The role of hysteroscopy in diagnosing endometrial cancer

Certain hysteroscopic findings correlate with the likelihood of endometrial carcinoma—and the absence of pathology. Here is a breakdown of hysteroscopic morphologic findings and hysteroscopic-directed biopsy techniques.

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IN THIS ARTICLE

For more than 45 years, gynecologists have used hysteroscopy to diagnose endometrial carcinoma and to associate morphologic descriptive terms with visual findings.[1] Today, considerably more clinical evidence supports visual pattern recognition to assess the risk for and presence of endometrial carcinoma, improving observer-dependent biopsy of the most suspect lesions (**VIDEO 1**).

In this article, I discuss the clinical evolution of hysteroscopic pattern recognition of endometrial disease and review the visual findings that correlate with the likelihood of endometrial carcinoma. In addition, I have provided 9 short videos that show hysteroscopic views of various endometrial pathologies in the online version of this article at https://www.mdedge.com/obgyn.

The negative hysteroscopic view defined

In 1989, Dr. Frank Loffer confirmed the diagnostic superiority of visually directed biopsy. He demonstrated the advantages of using hysteroscopy and directed biopsy in the evaluation of abnormal uterine bleeding (AUB) to obtain a more accurate diagnosis compared with dilation and curettage (D&C) alone (sensitivity, 98% vs 65%, respectively).[2]

Also derived from this work is the clinical application of the "negative hysteroscopic view" (NHV). Loffer used the following criteria to define the NHV: good visualization of the entire uterine cavity, no structural abnormalities of the cavity, and a uniformly thin, homogeneous-appearing endometrium without variations in thickness (**TABLE 1**). The last criterion can be expected to occur only in the early proliferative phase or in postmenopausal women.

Use of hysteroscopy therefore can predict accurately the absence of intrauterine and endometrial pathology when visual findings are negative and tissue sampling is not warranted (**FIGURE 1, VIDEO 2**).

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Efforts in hysteroscopic classification of endometrial carcinoma

Lesion morphologic characteristics. Sugimoto was among the first to describe the hysteroscopic identification of visual morphologic features that are most likely to be associated with endometrial carcinoma.[1] Patients with AUB were evaluated with hysteroscopy as first-line management

to describe lesion morphology and confirm biopsy with histopathology. Sugimoto classified endometrial carcinoma as circumscribed or exophytic with distinct forms, such as polypoid, nodular, papillary, and ulcerated (**FIGURE 2**). Diffuse or endophytic carcinoma is defined by an ulcerated type of lesion that indicates necrosis; this is most likely to represent an undifferentiated tumor. Sugimoto also described abnormal vascularity that often is associated with carcinoma.[1]

Endometrial features. Valli and Zupi created a nomenclature and classification for hysteroscopic endometrial lesions by prospectively grading 4 features: thickness, surface, vascularization, and color.[3] Features were scored based on the degree of abnormality and could be considered to be of low or high risk for the presence of carcinoma. High-risk hysteroscopic features included endometrial thickness greater than 10 mm, polymorphous surface, irregular vascularization, and white-grayish color. The sensitivity for accurately diagnosing endometrial lesions was 86.9% for mild lesions and 96% for severe lesions.[3] Also, these investigators confirmed the clinical value of the NHV and associated overall risk of precancer or cancer of the endometrium.

Amount of endometrial involvement. A few years later, Garuti and colleagues retrospectively related the hysteroscopic tumor features of known endometrial adenocarcinoma to stage, grade, and overall survival.[4] In this system, they focused on classification of tumor morphology as nodular (bulging), polypoid (thin pedicles), or papillary (numerous dendritic projections), as well as whether the amount of abnormal tissue present was less than or more than half of the endometrium and if the lesion involved the cervix.

Several important findings associated with this system may improve visual diagnosis. First, hysteroscopic evaluation had a 100% negative predictive value for the cervical spread of disease (**FIGURE 3, VIDEO 3**). Second, the hysteroscopic morphologic tumor type did not relate to surgical stage or pathologic grade. Third, when less than half of the endometrium was involved, stage I disease was found (97%, 33 of 34). Last, when more than half of the endometrium was involved, advanced disease beyond stage I was found (9 of 26, 6 of whom had poorly differentiated disease).[4]

Structured pattern analysis. Recently, Dueholm and co-investigators published a prospective evaluation of women with postmenopausal bleeding and an endometrial thickness of 5 mm or greater.[5] They used a structured system of visual pattern analysis during hysteroscopy that they termed the

TABLE 1 Negative hysteroscopic view (NHV) indicates likelihood of a normal uterine cavity and normal endometrium[a,2,3,6]

Criteria for NHV
• Good visualization of the entire uterine cavity
• No structural abnormalities of the cavity
• Uniformly thin, homogeneous-appearing endometrium without variations in thickness (early proliferative phase or in postmenopausal patients)

[a]Tissue sampling is not recommended with NHV.

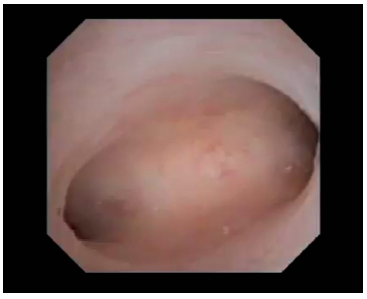

FIGURE 1 Negative hysteroscope view in a premenopausal woman
Image courtesy of Amy Garcia, MD.

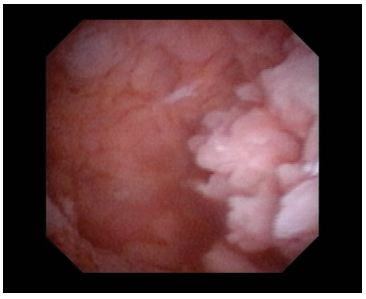

FIGURE 2 Papillary projections of adenocarcinoma
Image courtesy of Amy Garcia, MD.

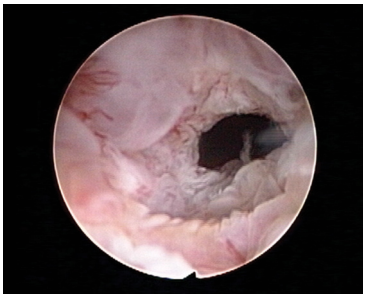

FIGURE 3 Adenocarcinoma with spread to the upper cervical canal near the internal os
Image courtesy of Amy Garcia, MD.

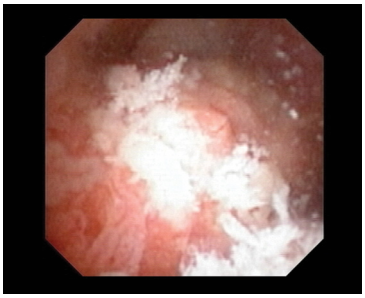

FIGURE 4 Cotton candy endometrium likely representing tissue necrosis
Image courtesy of Amy Garcia, MD.

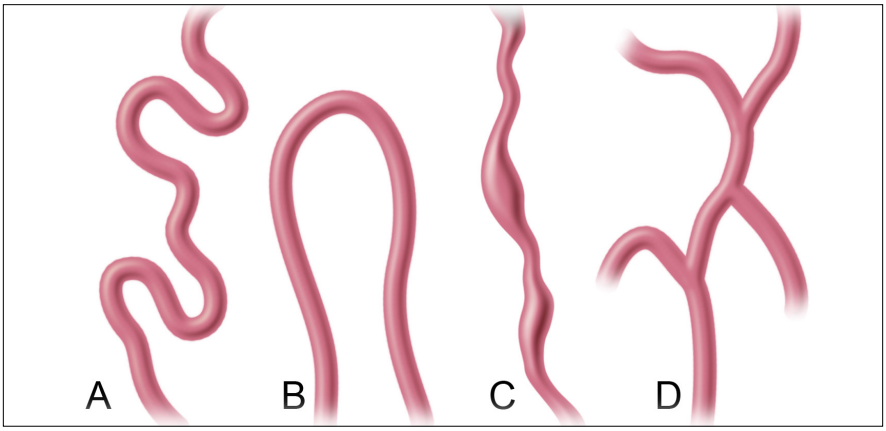

FIGURE 5 Hysteroscopic morphologic abnormal vessels of endometrial carcinoma (**A**) S-shaped; serpiginous. (**B**) Loop. (**C**) Irregular diameter. (**D**) Irregular branching.

hysteroscopic cancer (HYCA) scoring system. The HYCA scoring system is based on surface outline (uneven, polypoid, and papillary projections), necrosis (cotton candy endometrium [**FIGURE 4**], whitish-grayish areas without vessels on the surface), and vessel pattern (tortuous S-shaped, loops, irregular caliber, irregular branching, and irregular distribution [**FIGURE 5**]). Structured pattern analysis predicted cancer with higher accuracy than subjective evaluation.[5]

Morphologic variables as indicators. In 2016, Ianieri and colleagues published a retrospective study on a risk scoring system for diagnosing endometrial hyperplasia and adenocarcinoma via hysteroscopy.[6] They created a statistical risk model for development of the scoring system. A number of morphologic variables were prognostic indicators of atypical endometrial hyperplasia (AEH) and adenocarcinoma. These included widespread and irregular endometrial thickness, presence of multiple polyps with irregular aspects, dilated glandular orifices, irregular endometrial color (grey, white, or hyperemic), atypical vessels, crumbling of the endometrial neoplasms, and growth of cerebroid and arborescent aspects (**VIDEO 4**).

The scoring system for endometrial adenocarcinoma correctly classified 42 of 44 cancers (sensitivity, 95.4%; specificity, 98.2%), and AEH had a sensitivity of 63.3% and a specificity of 90.4%.[6] These investigators also showed a high negative predictive value of 99.5% for endometrial adenocarcinoma associated with a negative view at hysteroscopy. Similar to the Dueholm data, Ianieri and colleagues' morphologic pattern analysis predicted cancer with high accuracy.

Glomerular pattern association. Su and colleagues also showed that pattern recognition could aid in the accurate hysteroscopic diagnosis of endometrial adenocarcinoma.[7] They used the hysteroscopic presence of a glomerular pattern to predict the association with endometrial adenocarcinoma. A glomerular pattern was described as polypoid endometrium with a papillary-like feature, containing an abnormal neovascularization feature with "intertwined neovascular vessels covered by a thin layer of endometrial tissue" (**FIGURE 6,** page 40). The presence of a glomerular pattern indicated grade 2 or grade 3 disease in 25 of 26 women (96%; sensitivity, 84.6%, specificity, 81.8%)[7] (see video 4).

TABLE 2 summarizes significant morphologic findings relating to the presences of endometrial carcinoma.

Atypical endometrial hyperplasia: A difficult diagnosis

The most common type of endometrial cancer is endometrioid adenocarcinoma (type 1 endometrial carcinoma), and it accounts for

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TABLE 2 **Significant hysteroscopic morphologic findings relating to the presence of endometrial carcinoma or severity of disease**[1-7,9]

Authors	Hysteroscopic morphology associated with endometrial carcinoma
Sugimoto, 1975[1]	• Circumscribed (exophytic) —polypoid, nodular, papillary, ulcerated • Diffuse (endophytic) —ulcerated • Irregular vascularization
Loffer, 1989[2]	• NHV: —good visualization of the entire uterine cavity —no structural abnormalities of the cavity, and —uniformly thin, homogeneous-appearing endometrium without variations in thickness • NHV is predictive of normal endometrium
Valli and Zupi, 1995[3]	• Grading of 4 features: —thickness, surface, vascularization, and color • High-risk lesions: —endometrial thickness > 10 mm, polymorphous surface, irregular vascularization, and white-grayish color • Confirmed value of NHV
Garutti et al, 2001[4]	• Nodular, polypoid, or papillary lesion not associated with surgical stage or grade • 100% NPV for cervical spread • Less than half of endometrium involvement is more likely stage I disease • More than half of endometrium involvement is more likely stage II or III disease
Dueholm et al, 2015[5]	• Endometrial surface: —uneven surface texture pattern, polypoid surface, irregular surface, papillary projections • Necrosis: —cotton candy endometrium, whitish-grayish areas without vessels on the surface of a lesion • Vessel pattern: —irregular vessel pattern (tortuous S-formed, loops), irregular caliber, irregular branching, irregular distribution • Endometrial glands: —dilated glands and glands with irregular openings
Ianieri et al, 2016[6]	• Prognostic indicators: —widespread and irregular endometrial thickness —presence of multiple polyps with irregular aspects —dilated glandular orifices —irregular endometrial color (grey, white, hyperemic) —atypical vessels —crumbling of the endometrial neoplasms —growth of cerebroid and arborescent aspects • Confirmed value of NHV
Su et al, 2016[7]	• A glomerular pattern associated with grade 2 or grade 3 disease
De Franciscis et al, 2019[9]	• AEH: —focal or diffuse —papillary or polypoid —endometrial thickening —abnormal vascular patterns —evidence of glandular cysts —abnormal architecture features of the glandular outlets (thickening, irregular gland density, dilatation)

Abbreviations: AEH, atypical endometrial hyperplasia; NHV, negative hysteroscopic view; NPV, negative predictive value.

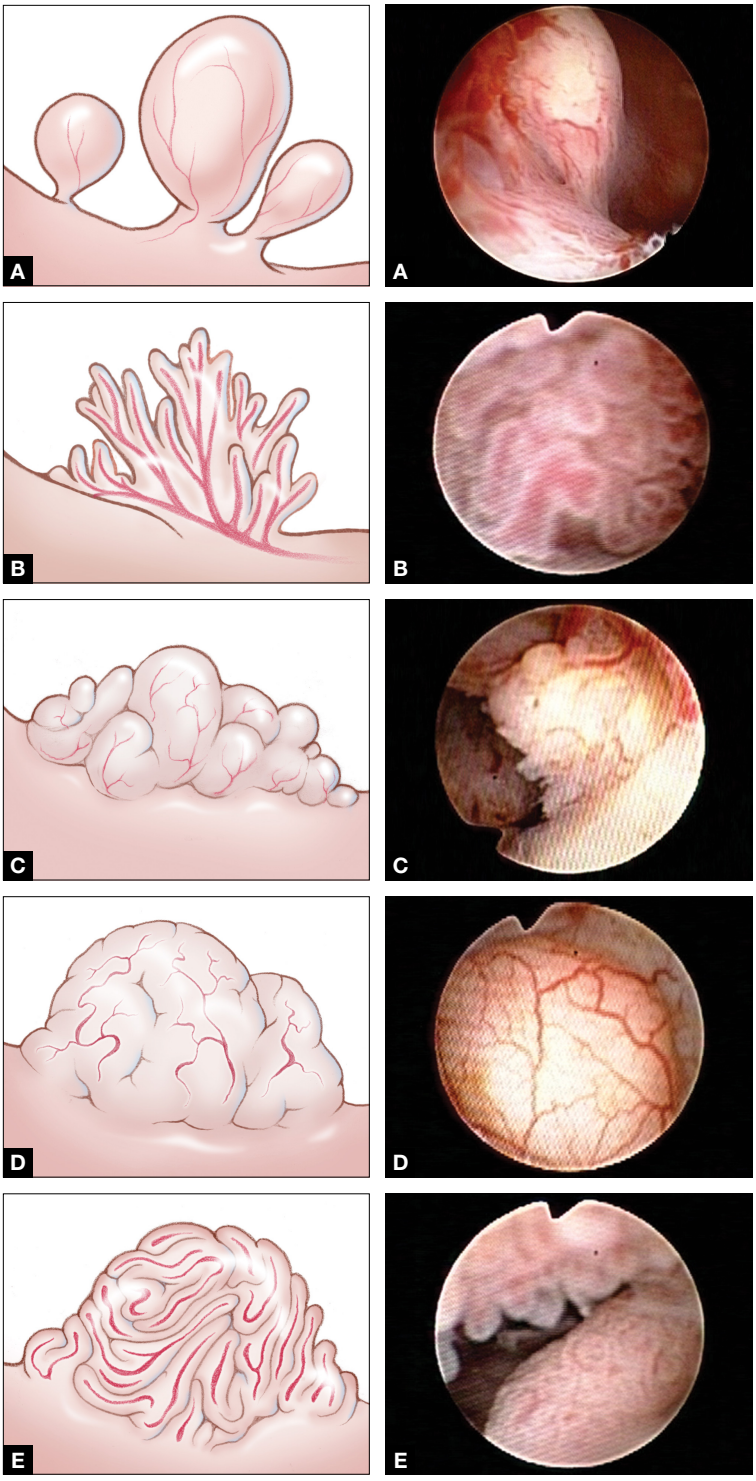

FIGURE 6 Hysteroscopic morphologic features of endometrial carcinoma (**A**) Polypoid; thin pedicles. (**B**) Papillary; numerous dendritic projections. (**C**) Nodular; bulging. (**D**) Cerebroid; nodular or polypoid with abnormal surface vessels. (**E**) Glomerular; polypoid with a papillary-like feature containing intertwined neovascular vessels covered by a thin layer of endometrial tissue. *Images courtesy of Amy Garcia, MD.*

approximately 75% to 80% of endometrial cancer diagnoses.[8] Risk factors include prolonged unopposed estrogen exposure, obesity, diabetes, and age. Type 1 endometrial carcinoma follows a progressive continuum of histopathologic change: from endometrial hyperplasia without atypia to endometrial hyperplasia with atypia (AEH) to well-differentiated endometrial cancer. Therefore, it is possible for endometrial carcinoma to be present simultaneously with AEH. The reported prevalence of concurrent endometrial carcinoma among patients with AEH on biopsy is between 17% and 52%.[8] Thus, the clinical consideration is for hysterectomy, especially in the postmenopausal patient with a diagnosis of AEH.

Hysteroscopic diagnosis of AEH, however, is more difficult than identification of endometrial carcinoma because a range of morphologic characteristics exist that resemble normal endometrium as well as more progressive disease (**VIDEO 5**). De Franciscis and colleagues based a hysteroscopic diagnosis of hyperplasia on one or more of the following findings: focal or diffuse, papillary or polypoid, endometrial thickening; abnormal vascular patterns; evidence of glandular cysts; and abnormal architecture features of the glandular outlets (thickening, irregular gland density, or dilatation)[9] (**VIDEO 6**).

Additional studies, including that from Ianieri and colleagues, also have determined that AEH is difficult to discern visually from normal endometrium and other endometrial pathologies.[6] In another investigation, Lasmar and coauthors reported a retrospective analysis of 4,054 hysteroscopic procedures with directed biopsies evaluating for concordance between the hysteroscopic view and histopathology.[10] Agreement was 56.3% for AEH versus 94% for endometrial carcinoma. Among those with a histologic diagnosis of AEH, in 35.4% benign disease was suspected; in 2.1%, endometrial carcinoma was suspected; and in 6%, normal findings were presumed.[10]

Because of the similarities in morphologic features between AEH and endometrial carcinoma, tissue biopsy under direct

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Video 1. Endometrial carcinoma and visually directed biopsy

Nodular endometrioid adenocarcinoma grade 1 (type 1 endometrial carcinoma), benign endometrial polyps, and endometrial atrophy in a postmenopausal woman with bleeding. This video demonstrates visually directed biopsy to assure sampling of the most significant lesion.

Video 2. Negative hysteroscopic view

Digital flexible diagnostic hysteroscopy showing a negative hysteroscopic view in a premenopausal woman.

Video 3. Cervical spread of adenocarcinoma and visually directed biopsy

Diffuse endometrioid adenocarcinoma spread to the upper cervical canal near the internal cervical os. Hysteroscopic directed biopsy is performed.

Video 4. Endometrial adenocarcinoma

Fiberoptic flexible diagnostic hysteroscopy demonstrating diffuse endometrioid adenocarcinoma grade 3 with multiple morphologic features: polypoid, nodular, papillary, and glomerular with areas of necrosis.

Video 5. Endometrial polyp and atypical hyperplasia

Large benign endometrial polyp in an asymptomatic postmenopausal woman with enlarged endometrial stripe on pelvic ultrasound. The endometrium is atrophic except for a small whitish area on the anterior wall, which is atypical hyperplasia. This video highlights the need for visually directed biopsy to assure sampling of the most significant lesion.

Video 6. Nodular, polypoid atypical hyperplasia

Fiberoptic flexible diagnostic hysteroscopy showing diffuse nodular and polypoid atypical hyperplasia with abnormal glandular openings in a postmenopausal woman. Hysterectomy was performed secondary to the significant likelihood of concomitant endometrial carcinoma.

Video 7. Visually directed endometrial biopsy

Hysteroscopic-directed biopsy showing the technique of grasping and removing tissue of a benign adenomyosis cyst and proliferative endometrium.

Video 8. Carcinosarcoma

Carcinosarcoma (type 2 endometrial carcinoma) presents as a large intracavitary mass with soft, polypoid-like tissue in a symptomatic postmenopausal woman with bleeding.

Video 9. Carcinosarcoma

Carcinosarcoma (type 2 endometrial carcinoma) presents as a dense mass in a symptomatic postmenopausal woman with bleeding. This video shows the mass is nodular. These cancers typically grow into a spherical mass within the cavity.

visualization is warranted to assure sampling of the most significantly abnormal tissue and to confirm visual interpretation of findings.

Techniques for hysteroscopic-directed biopsy

Using a visual assessment of endometrial abnormalities allows the surgeon to examine the entire uterine cavity and to biopsy the most suspicious and concerning lesions. The directed biopsy technique can involve a simple grasping maneuver: With the jaws of a small grasper open, push slightly forward to accumulate tissue within the jaw, close the jaw, and remove the tissue carefully through the cervix (**VIDEO 7**). The size of the sample may be limited, and multiple samples may be needed, depending on the quantity of the tissue retrieved.

Another technique involves first creating a plane of tissue to be removed with scissors

and subsequently grasping and removing the tissue (see video 1 and video 3). This particular technique will yield more tissue with one pass of the hysteroscope into the cavity. Careful removal of tissue through the cervix is facilitated by withdrawing the sample in the grasper and the hysteroscope together at the same time, without pulling the sample through the operative channel of the hysteroscope. Also, by turning off the inflow port, the stream of saline does not wash the sample off the grasper at hysteroscope removal from the cervix.

Blind biopsy. If visual inspection reveals a diffuse process within the uterine cavity such that no normal endometrium is noted and the abnormality is of equal degree throughout the endometrial surface, a decision can be made to replace directed biopsy with a blind biopsy. In this scenario, the blind biopsy is certain to sample the representative disease process and not potentially miss significant lesions (see video 4 and video 6). Otherwise, the hysteroscope-directed biopsy would be preferable.

FAST TRACK

If visual inspection reveals a diffuse process within the uterine cavity such that no normal endometrium is noted and the abnormality is of equal degree throughout, a decision can be made to replace directed biopsy with blind biopsy

Potential for intraperitoneal dissemination of endometrial cancer

There is some concern about intraperitoneal dissemination of endometrial carcinoma at the time of hysteroscopy and effect on disease prognosis. Chang and colleagues conducted a large meta-analysis and found that hysteroscopy performed in the presence of type 1 endometrial carcinoma statistically significantly increased the likelihood of positive intraperitoneal cytology.[11] In the included studies that reported survival rates (6 of 19), positive cytology did not alter the clinical outcome. The investigators recommended that hysteroscopy not be avoided for this reason, as it helps in the diagnosis of endometrial carcinoma, especially in the early stages of disease.[11]

In a recent retrospective analysis, Namazov and colleagues included only stage I endometrial carcinoma (to exclude the adverse effect of advanced stage on survival) and evaluated the assumed isolated effect of hysteroscopy on survival.[12] They compared women in whom stage I endometrial carcinoma was diagnosed: 355 by hysteroscopy and 969 by a nonhysteroscopy method (D&C or office endometrial biopsy). Tumors were classified and grouped as low grade (endometrioid grade 1-2 and villoglandular) and high grade, consisting of endometrioid grade 3 and type 2 endometrial carcinoma (serous carcinoma, clear cell carcinoma, and carcinosarcoma) (**VIDEOS 8 AND 9**). Positive intraperitoneal cytology at the time of surgery was 2.3% and 2.1% (P = .832), with an average interval from diagnosis to surgery of 34.6 days (range, 7–43 days).

The authors proposed several explanations for the low rate of intraperitoneal cytology with hysteroscopy. One possibility is having lower mean intrauterine pressure below 100 mm Hg for saline uterine distension, although this was not standardized for all surgeons in the study but rather was a custom of the institution. In addition, the length of time between hysteroscopy and surgery may allow the immune-reactive peritoneum to respond to the cellular insult, thus decreasing the biologic burden at the time of surgery. The median follow-up was 52 months (range, 12–120 months), and there were no differences between the hysteroscopy and the nonhysteroscopy groups in the 5-year recurrence-free survival (90.2% vs 88.2%; P = .53), disease-specific survival (93.4% vs 91.7%; P = .5), and overall survival (86.2% vs 80.6%; P = .22). The authors concluded that hysteroscopy does not compromise the survival of patients with early-stage endometrial cancer.[12]

Retrospective data from Chen and colleagues regarding type 2 endometrial carcinoma indicated a statistically significant increase in positive intraperitoneal cytology for carcinomas evaluated by hysteroscopy versus D&C (30% vs 12%; P = .008).[13] Among the patients who died, there was no difference in disease-specific survival (53 months for hysteroscopy and 63.5 months for D&C; P = .34), and there was no difference in overall recurrence rates.[13] Compared with type 1 endometrial

carcinoma, type 2 endometrial carcinoma behaves more aggressively, with a higher incidence of extrauterine disease and an increased propensity for recurrence and poor outcome even in the early stages of the disease. This makes it difficult to determine the role of hysteroscopy in the prognosis of these carcinomas, especially in this study where most patients were diagnosed at a later stage.

Key takeaways

Hysteroscopy and directed biopsy are highly effective for visual and histopathologic diagnosis of atypical endometrial hyperplasia and endometrial carcinoma, and they are recommended in the evaluation of AUB, especially in the postmenopausal woman. When the hysteroscopic view is negative, there is a high correlation with the absence of uterine cavity and endometrial pathology. Hysteroscopic diagnostic accuracy is improved with structured use of visual grading scales, well-defined descriptors of endometrial pathology, and hysteroscopist experience.

Low operating intrauterine pressure may decrease the intraperitoneal spread of carcinoma cells during hysteroscopy, and current evidence suggests that there is no change in type 1 endometrial carcinoma prognosis and overall outcomes. Type 2 endometrial carcinoma is more aggressive and is associated with poor outcomes even in early stages, and the effect on disease progression by intraperitoneal spread of carcinoma cells at hysteroscopy is not yet known. Hysteroscopic evaluation of the uterine cavity and directed biopsy is easily and safely performed in the office and adds significantly to the evaluation and management of endometrial carcinoma. ●

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