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Narrow-Band Imaging in Diagnosis of Endometrial Cancer and Hyperplasia: A New Option?

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ABSTRACT **Study Objective:** To estimate whether the use of narrow-band imaging (NBI) hysteroscopy increases concordance between visual identification and a histologic diagnosis of endometrial cancer and hyperplasia.
Design: Prospective study (Canadian Task Force classification: II-2).
Setting: Department of obstetrics and gynecology, University of Eastern Piedmont, Novara, Italy.
Patients: 209 consecutive patients with abnormal uterine bleeding.
Interventions: White-light hysteroscopy and NBI hysteroscopy followed by direct biopsy.
Measurements and Main Results: The sensitivity and specificity of conventional hysteroscopy in predicting a diagnosis of cancer and hyperplasia were, respectively, 84.21% (95% confidence interval [CI], 79.27–89.15) and 99.47% (95% CI, 98.49–100.0), and 64.86% (95% CI, 58.39–71.34) and 98.77% (95% CI, 97.27–100.0), and of NBI hysteroscopy were 94.74% (95% CI, 91.71–97.76) and 97.89% (95% CI, 95.95–99.84), and 78.38% (95% CI, 72.8–83.96) and 97.67% (95% CI, 96.63–99.72). The concordance of conventional and NBI hysteroscopy with the histopathologic findings (measured using the Cohen κ) was, respectively, 88.80% (95% CI, 86.2%–96.3%) and 91.78% (95% CI, 89.6%–98.2%), a difference of 2.98% (95% CI, 0–9) in favor of NBI.
Conclusion: Narrow-band imaging hysteroscopy can accurately predict a histologic diagnosis of endometrial cancer or hyperplasia. Journal of Minimally Invasive Gynecology (2010) 17, 620–625 © 2010 AAGL. All rights reserved.

Keywords: Endometrial cancer; Endometrial hyperplasia; Hysteroscopy; Narrow-band imaging

In 1971, Folkman [1] first reported that tumor growth and progression depend on angiogenesis, and since then, further evidence has been collected that indicates that angiogenic intensity may have a prognostic role in a number of malignant lesions including endometrial cancer and its precursors. In 1999, Abulafia et al [2] evaluated angiogenesis in uterine specimens from patients with endometrial hyperplasia and cancer, and observed that complex hyperplasia was significantly more angiogenic than simple hyperplasia and that the microvessel count was significantly lower in hyperplastic specimens. Subsequently, in 2006, Stefansson et al [3] observed that vessels associated with endometrial cancer are structurally and functionally abnormal and that the structural changes are associated with more frequent vascular invasion and decreased survival.

Hysteroscopy is useful for diagnosing symptomatic endometrial diseases. However, Lasmar et al [4] have reported that its sensitivity is no more than 80% for endometrial cancer, and 56.3% for hyperplasia, which suggests that the subjective interpretation of morphologic changes in the endometrial mucosa is not sufficient to draw diagnostic conclusions. Hysteroscopy with direct biopsy is currently considered the criterion standard for diagnosis of endometrial diseases, and has advantages over dilation and curettage, in particular when diagnosing focal intracavity diseases [5].

Narrow-band imaging (NBI) is a new real-time imaging technique based on modifying spectral features by narrowing the bandwidth of spectral transmittance using optical filters. This highlights the tissue microvasculature primarily as

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a result of the differential optical absorption of light by hemoglobin, in particular in the blue range. The NBI filter is placed in the light path in front of a red-green-blue rotatory filter and cuts all but the 2 wavelengths of 415 and 540 nm. The first penetrates the surface mucosa and provides information about its capillary pattern; the second penetrates the tissue more deeply and enables visualization of the thicker submucosal vessels. An image processor creates a composite color image on a monitor, with the 415-nm beam being allocated to the B and G channels, and the 514-nm beam to the R channel, which is why the capillary vessels appear brown-black. In addition to magnification, NBI enables visualization of the mucosal pattern and surface microvasculature by means of an on-off switch located on the head of the endoscope [6–9].

A number of recently published studies have highlighted the potential role of NBI in the early detection of head and neck cancers [10], follow-up of patients with recurrent non-muscle invasive bladder carcinoma [11], and identification of dysplastic and malignant airway lesions in patients at risk [12]. Most of the authors who have used the NBI magnification system in gastrointestinal diseases have concluded that it will soon become the endoscopy standard because of its ability to enable identification of abnormal microvessels that are difficult or impossible to visualize using conventional methods [7,13].

Narrow-band imaging has been used by gynecologists to detect peritoneal endometriosis implants during laparoscopy, and some studies have demonstrated that it can be used to identify and remove even small implants [14,15]. We first suggested using the NBI system to detect endometrial lesions in 2009 [9]; however, to our knowledge, there are still no published studies describing the results. The objective of the present study was to estimate the diagnostic accuracy of NBI hysteroscopy in enabling visual identification of endometrial cancer and hyperplasia.

Materials and Methods

209 consecutive patients referred to the department of obstetrics and gynecology at the University of Eastern Piedmont, Novara, Italy, underwent NBI hysteroscopy between December 2007 and December 2008. Inclusion criteria were abnormal uterine bleeding (AUB), no evidence of abnormalities on a Papanicolaou smear test, no use of anticoagulant agents, and a transvaginal ultrasonographic endometrial thickness greater than 4 mm in the case of menopausal patients [16]; and exclusion criteria were inability to provide written informed consent, age younger than 18 years, ongoing gonadotropin-releasing hormone agonist therapy, and a history of endometrial cancer.

In all of the procedures, the same endoscope system (Olympus EXERA II Video; Olympus Medical Systems Corp., Tokyo, Japan) was used. Hysteroscopy was performed using a 5-mm hysteroscope with a 1.5-mm operating channel (Karl Storz GmbH & Co., Inc., Tuttlingen, Germany) according to the vaginoscopic technique in 72 cases. The distention medium was physiologic saline solution delivered at a working pressure of 80 to 100 mm Hg.

Biopsies were performed using 5F grasping forceps inserted through the operating channel or a Novak curette, and polypectomy was performed using scissors or a bipolar electrode (Versapoint Electrosurgery System, Ethicon, Inc., Somerville, NJ). If ultrasonography revealed the presence an intracavitary lesion larger than 2 cm or if the patient did not want to feel pain, operative hysteroscopy was performed as inpatient day surgery using general or spinal anesthesia. The cervix was grasped with a tenaculum and dilated to Hegar 9, and an 8.5-mm diameter outer sheath resectoscope (Olympus Medical Systems Corp.) equipped with a 12° optic was inserted. The uterine cavity was distended using saline solution delivered at a pressure of 70 to 100 mm Hg from 5-L pressure bags. The procedures were performed using a loop electrode, with the electrosurgical generator set at 170 W for vaporization, and 80 W for coagulation. Intravenous injection of 2 g of piperacillin was always administered intraoperatively as antibiotic prophylaxis, and the patients were discharged 6 hours after the procedure.

In premenopausal patients, hysteroscopy was scheduled during the follicular phase of the menstrual cycle, when there is little or no AUB [17], although a histologic diagnosis of hyperplasia is difficult in this phase because bleeding can hamper recognition of lesions because the entire uterine cavity appears brown-black.

The criteria used to evaluate the endometrium using white-light imaging (WLI) hysteroscopy have been previously described [4,18]. It has been reported that diagnosis of endometrial diseases is aided by considering both the morphologic and vascular aspects of the lesions. The NBI system provides a better view of the vascular pattern of endometrial lesions and enables identification of the smaller vessels that cannot be seen using WLI because the vasculature appears brown-black against the normal white-pink mucosa [4,5,18].

In our experience, the characteristics associated with a histologic diagnosis of hyperplasia are hyperemic mucosal regions with abundant thin or minimally swelled, sometimes corkscrew-like, regularly separated, arborescent microvessels of homogeneous diameter, and invisible or very narrow vessels running between papillary excrescences (Fig. 1A and 1B); those associated with cancer have a complex, chaotic vascular architecture, with unevenly sized, elongated, and coiling, tortuous, thin-walled, and thickly branched microvessels irregularly located on the lesion surface (Fig. 2A and B). Invisible or thin regular vessels, vascularization of the pedicle alone, and vascular proliferation in the direction of lesion growth are particular to benign diseases (Videos 1–5).

The surgeon initially observed the uterine cavity using WLI hysteroscopy, and made a diagnostic impression that was recorded on a spreadsheet (Excel; Microsoft, Redmond, WA). Subsequently, after pressing the button on the telescope, NBI was used to reevaluate the endometrial mucosa

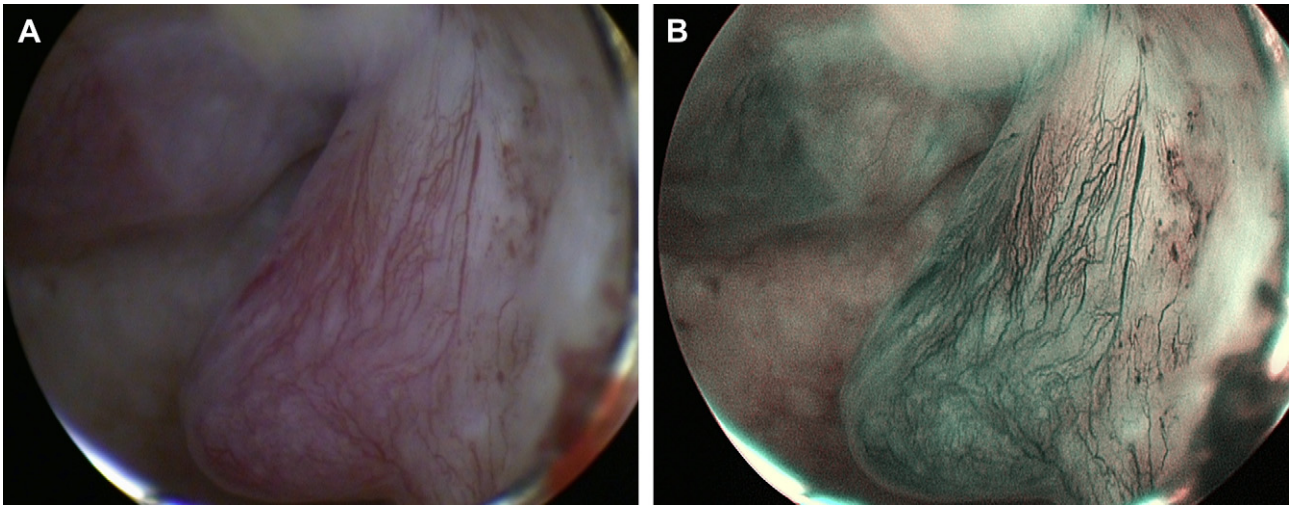

Fig. 1. Images of conventional (A) and narrow-band imaging (B) hysteroscopy because of endometrial hyperplasia.

by studying its microvascular features (the thickness and irregularity of capillary vessels on surface mucosa), and the surgeon confirmed or changed the diagnostic hypothesis, which was again recorded on the spreadsheet. Time for observation of the uterine cavity was about 30 seconds in both cases. The surgeon then obtained direct biopsy specimens for pathologic analysis.

Patients with evidence of benign disease (polyps and myomas) were immediately treated at surgical hysteroscopy. All of the procedures were performed by the same specialist (L.L.), who has more than 10 years of experience. The hysteroscopist was not aware of the ultrasound results, and the pathologists who analyzed the biopsy specimens were blinded to the endoscopic findings.

In 1 patient, the specimens were insufficient to make a diagnosis, and in 1 case, the surgeon did not give a diagnostic impression because of heavy bleeding; thus, comparison of the 2 hysteroscopic diagnostic hypotheses with the biopsy results (taken as the criterion standard) was based on 209 cases.

All study protocols and procedures were approved by the Ethics Committee of Ospedale Maggiore della Carità, Novara, Italy, and all study participants gave informed consent.

The sample size was calculated using prestudy power analysis, which indicated that 202 patients were necessary to obtain 80% power at a significance level of $p = .05$. Histologic results were compared with the examiner's diagnostic hypotheses after conventional and NBI hysteroscopy. Categorical variables are given as absolute numbers and percentages, and continuous variables as mean (SD). Sensitivity and specificity were calculated with their 95% confidence intervals (CIs) for the diagnoses of endometrial cancer and hyperplasia, and the χ^2 test was used to analyze categorical variables. Agreement between the criterion standard and the 2 endoscopic techniques was measured using the Cohen κ test for multiple choices, and the differences between the concordances (the related 95% CIs) were calculated. Data were analyzed using Epi Info statistical software, version 3.5. A p value of $<.05$ was considered statistically significant.

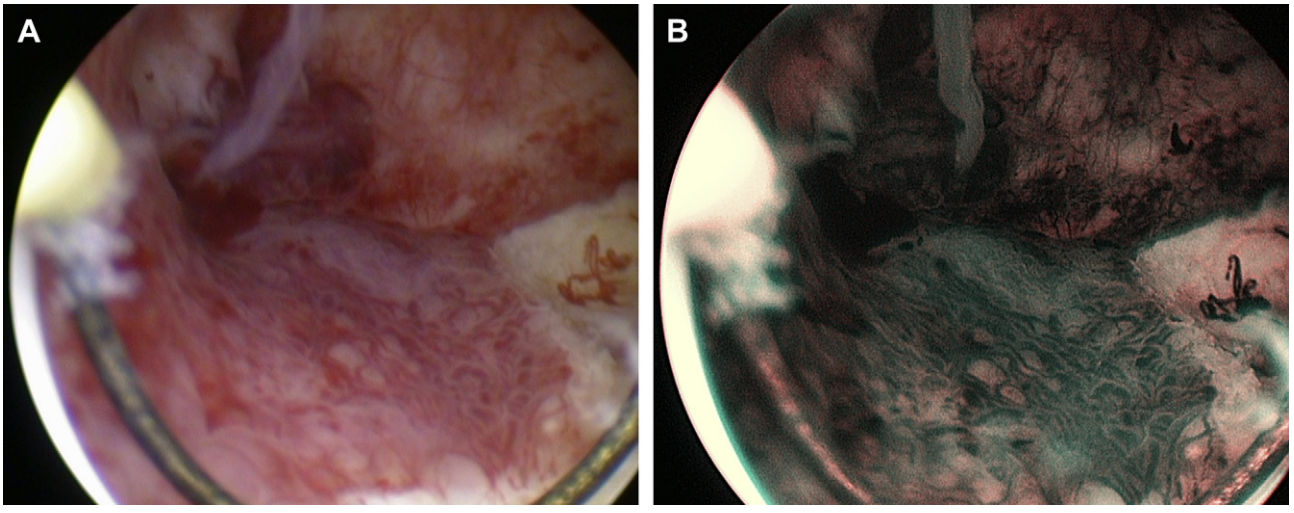

Fig. 2. Images of conventional (A) and narrow-band imaging (B) hysteroscopy because of endometrial cancer.

Table 1
Patient Characteristics*

Characteristic	EC+	EC−	Total	p Value
Age, yr	69.57	58.22	59.25	<.05
Body mass index	24.83	23.84	23.93	>.05
Menopause	19	140	159	>.05
Premenopause	0	50	50	>.05
HRT	0	11	11	>.05
Tamoxifen	0	4	4	>.05
No therapy	19	175	194	>.05

EC+ = with endometrial cancer; EC− = without endometrial cancer; HRT = hormone therapy.
* Data are given as the mean or as the number of patients.

Table 2
Relationship between histopathologic results and conventional hysteroscopic view

	Histopathologic results					
Conventional Hysteroscopy	Cancer	Hyperplasia	Myoma	Normal	Polyp	Total
Cancer	16	0	0	0	0	16
Hyperplasia	2	24	0	0	0	26
Myoma	0	0	4	0	0	4
Normal	1	9	0	87	0	97
Polyp	0	4	0	0	62	66
Total	19	37	4	87	62	209

χ^2 = 6 928 182; p = .000; observed concordance, 92.34%; expected concordance determined by (Column result × Row result)/Observed, 31,62%; Cohen κ, 88,80%.

Results

The enrolled patients had a mean (SD) age of 59 ($11^1/_2$) years, and included 159 postmenopausal women (76.1%; 95% CI, 69.7–81.7) and 50 premenopausal women (23.9%; 95% CI, 18.3–30.3). Eleven patients (5.3%; 95% CI, 2.7–9.2) were receiving hormone therapy, 4 (1.9%; 95% CI, 0.5–4.8) reported taking tamoxifen, and 194 (92.8%; 95% CI, 88.4–95.9) were not receiving any treatment. As expected, the group of patients with endometrial cancer were older (mean, 69.6 vs 59.2 years) (Table 1).

No adverse events such as uterine perforation, pelvic infection, or secondary hemorrhage occurred during the procedures.

At histopathologic analysis, endometrial biopsy findings indicated the presence of endometrial cancer in 19 patients (9.1%; 95% CI, 5.6–13.8), including 2 with concomitant atypical hyperplasia, and endometrial hyperplasia in 37 (17.7%; 95% CI, 12.8–23.6), 33 with simple and 4 with complex hyperplasia without atypia; a myoma was found in 4 patients (1.9%; 95% CI, 0.5–4.8), and a polyp in 62 (29.7%; 95% CI, 23.6–36.4). The remaining 87 biopsy specimens (41.6%; 95% CI, 34.8–48.6) were normal.

Histological findings were first compared with the surgeon's diagnostic hypothesis based on conventional WLI hysteroscopic visualization of the endometrial mucosa (Table 2). The diagnosis was correct in 16 patients with endometrial cancer and 24 with hyperplasia. The sensitivity and specificity of WLI hysteroscopy in detecting endometrial cancer were, respectively, 84.21% (95% CI, 79.27–89.15) and 99.47% (95% CI, 98.49–100.0), and for hyperplasia were 64.86% (95% CI, 58.39–71.34) and 98.77% (95% CI, 97.27–100.0).

Comparison of the histopathologic findings with the surgeon's diagnostic hypothesis after NBI hysteroscopy (Table 3) showed agreement in 29 patients with hyperplasia and 18 with endometrial cancer. The sensitivity and specificity of NBI hysteroscopy in detecting cancer were, respectively, 94.74% (95% CI, 91.71–97.76) and 97.89% (95% CI, 95.95–99.84), and for hyperplasia were 78.38% (95% CI, 72.8–83.96) and 97.67% (95% CI, 96.63–99.72). The positive and negative predictive values of NBI hysteroscopy in comparison with histologic analysis were, respectively, 94.12% (95% CI, 90.93–97.31) and 94.44% (95% CI, 91.33–97.55).

Use of the NBI system significantly increased sensitivity (p <.05) in diagnosing both endometrial cancer and hyperplasia; there was a slight decrease in specificity, but this was not statistically significant (p >.05).

Insofar as diagnostic accuracy, the observed concordance of conventional and NBI hysteroscopy with histopathologic analysis was, respectively, 92.34% (Cohen κ, 88.8%) and 94.26% (Cohen κ, 91.78%), with a statistically significant difference of 2.98% (95% CI, 0–9).

Discussion

It has been reported that a diagnosis based on mucosal pattern correlates with histologic findings [4,19]; however, a number of studies have found that a subjective hysteroscopic evaluation based on experience does not always enable identification of endometrial cancer and hyperplasia [4,20]. Angiogenesis is considered essential for transition from premalignant to malignant endometrial disease; thus, evaluation of irregularities in mucosal vessels might be an ideal means of identifying hyperplasia and early-stage cancer [2,3].

Narrow-band imaging is a new optical technology that uses special narrow-band filters in the endoscopic system. In particular, the blue filter is designed to correspond to the peak absorption spectrum of hemoglobin to emphasize the image of capillaries on the surface mucosa. The NBI system has thus far been recognized as a potentially powerful means of diagnosing gastrointestinal diseases, head and neck cancers, urothelial carcinoma of the bladder, and precancerous airway lesions. However, to our knowledge, the present study is the first designed to assess whether it can increase concordance between hysteroscopy and histologic findings in the diagnosis of endometrial diseases.

We used both conventional and NBI hysteroscopy to examine the uterine cavity in 209 patients referred to our department because of AUB. Histologic analysis revealed

Table 3
Relationship between histopathologic result and NBI hysteroscopic view

NBI hysteroscoopy	Histopathologic results					
	Cancer	Hyperplasia	Myoma	Normal	Polyp	Total
Cancer	18	4	0	0	0	22
Hyperplasia	1	29	0	2	1	33
Myoma	0	0	4	0	0	4
Normal	0	3	0	85	0	88
Polyp	0	1	0	0	61	62
Total	19	37	4	87	62	209

NBI = narrow-band imaging.
χ^2 = 7 110 052; p = .000; observed concordance, 94,26%; expected concordance determined by (Column result – Row result)/Observed, 30,12%; Cohen κ, 91,78%.

a higher percentage of women with endometrial cancer and hyperplasia than that observed in the series by Lasmar et al [17], a difference that may be explained in that 51.3% of their patients were younger than 45 years, whereas 76.1% of our patients were menopausal, and we routinely performed transvaginal ultrasonography before study enrollment, which, according to Gull et al [16], makes it possible to exclude patients at no risk of malignant disease.

The conventional hysteroscopic classification was based on previously reported criteria (4,18), whereas NBI enabled clear identification of the vascular patterns associated with hyperplasia (abundant, thin, homogeneous surface vessels) and cancer (thick, diffuse, irregular vessels). We observed that the sensitivity of NBI hysteroscopy in detecting endometrial cancer and hyperplasia was significantly greater than that of WLI hysteroscopy, with no significant difference in specificity, and NBI improved the accuracy of white-light hysteroscopy in predicting histologic findings of endometrial cancer and hyperplasia by a statistically significant 2.9%. As expected, there was no improvement in the diagnoses of normal endometrium or benign diseases because NBI is more useful in the case of diseases characterized by an abnormal vascular pattern.

Using NBI led to an increase in the number of false-positive findings; however, almost all of these were related to the first 100 procedures, and if these are excluded, NBI specificity was 98.36% (95%CI, 96.00–99.99) for cancer and 98.88% (95%CI, 96.9–99.9) for hyperplasia. The reason for this may be that the surgeon must become used to the effect of NBI on capillary enhancement and memorize the patterns correlated with each histologic finding. The sensitivity of conventional hysteroscopy in detecting cancer and hyperplasia was slightly higher than that reported by Lasmar et al [17], possibly because all of our procedures were performed by the same skilled surgeon.

Despite the promising results, our study has some limitations. First, it involved only a small number of patients and was conducted at a single academic institution. Second, the accuracy of NBI hysteroscopy in predicting histologic findings was not tested by assessing interobserver variability; however, all of the procedures were performed by the same skilled surgeon, who may have been influenced by the white-light appearance of the lesions. Third, although it can make it difficult to diagnose hyperplasia at histologic analysis, we decided to perform the procedures during the proliferative phase of the menstrual cycle, when there is little or no AUB, because bleeding can hamper NBI visualization of lesions. None of our patients had severe anemia or chronic endometritis; however, we can speculate that these conditions may alter the accuracy of NBI because of the reduced absorption of blue light by hemoglobin or hypervascularization.

In our opinion, NBI could become a useful additional method for early identification of endometrial diseases, in particular, hyperplasia, which currently represents a challenge for gynecologists because of the lack of highly sensitive morphologic criteria. However, we were unable to identify any NBI criteria for the differential diagnosis of simple, complex, and atypical hyperplasia because of the limited number of cases with complex and atypical hyperplasia in our series. Another interesting question is whether the increased diagnostic accuracy observed in the present study will be confirmed by a series of procedures performed by residents.

Conclusion

Conventional WLI hysteroscopy is a well-established, highly sensitive, and highly specific means of diagnosing intrauterine diseases. However, our results demonstrate that use of the NBI system by an experienced surgeon can increase its diagnostic accuracy. Large-scale, multicenter, randomized trials are needed to confirm the potential of NBI for studying the endometrium.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jmig.2009.10.014.

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