gynecology, University of Bologna, Bologna, Italy. [8]Department of Obstetrics and Gynecology, SS. Antonio e Biagio e Cesare Arrigo Hospital, Alessandria, Italy. [9]Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy.
[10]Department of Obstetrics and Gynecology, Treviso Hospital, Treviso, Italy.
[11]Department of Obstetrics and Gynecology, Biomedical and Clinical Sciences Insttute L. Sacco, University of Milan, Milan, Italy. [12]Department of Gynecology, Mauriziano Umberto I Hospital, Turin, Italy. [13]Department of Obstetrics and Gynecology, University of Pisa, Pisa, Italy. [14]Department of Gynecology, ICCS, Milan, Italy.

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