

Improving tissue characterization, differentiation and diagnosis in gynecology with the narrow-band imaging technique: A systematic review

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Abstract. Narrow-band imaging (NBI), an on-demand, real-time endoscopic imaging technique, was developed to enhance visualization of the mucosal vascular network and surface texture. The present article provides a systematic review of studies that assessed the use of NBI in gynecological endoscopy. The following electronic databases were searched: PubMed (1950-2020), Google Scholar (2004-2020) and Cochrane Library (2010-2020). In the initial search, 3,836 entries were identified, of which 31 were finally included in the systematic review. Of the selected studies, 10 (32%) were case reports, 19 (61.2%) were prospective studies and 2 (6.4%) were randomized controlled trials with control groups. The selected studies reported on the use of NBI in hysteroscopy, laparoscopy and colposcopy. It was revealed that NBI utilization in hysteroscopy increased the accuracy, sensitivity and specificity in detecting malignant and premalignant lesions. NBI improved the specificity and sensitivity in the detection of endometriotic lesions and cervical lesions. Conventional white light endoscopy in gynecology may be significantly improved by the use of NBI. Further studies with larger cohorts and improved design are required to achieve more reliable results. It is of special interest that utilization of

this method requires apparatus which is expensive; concerns are the long training and experience of staff required and the long learning curve.

Introduction

Narrow-band imaging (NBI), an on-demand, real-time, endoscopic imaging technique, was developed to enhance the visualization of the mucosal vascular network and surface texture for the purpose of improving tissue differentiation, characterization and diagnosis (1).

The interaction of particular tissue structures with light is wavelength-dependent and augmentation of particular mucosal features via NBI is achieved through observation of light transmission at selected wavelengths (or colors) (2).

In the NBI system, selective light transmittance is conducted via optical filtering of white light (WL). Specifically, NBI uses two discrete bands of light, a blue band at 415 nm and a green band at 540 nm, to create a high-contrast image of the tissue surface, which allows enhanced visualization of blood vessels (3). The two bands correspond to the peak light absorption of hemoglobin, thus permitting NBI to visualize the blood vessels with greater clarity and accuracy on the surface of the analyzed tissues than observation with WL (3).

In clinical practice, there is currently widespread use of NBI to provide an improved examination of the gastrointestinal system, including the stomach and large intestine, esophagus and pharynx, as well as of the lungs, urinary tract and oropharynx. This technique, which has been termed 'optical biopsy', has brought achievements of earlier diagnosis by substantially improving the qualitative diagnosis of the depth and grade of invasion of atypical lesions (4).

The aim of the present study was to perform a systematic review of all available studies evaluating the use of NBI in

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gynecology clinical practice for the detection of benign and malignant lesions.

Materials and methods

Search strategy. The following electronic databases were searched: PubMed (1950–2021), Google Scholar (2004–2021) and Cochrane Library (2010–2021). The electronic literature search was mostly performed between January 2020 to February 2021. The search included the following medical subject headings or keywords: ‘Narrow-band imaging’ and ‘gynecology’. The last search was performed on 08/02/2021.

The systematic review was performed and the flowchart diagram was drawn according to the Preferred Reporting Items for Systematic Reviews and Metanalyses statement (5).

Inclusion criteria. Full-text articles published in peer-reviewed journals and written in the English language were deemed eligible to be included in the review. Studies that did not fulfill the following criteria were excluded from the review: i) Conference abstracts and studies not providing sufficient clinical data; and ii) studies reporting narrow-band imaging utilization in animals, in surgical specimens or in an *in vitro* environment.

All types of studies were included, namely randomized controlled or observational studies, case series and case reports. The selected eligible articles were compared and discrepancies were resolved by discussion. The final decision on eligibility was made by the senior investigator (PP) whenever discrepancies had not been resolved through discussion.

Data extraction. Two authors (PP and KK) independently extracted information, while SS, CK, VA, PT and NA checked the extracted information and tabulated the data. NV checked the results and approved the study.

From the eligible studies, the following clinical data were obtained: Author and year of publication; the time period of enrolment of the study population; the country and city in which the study was performed; the type of study; the setting of the hospital (single- or multi-university study); the number of patients; the age of the patients; the inclusion criteria for surgery; the interventions performed; the endoscopic system used in each study; the outcome of the studies; and comments on different studies. The references of the selected studies were scrutinized for additional information not obtained by the initial search.

The Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool was used to assess the quality of the primary diagnostic accuracy studies. Via this tool, risks for bias may be evaluated in the following four key domains: i) Selection of participants; ii) index (diagnostic) test; iii) reference standard; and iv) flow and timing of the study (6).

Through the use of the Case Report (CARE) guidelines checklist, the information quality of case reports was evaluated, specifically assessing the following items: Patient information, the presence of timeline information, diagnostic assessment, clinical findings, therapeutic intervention and outcomes (7,8).

Statistical analysis. Data obtained from the selected studies were entered into an Excel v160 spreadsheet (Microsoft Corporation 2018). Descriptive statistical analyses was performed using SPSS version 23 (IBM Corporation) and

Excel version 16.0 (Microsoft Corporation, 2018). The number of publications were calculated per year and per country, and the median age of participants in the selected studies was also calculated.

Results

Literature search and selection. The literature search identified a total of 3,836 studies, i.e., 3,800 articles through Google Scholar, 32 articles through the PubMed database and four through the Cochrane Library database. The flowchart of the study selection process is displayed in Fig. 1. After removing duplicates and irrelevant articles, 256 articles were considered for further evaluation. Further assessment excluded 215 articles for various reasons (non-eligible, non-English literature, animal studies and articles providing insufficient information). Finally, 31 studies reporting on a total of 3,128 female patients were included in the review.

Of the selected studies, 10 (32%) were case reports (9–18), 19 (61.2%) were prospective studies (11,12,18–32) and two studies (6.4%) were randomized controlled trials (33,34). The selected studies had publication dates ranging from 2007 to 2020.

The frequency of publications per year and the percentage of publications by country are presented in Fig. 2. The years with the highest frequency of publications were 2010 and 2011 with 5 studies produced each year and the country which produced the highest number of studies was Japan with 11 studies (13,18,21,22,28,31–33,35), followed by Italy with 8 studies (9,10,15–17,19,20,36).

Study properties. A total of 11 studies described the use of NBI in hysteroscopy for the detection of endometrial pathologies (9,10,19–25,36,37) and another 11 studies reported the use of NBI in laparoscopy for the detection of peritoneal endometriosis (11–13,26–30,33,34,37,38). Furthermore, three articles dealt with the use of NBI in digital colposcopy for the detection of lower genital tract pathologies (14,31,32) and three articles reported on the use of NBI in laparoscopy for the detection of peritoneal metastases associated with ovarian cancer and other gynecological malignancies (15–17).

NBI in endometrial pathology. Details on the selected studies reporting the use of NBI in hysteroscopy are presented in Table I. A total of 11 studies were included in the review, dating from 2009–2020 with a combined cohort of 2,424 female patients (9,10,19–25,36,37). Of these, eight studies were prospective studies (Canadian Task Force classification, II–2) (19,23,36) and two studies were case reports (9,10). All studies were designed in university settings, two studies were performed in multicentric university settings (20,36) and two studies were reported at international congresses as conference reports (10,24). All of the patients presented with abnormal uterine bleeding (AUB). The median age of the patients was 45.5 ± 10.5 years. A total of four studies were performed in outpatient office settings using a vaginoscopic approach without any general anesthesia (19,21,23,36). Conventional hysteroscopy under general anesthesia was performed in seven studies (10,24,25). Operative hysteroscopy was performed in all cases and histology specimens were obtained in each case. Olympus Exera II (Olympus Corporation) was the main video system used in the majority of studies.

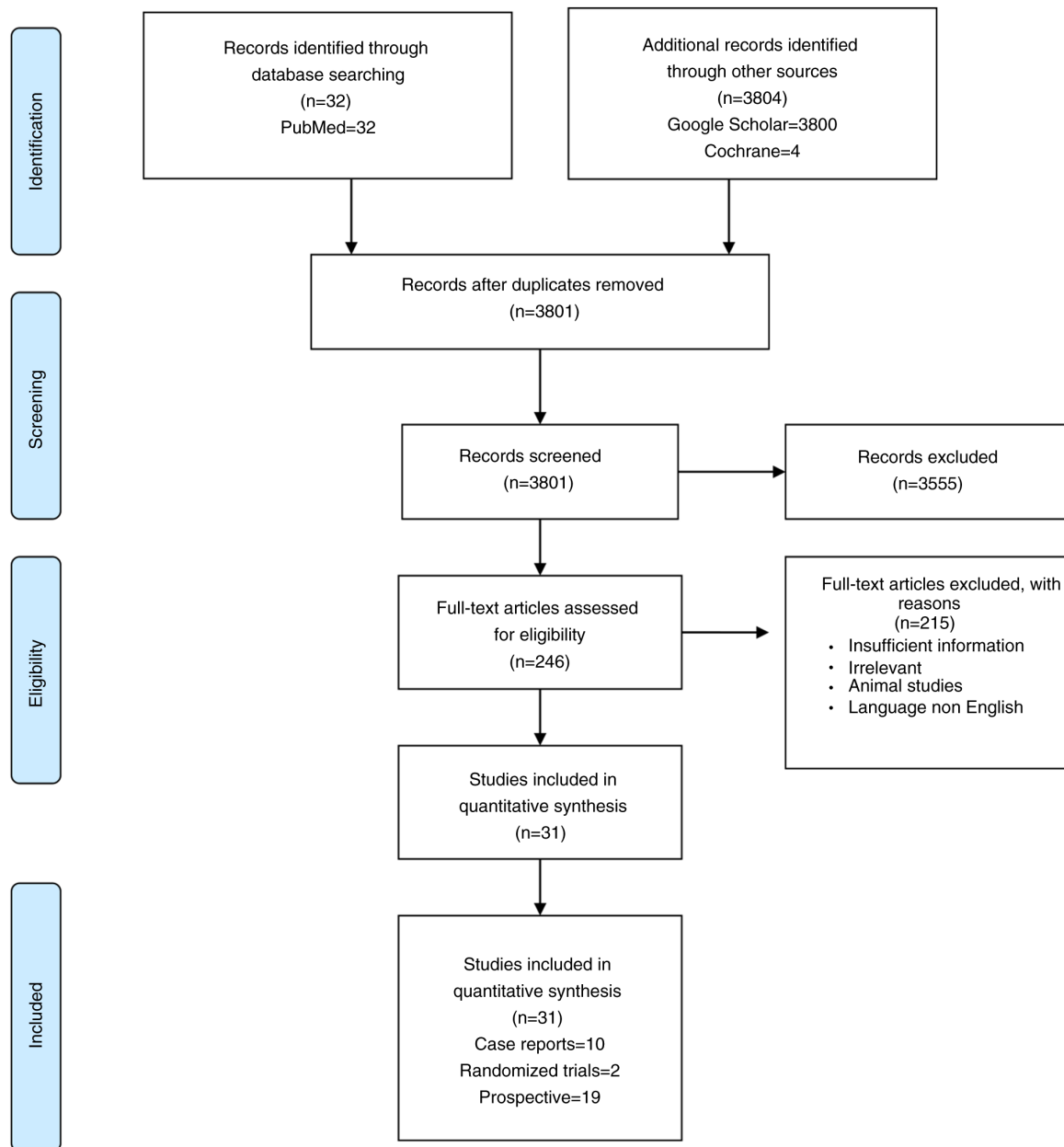


Figure 1. Flowchart diagram of the study selection for systematic review according to the Preferred Reporting Items for Systematic Reviews and Metaanalyses guidelines.

NBI hysteroscopy demonstrated increased sensitivity compared with WL imaging hysteroscopy for the detection of endometrial cancer in four studies (20,23,24).

The sensitivity of NBI and WL hysteroscopy for endometrial cancer reported by individual studies was 78.6 vs. 63.7%, $P<0.001$ (23), 93 vs. 81%, $P<0.05$ (36), 94.7 vs. 84.4%, $P<0.05$ (20) and 98.1 vs. 73.6% $P<0.001$ (24). Increased sensitivity of NBI vs. WL for the detection of atypical endometrial hyperplasia - high-risk hyperplasia (HRH) was reported in five studies (10,20-23). The reported sensitivity of NBI vs. WL for HRH was 60 vs. 20%, $P<0.005$ (36), 78.38 vs. 64.86%, $P<0.005$ (20), 78.6 vs. 63.7%, $P<0.001$ (23), 93.5 vs. 82.6%, $P=0.006$ (24) and 97.2 vs. 82.6%, $P<0.005$ (21).

None of the 11 studies reported any adverse effects or complications related to the surgical techniques in all instances.

NBI in endometriosis. Details on the selected studies reporting on the use of NBI in laparoscopy for the detection of peritoneal endometriosis are provided in Table II. A total of 11 studies were included in the present review, dating from 2007 to 2019 with a population of 626 female patients in total (11-13,26-30,33,34,38). The mean age was 35.5 ± 3.6 years. A total of three studies were case reports (11,12,29), three were studies with a randomized design (13,34,38) and five were had a prospective design lacking randomization (26-29,33). In all studies, laparoscopy with a 0-degree 10-mm scope was performed, except for two studies where intestinal endoscopy was utilized (13), while one study reported on the use of a 0-degree 12-mm scope (30). NBI improved the detection rate by 53% for smaller endometriotic lesions previously not detected on WL imaging laparoscopy (26). Another study reported that 82.7% of endometriotic lesions were detected using NBI compared with 55.9% of lesions detected

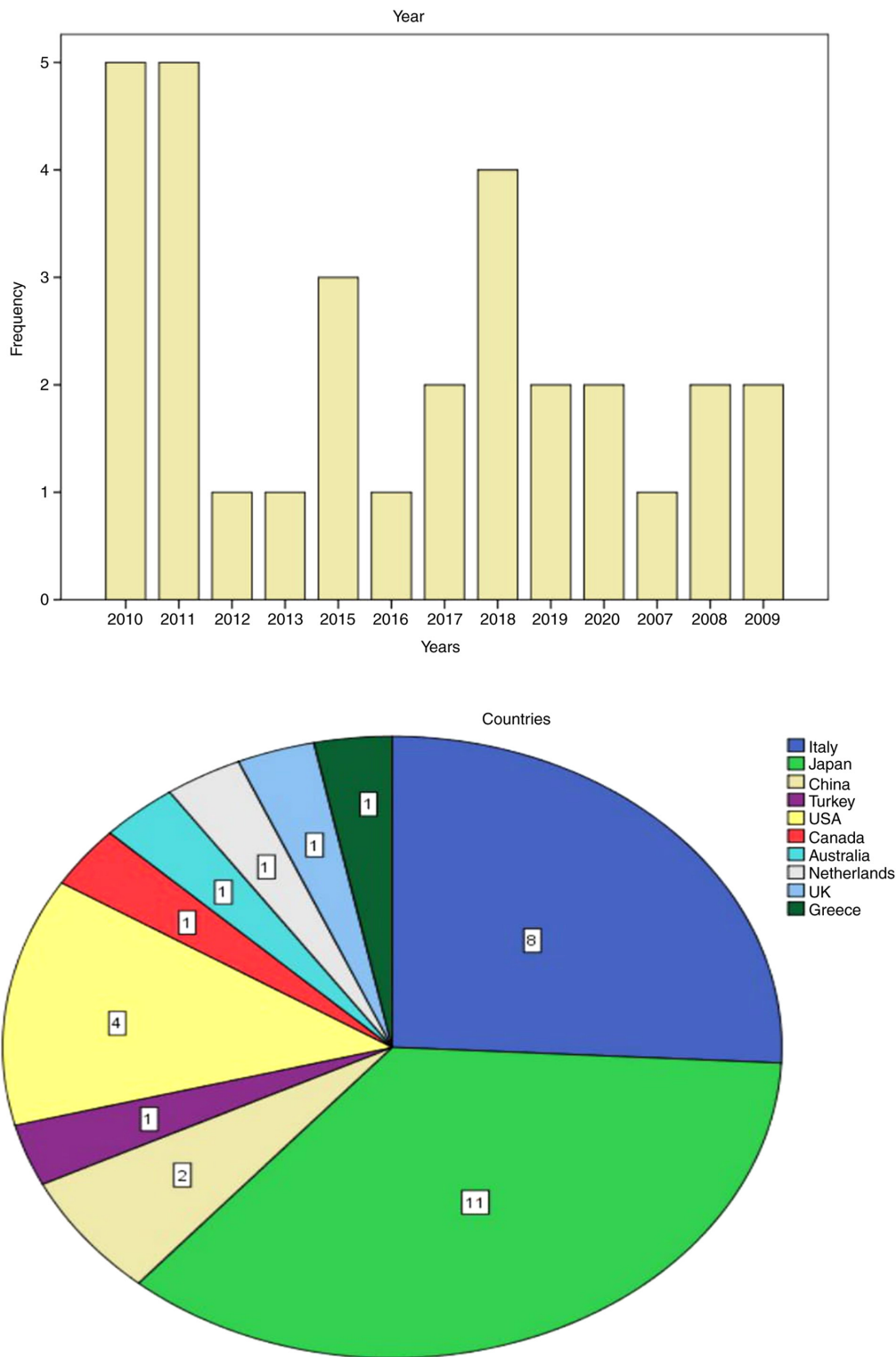


Figure 2. Frequency of publications per year and per country. A Histogram and pie chart are provided in order to present the frequency of selected publications per country and per year.

by WL imaging (27). The detection rate of endometriotic lesions with NBI was 100% in a randomized controlled trial with 167 female patients (34). Another randomized controlled trial assessed quality of life in two study groups: One group underwent laparoscopy with WL and the other with NBI. No difference in pain and quality of life was observed between the two study groups (34). When combined with WL, NBI was reported to provide an additional predictive value of 86% for the

detection of endometriotic lesions, if a positive diagnosis was made under WL imaging alone (29). NBI and WL combined with 3D imaging was able to increase the sensitivity rate up to 91% (13).

Olympus Exetera (Olympus Corporation) was the system used for NBI in all of the studies. None of the 11 studies reported any adverse effects or complications related to the surgical techniques.

Table I. Comparison of studies reporting on the use of hysteroscopy with NBI.

Author (year)	Time period	Country, city	Type of study	Institutes	Number of subjects	Age, years	Inclusion criteria	Interventions	System	Outcomes	Conclusion	(Refs.)
Surico, <i>et al</i> (2009)	2009	Italy, Novara	Case report	Single univ.	1	NS	AUB	Conventional hysteroscopy 30° 4 mm WL&NBI in G2 endometrial CA	Olympus Exera II	Detection of atypical irregular microvessels	NBI was able to increase accuracy in hysteroscopic detection of hyperplasia and endometrial CA	(9)
Cicinelli, <i>et al</i> (2010)	2008-2009	Italy, Bari	Prospective controlled	Single univ.	395	42.6±10.7	AUB	Fluid minihysteroscopy 105° 2.7 mm WL & NBI office setting without anesthesia compared with histology	Olympus Exera II	Increased sensitivity of NBI vs. WL: Proliferating endometrium, 0.93 vs. 0.78, P<0.005; chronic endometritis, 0.88 vs. 0.70, P<0.005; LRH, 0.88 vs. 0.70, P<0.05; HRH, 0.60 vs. 0.40, P<0.05	NBI increased sensitivity, decreased false negative biopsies and increased sensitivity in detecting endometrial pathology	(19)
Surico, <i>et al</i> (2010)	2007-2008	Italy, Novara	Prospective controlled	Multi univ.	209	59±11	AUB PMB	Hysteroscopy 5 mm WL&NBI with a 1.5 mm operating channel under general anesthesia compared with histology	Olympus Exera II	Increased sensitivity of NBI vs. WL in endometrial CA detection 94.7 vs. 84.4% hyperplasia detection 78.38 vs. 64.86% slight decrease in specificity (P>0.05)	NBI use by an experienced surgeon may increase diagnostic accuracy	(20)
Kisu, <i>et al</i> (2011)	2009-2010	Japan, Tokyo	Prospective controlled	Single univ.	104	NS	AUB	Flexible hysteroscope 3.1 mm WL&NBI office setting without anesthesia compared with histology	Olympus Xenon Light	Increased sensitivity of NBI vs. WL for atypical endometrial hyperplasia 97.2 vs. 82.6% P<0.005	NBI may be a useful tool in the detection of malignant endometrial lesions	(21)
Kuroda, <i>et al</i> (2011)	2009	Japan, Tokyo	Prospective controlled	Single univ.	14	40-42	AUB	Rigid 3.8 mm hysteroscopy Flexible 4 mm hysteroscopy with WL and NBI under GA in 6 cases with submucous myoma and 8 cases with normal endometrium	Olympus Xenon Light	Flexible scope in WL showed greater vascular densities than with rigid scope NBI with rigid and flexible scope did not show statistically significantly increased vascular densities	NBI may be a useful technology in the detection of malignant cells exhibiting neoangiogenesis. NBI has superior ability in observing the endometrial cavity because no high fluid pressure is required	(22)

Table I. Continued.

Author (year)	Time period	Country, city	Type of study	Institutes	Number of subjects	Age, years	Inclusion criteria	Interventions	System	Outcomes	Conclusion	(Refs.)
Kisu, <i>et al</i> (2011)	2009-2010	Japan, Tokyo	Prospective	Single univ.	71	41.9±12.5	AUB	Flexible hysteroscopy 3.1 mm WL&NBI in office setting without anesthesia compared with histology findings	Olympus Xenon Light	Higher sensitivity for hyperplasia and CA of endometrium for all raters with NBI. Average sensitivity was significantly higher in NBI group compared to WL (78.6 vs. 63.7%, P<0.001)	NBI system allows better view of the mucosal blood vessels than WL. Larger studies with randomization design required to establish conclusions	(23)
Tinelli, <i>et al</i> (2011)	2008-2010	Italy, Bari	Prospective	Multi univ.	801	41.9±9.8	AUB	Fluid minihysteroscopy 2.7 mm WL & NBI in office setting without anesthesia compared with histology	Olympus Exera II	NBI increased sensitivity for endometrial CA to 93 vs. 81%, P<0.05; for LRH to 82 vs. 56%, P<0.05; and for HRH to 60 vs. 20%, P<0.005. No alterations in specificity and NPV	NBI increased sensitivity in detecting LRH, HRH and endometrial CA. A useful tool for reducing missed pathologies and unnecessary biopsies. NBI increased recognition of preneoplastic and neoplastic lesions misdiagnosed as benign by WL hysteroscopy	(26)
Raimondo, <i>et al</i> (2012)	2012	Italy, Rome	Case report	Single univ.	1	54	AUB	NBI-hysteroscopy under GA anesthesia 30-degree 4-mm biopsy of endometrial lesions	Olympus Exera II	Exhibition of vascular network consistent with adenomyosis. Histology confirmed adenomyosis	NBI in hysteroscopy may be a useful tool in the detection of adenomyosis	(10)
Kong, <i>et al</i> (2015)	2011-2013	China, Beijing	Prospective	Single univ.	213	43	AUB	Conventional hysteroscopy 5 mm WL&NBI under general anesthesia compared with histology	NS	NBI increased sensitivity for endometrial CA to 98.1 vs. 73.6% P<0.001; for LRH to 79.6 vs. 49%, P=0.003; and for HRH to 93.5 vs. 82.6%, P=0.006	NBI increased sensitivity in detecting LRH, HRH and endometrial CA	(24)
Ozturk, <i>et al</i> (2016)	2010-2011	Turkey, Ankara	Prospective	Single univ.	86	40	AUB n=71 PMB n=15	Hysteroscopy 5 mm WL&NBI with a 1.5 mm operating channel under general anesthesia compared with histology	Olympus Exera II	Detection of 7 cases of endometritis with NBI and of 1 case of endometritis with WL (7/8, 87%, 95%CI 0.52-0.97)	NBI may be useful combined with WL in detecting conditions such as chronic endometritis	(25)

Table I. Continued.

Author (year)	Time period	Country, city	Type of study	Institutes	Number of subjects	Age, years	Inclusion criteria	Interventions	System	Outcomes	Conclusion	(Refs.)
Wang, <i>et al</i> (2020)	2012-2014	China, Beijing	Prospective	Single univ.	529	40.3	No symptoms	Hysteroscopy 5 mm WL&NBI with a 1.5 mm operating channel under general anesthesia compared with histology	Olympus Exera II	Three levels of trainees achieved higher diagnostic accuracy with NBI utilization than with WL during hysteroscopy	NBI may increase the skill of trainees, particularly those with previous training	(37)

AUB, abnormal uterine bleeding, PMB, postmenstrual bleeding, NBI, narrow-band imaging; WL, white light; HRH, high-risk hyperplasia; LRH, low-risk hyperplasia; CA, carcinoma/cancer; univ. university, GA-General Anesthesia.

NBI in cervical pathology and peritoneal implants. Details on the selected studies reporting on the use of NBI in laparoscopy for the detection of cervical lesions and gynecological malignancies are listed in Table III. A total of 9 studies were included in the review, dating from 2010 to 2020. Of these, four studies were prospective studies (31,32,35,39) and five studies were case reports (14-18). The total number of patients was 156 and the mean age was 43.3±17.25 years. Uterine cervical pathology was investigated with NBI in five studies (14,18,31,32,35) and peritoneal implants were investigated with NBI in four studies (15-17,39).

The vascular pattern of lesions was examined in 21 patients with early and *in situ* cervical adenocarcinoma using NBI (13). The authors classified the colposcopic lesions according to the pattern described by Wright (40). The vascular pattern was visualized in 18 patients (86%); the authors concluded that NBI colposcopy depicts the vascular pattern on the cervix in early glandular disease better than conventional colposcopy. Nishiyama *et al* (32) proposed a novel microvascular classification. They used flexible magnifying endoscopy with NBI in 10 patients with cervical lesions; the detection rate was 90% (9/10) (32). NBI assisted in the detection of a rare melanoma of the cervix in a case report (14). Furthermore, NBI was utilized in laparoscopy for the detection of peritoneal metastasis in a series of 95 female patients undergoing surgery for various gynecological malignancies, as reported by Aloisi *et al* (39). They determined that NBI increased the number of the detected peritoneal abnormalities; however, no statistically significant differences were observed in the identification of histologically confirmed metastatic disease (P=0.18) (39).

A significantly greater number of peritoneal abnormalities were identified with NBI than with standard WL imaging. However, no statistically significant differences were observed in the identification of histologically confirmed metastatic disease (39). In addition, NBI proved to be useful in the laparoscopic detection of early peritoneal implants in three case reports (15-17). Kobara *et al* (18) indicated that NBI increased the sensitivity, specificity, accuracy and positive predictive value for the detection of cervical intraepithelial lesions-3 (CIN-3) in comparison with conventional colposcopy. NBI with a gastro-scope assisted the detection of high-grade cervical intraepithelial lesions in two patients, while these lesions were not identified by conventional colposcopy (18,35). None of the nine studies reported any adverse effects or complications related to the surgical techniques.

Quality assessment of case reports. The CARE guidelines were followed to perform the quality assessment of the case reports (7). A total of 10 case reports were assessed for their quality (9-18). The results are presented in Fig. 3. Approximately 30% of the case reports had a low quality in terms of presentation of demographic information. In total, 55% of the case reports included had low quality regarding the presentation of the patients' history with timeline information. Furthermore, 45% of the case reports were of poor quality in terms of information about differential diagnosis.

Quality assessment with QUADAS-2. The QUADAS-2 tool was used to assess the risk of bias in four domains. The results are presented in Fig. 4. In total, 19 studies were assessed. Of

Table II. Comparison of studies reporting on the use of NBI in patients with endometriosis.

Author (year)	Time period	Location	Type of study	Institutes	Number of subjects	Median age, years	Inclusion criteria	Interventions	System	Outcomes	Conclusion	(Refs.)
Farrugia, <i>et al</i> (2007)	2007	UK, East Kent	Case report	Single univer.	1	NS	Suspected endometriosis	Laparoscopy 0-degree 10-mm with WL&NBI; spectrum, 415 nm; excision of lesions	Olympus Exera II	Identification of smaller lesions of endometriosis	NBI may help distinguish active endometriosis from fibrosis and changes from previous surgery	(11)
Barrueto, <i>et al</i> (2008)	2008	USA, Baltimore	Prospective pilot	Single univer.	21	36	Suspected endometriosis	Laparoscopy 0-degree 10-mm with WL&NBI; spectrum, 415 & 540 nm; excision of lesions	Olympus Exera II	14 patients had lesions identified by NBI, previously not detected by WL. 38 biopsy specimens were taken using NBI; 20 (53%) confirmed endometriosis	NBI may be able to better identify the smaller lesions and excise a maximum number of lesions, thus delaying the recurrence of endometriosis	(26)
Chandakas, <i>et al</i> (2008)	2008	Greece, Athens	Prospective pilot	Multi univer.	95	33.9	Suspected endometriosis	Laparoscopy 0-degree 10-mm with WL&NBI; spectrum, 415 & 540 nm; excision of lesions	Olympus Exera II	Lesions were collected from 95 patients, 82.7% of the endometriotic lesions detected by NBI and 55.9% detected by WL	NBI may detect endometriotic lesions more easily than WL	(27)
Kuroda, <i>et al</i> (2009)	2009	Japan, Tokyo	Prospective pilot	Single univer.	23	35	Suspected endometriosis	Laparoscopy 0-degree 10-mm with WL&NBI; measurement of vascular density (red, black, white) lesions in peritoneal endometriosis with vascular analysis software	Olympus Exera II	23 patients diagnosed with peritoneal endometriosis. Median difference of vascular density by NBI was significantly higher in red lesions (4.5%, P<0.001)	NBI provides an accurate objective evaluation of vascular density, particularly for the red lesions, which are indicative of early-stage endometriosis with angiogenesis	(28)

Table II. Continued.

Author (year)	Time period	Location	Type of study	Institutes	Number of subjects	Median age, years	Inclusion criteria	Interventions	System	Outcomes	Conclusion	(Refs.)
Kuroda, <i>et al</i> (2010)	2008	Japan, Tokyo	Prospective control	Single univer.	73	24-49	Suspected endometriosis	Laparoscopy 0-degree 10-mm with WL&NBI; Patients allocated to 4 groups: i) Endometriosis group with GnRH; ii) Endometriosis group no GnRH; iii) non-endometriosis group with GnRH; iv) non-endometriosis group no GnRH. Assessment of peritoneal vascular density with vascular analysis software and cytokine concentration in peritoneal fluid in 4 groups	Olympus Exera II	Increased vascular density detected by NBI in patients with endometriosis (P<0.01). Increased cytokine levels in patients with endometriosis	NBI may detect early vascular lesions in patients with endometriosis	(33)
Barrueto, <i>et al</i> (2015)	2015	USA, Baltimore	Randomized controlled	Multi univer.	167	30-33.6	Suspected endometriosis	Laparoscopy 0-degree 10-mm. All patients received WL/WL (Control arm) or WL/NBI (Intervention arm). Spectrum, 415 & 540 nm; excision of lesions	Olympus Exera II	255 lesions were detected and confirmed as endometriosis. 255 (100%) were detected by NBI	The contribution of NBI to WL increased the detection of endometriotic lesions	(34)
Gallicchio, <i>et al</i> (2015)	2011-2013	USA, Baltimore	Randomized controlled	Multi univer.	167	30-33.2	Suspected endometriosis	Laparoscopy 0-degree 10-mm. All patients received WL (3:1 ratio) or WL/WL. Pain and quality of life assessment with questionnaire EHP*	Olympus Winter	Pain and quality of life similar in both study groups (WL vs. NBI)	WL and NBI have similar pain and quality of life outcomes	(38)
Murnaghan, <i>et al</i> (2017)	2017	Canada Ottawa	Case report	Single univer.	1	39	Suspected endometriosis	Laparoscopy 0-degree 10-mm with WL/NBI; excision of lesions	Olympus Exera II	Identification of smaller lesions not visible with WL	Contribution of NBI to WL increased the detection of endometriotic lesions	(12)

Table II. Continued.

Author (year)	Time period	Location	Type of study	Institutes	Number of subjects	Median age, years	Inclusion criteria	Interventions	System	Outcomes	Conclusion	(Refs.)
Ma, <i>et al</i> (2019)	2014-2015	Australia, Victoria	Prospective control	Single univer.	57	30	Suspected endometriosis	Laparoscopy 0-degree 5-mm with WL&NBI. Excision of lesions	Olympus Exera II	Total 32 patients with lesions detected by WL. 24 of them were positive for Endometriosis. Assessment of these 24 with NBI led to diagnosis of 6 new positions of endometriosis. Additional predictive value of 86% if a positive diagnosis was made under WL imaging	NBI appears beneficial in identifying new areas of endometriosis that may be missed if endometriosis is suspected by WL. NBI was not beneficial if WL was negative	(29)
Kazama, <i>et al</i> (2019)	2018	Japan, Saitama	Case report	Single univer.	1	44	Pelvic pain Occult fecal blood	Intestinal endoscopy with WL&NBI	NS	Lesions of rectal endometriosis (Dienogest treatment)	NBI may assist in the detection of small lesions in cases of intestinal endometriosis	(13)
Lier, <i>et al</i> (2020)	2016-2017	Netherlands, Amsterdam	Prospective randomized	Single univer.	20	34.5	Endometriosis III-IV (ASRM)	Laparoscopy 0-degree 12-mm with WL, NBI, NIR-ICG and 3D imaging. Excision of lesions	Olympus Exera II	3D increased the sensitivity rate (P=0.0016). Combined 3D and NBI increased the sensitivity rate 91.2% (P<0.001)	3D WL combined with NBI improved the detection rate of peritoneal endometriosis	(30)

NBI, narrow-band imaging; WL, white light; NS, not stated; NIR-ICG, near-infrared imaging with indocyanine green; univ. university; EHP, endometriosis health profile.

Table III. Comparison of studies reporting on the use of NBI in patients with cervical pathology and peritoneal implants.

Author (year)	Time period	Country, city	Type of study	Institute	Number of subjects	Age, years	Inclusion criteria	Interventions	System	Outcomes	Conclusion	(Refs.)
Fujii, <i>et al</i> (2010)	2007-2009	Japan, Tokyo	Prospective pilot	Single univer.	21	36.3	Patients with diagnosis of <i>in situ</i> cervical adenoCA early cervical adenoCA	NBI digital colposcopy; biopsy of lesions and immunochemistry with CD31 antibody; evaluation of vascular pattern	Olympus	Vascular pattern was classified as waste thread-like pattern, dot-like pattern and root-like pattern. Vascular patterns were displayed in 18 (86%) of cases of cervical adenoCA	Digital NBI colposcopy depicts vascular pattern on cervix more clearly than conventional colposcopy, thus diagnosing early disease	(31)
Fanfani, <i>et al</i> (2010)	2010	Italy, Rome	Case report	Single univer.	1	NS	Borderline ovary	Laparoscopy 0-degree 10-mm with WL&NBI. Excision of lesions	Olympus Exera II	Identification of peritoneal implants not clearly visible by WL	NBI in laparoscopy a useful advancement for identifying early preneoplastic and neoplastic lesions and assisting in making intraoperative decisions	(15)
Fanfani, <i>et al</i> (2011)	2011	Italy, Rome	Case report	Single univer.	1	NS	Cervical CA	Laparoscopy 0-degree 10-mm with WL&NBI. Excision of lesions	Olympus Exera II	Identification of peritoneal implants not clearly visible by WL in a case after laparoscopic hysterectomy for cervical CA	NBI may be a useful tool in the detection of early neoplastic peritoneal implants	(16)
Gagliardi, <i>et al</i> (2013)	2013	Italy, Roma	Case report	Single univer.	2	1st 632nd 67	Recurrent Ovarian CA 1 case of FIGO IC and 1 case of FIGO IIIC	Laparoscopy 0-degree 10-mm with WL&NBI	Olympus Winter	Identification and NBI target biopsy of peritoneal implants of recurrent disease	NBI facilitates diagnosis of recurrence of malignant disease	(17)
Nishiyama, <i>et al</i> (2017)	2014-2015	Japan, Kagawa	Prospective pilot	Single univer.	10	39	Patients with squamous cervical pathology LGSIL-cervical CA	Flexible magnifying endoscopy with NBI evaluating microvascular patterns. Colposcopy and biopsy of lesions	Olympus Exera II	Report of NBI-ME microvascular findings as follows: -Presence of dots in 7 (70 %) -Irregular arrangement of dots in 5 (50%) -High-density of dots in 5 (50%) -High vessel caliber in 2 (20%) -New tumor vessel in 1 (10%) -Detection rate, 90% (9/10 patients)	Establishment of a novel microvascular classification system via NBI-ME of cervical lesions	(32)

Table III. Continued.

Author (year)	Time period	Country, city	Type of study	Institute	Number of subjects	Age, years	Inclusion criteria	Interventions	System	Outcomes	Conclusion	(Refs.)
Aloisi, <i>et al</i> (2018)	2011-2014	USA, New York	Prospective Comparative	Single univer.	94	55.5	Patients undergoing laparoscopic surgery for gynecologic CA of all types	Laparoscopy 0-degree 10-mm with WL&NBI	Olympus Exera II	Higher number of peritoneal abnormalities detected by NBI vs. WL (P=0.0239). No scientific significance in the detection of peritoneal metastasis (P=0.18)	NBI provides unique contrast between peritoneum and microvascular patterns. NBI does not provide better detection of peritoneal malignancy than WL	(39)
Uchita, <i>et al</i> (2018)	2016	Japan	Prospective diagnostic	Multi univer.	24	40	Patients underwent colposcopy and NBI of cervix. Patients underwent conisation	NBI with gastroscop	Olympus	NBI revealed 3 abnormal findings: -Light white epithelium -Heavy white epithelium -Atypical intracapillary papillary loop	NBI demonstrated 100% sensitivity, specificity, accuracy, positive predictive value for lesions >CIN-3	(35)
Anko, <i>et al</i> (2019)	2020	Japan, Kanagawa	Case report	Single univer.	1	54	Patient with melanoma of cervix	NBI digital colposcopy	NS	Report of atypical vessels and transparent mucosal surface	NBI colposcopy may be useful in melanoma diagnosis	(14)
Kobara, <i>et al</i> (2020)	2020	Japan, Kagawa	Case report	Multi univer.	2	39, 37	Patients with cervical HGSIL	NBI with gastroscop	Olympus	Detection of atypical lesion not identified by colposcopy	NBI may assist in the diagnosis of HGSIL if not identified by	(18)

NBI, narrow-band imaging; WL, white light; NS, not stated; HGSIL, high-grade squamous intraepithelial lesion; LGSIL, low-grade squamous intraepithelial lesion; CA, carcinoma/cancer; FIGO, International Federation of Gynecology and Obstetrics; univ. university; CIN, cervical intraepithelial neoplasia.

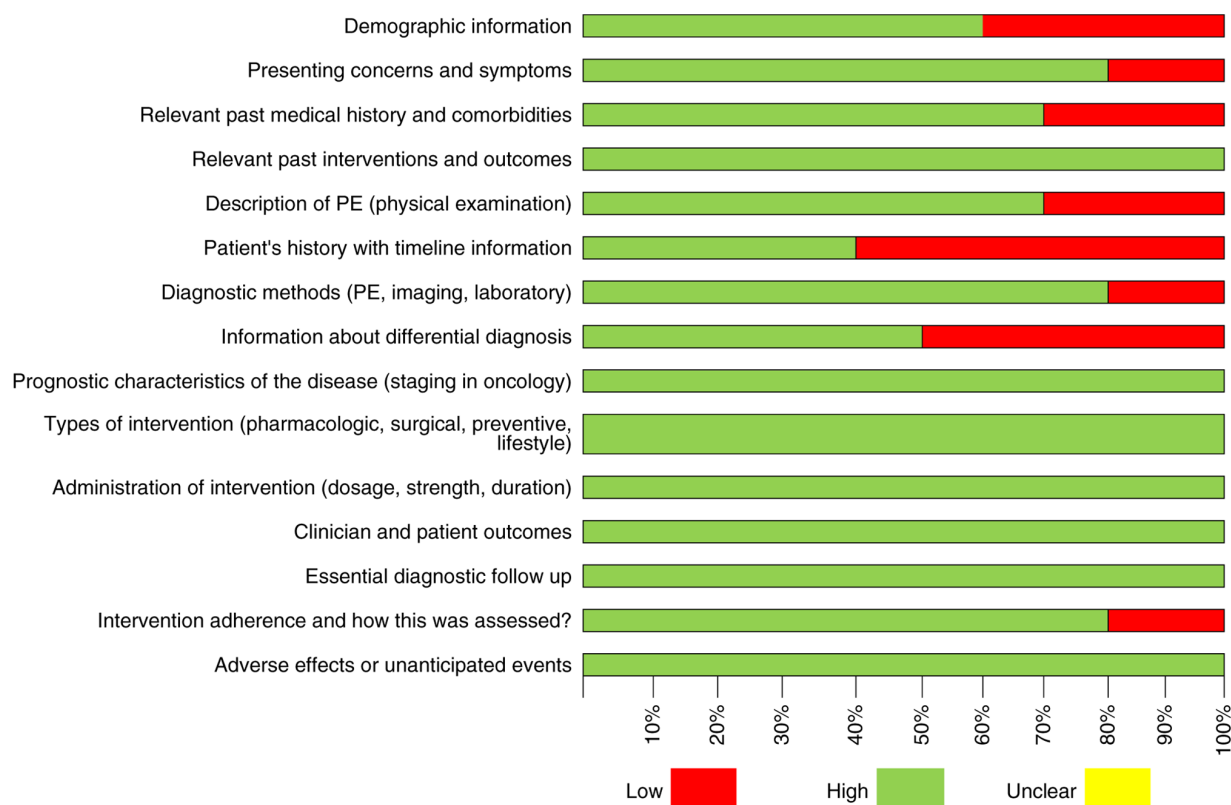


Figure 3. Quality assessment of case reports according to Case Report guidelines. Quality is rated as high, low or unclear.

these, 17 had a prospective design lacking randomization and two were randomized controlled trials with control groups. A total of 9 studies were indicated to have a high risk of bias (24,25,27,29,30-32,34,36) and 10 studies were determined to have a low risk of bias (19-21,23,28,30,32,37-39).

NBI in gynecological endoscopy and special precautions in view of the Coronavirus Disease 2019 (COVID-19) pandemic. The outbreak of the COVID-19 pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has produced a public health emergency of international concern, with all of the data demonstrating that the spread of the virus mainly occurs via respiratory droplets during close contact (41,42). During this ongoing pandemic, recommendations regarding laparoscopy and endoscopy with NBI should follow the general international recommendations for laparoscopy.

However, the potential risk of infection through endoscopically generated bioaerosols may possibly be increased as a result of three important factors pertaining to laparoscopy. These are the following: i) Use of gas insufflation during entry and intra-operatively; ii) generation of bioaerosols via electrosurgery, which is a cornerstone of endoscopy; and iii) the potential for gas leaks in the operation room, which may lead to elevated viral loads in the air (41,42). Precautions should be taken during gynecological endoscopy with NBI, adhering to the international recommendations concerning SARS-CoV-2 (41-43).

Regarding elective surgery, it is recommended that universal testing for SARS-CoV-2 infection is conducted whenever possible within 40 h preceding surgery. Should a case of SARS-CoV-2 be positively confirmed, it is advisable to delay

surgery, although exceptions may be made for urgent cases, e.g. malignancies.

It has been reported that laparoscopies have a larger potential for aerosol spread than hysteroscopies (41-43), while laparotomies have a lower risk of aerosol spread in comparison to laparoscopies (41-43). However, endoscopy is generally preferred due to the one-day stay and the smaller exposure to a hospital environment.

Strict safety measures regarding the pressure of the gas and pressure of the fluid should be applied to minimize the possibility of spread. In cases where local anesthesia may be used, it is expected to be beneficial for the patient, minimizing the risk of infection, which may occur after the intubation and the extubation procedure.

Further guidelines issued by the different medical associations such as International Society for Gynecologic Endoscopy (ISGE; www.isge.org) and American Society of Gynecologic Laparoscopists (AAGL; <https://www.aagl.org/>) (42,43) will provide additional pertinent and vital data during the current fight against the pandemic.

Strengths and limitations. NBI, which is now regularly used in gynecology, is a relatively new optical technology and the present systematic review is, to the best of our knowledge, the most updated and extensive of its kind that has been provided on this method to date. Due to the relatively small number of randomized controlled trials, observational studies were included in spite of providing a lower level of evidence. While precise and clear inclusion criteria were employed for the preparation of the present review, the small sample size of the trials included and the overall absence of definitions of primary

		Risk of Bias				Applicability		
		Patient	Index	Reference	Flow and	Patient	Index	Reference
Study authors	Year	Selection	Test	Standard	Timing	Selection	Test	Standard
Barrueto ²⁶	2008	L	L	L	H	L	L	L
Chandakas ²⁷	2008	U	U	H	H	U	U	H
Kuroda ²⁸	2009	L	L	L	L	L	L	L
Fujii ³¹	2010	L	L	H	L	L	L	L
Cicinelli ¹⁹	2010	L	L	L	L	L	L	L
Surico ⁹	2010	L	L	L	L	L	L	L
Kisu ²¹	2011	L	L	L	L	L	L	L
Kuroda ²²	2011	L	L	L	L	L	L	L
Kisu ²³	2011	L	L	L	L	L	L	L
Tinelli ³⁶	2011	U	L	L	H	U	L	L
Kong ²⁴	2015	L	L	L	H	L	L	H
Gallichio ³⁸	2015	L	L	L	L	L	L	L
Ozturk ²⁴	2016	L	L	L	H	H	L	L
Barrueto ³⁴	2015	U	L	H	L	L	L	L
Nishyama ³²	2017	L	L	L	L	L	L	L
Aloisi ³⁹	2018	L	L	L	L	L	L	L
Ma ²⁹	2019	L	L	H	L	L	L	L
Lier ³⁰	2020	L	L	L	U	L	L	L
Wang ³⁷	2020	L	L	L	L	L	L	L

Low= **L** Unclear= **U** High= **H**

Figure 4. Quality Assessment of Diagnostic Accuracy Studies 2 assessment of studies. Risk of bias is designated as L, H or U. L, low; H, high; U, unclear.

outcomes inevitably reduced the quality of the present review. Furthermore, risk of bias in the flow and timing domains was frequently present. Therefore, it was not possible to perform a pooled data-analysis or meta-analysis. While case reports were included, the majority of these studies were well-designed and mostly provided their evidence clearly and accurately, according to the quality assessment using the CARE (Case report) guidelines.

Discussion

The NBI system for image-enhanced endoscopy was first conceived and developed in May 1999 and the product was launched by Olympus Corporation in May 2006 (21).

The major advantages of the NBI system are the enhancement of endoscopic visualization of superficial neoplastic lesions and their microvascular architecture. Conventional endoscopic diagnosis using WL, by contrast, is based on subtle morphological changes, e.g., superficially elevated, flat or depressed lesions, and on minimal changes in color such as reddish discoloration (19).

The present systematic review demonstrated that the application of NBI in gynecological endoscopy has the

potential to improve the diagnosis of endometriosis. It may also have the potential to enhance the diagnosis of premalignant and malignant lesions in the fields of hysteroscopy, laparoscopy and colposcopy.

While Kisu *et al* (44) performed a review in 2012, the present systematic review is substantially updated and includes quality assessment of the studies according to the QUADAS-2 and the CARE guidelines (6,7).

NBI has proven to be an efficacious approach for the diagnosis of endometrial cancer and hyperplasia, while thorough training improves the trainee's diagnostic skills to an extent depending on their previous hysteroscopic experience (37). However, it must be stressed that NBI laparoscopy was not superior in the detection of peritoneal metastases in comparison with standard WL laparoscopy alone, which was reported by Aloisi *et al* (39) and Schnelldorfer *et al* (45).

A significantly greater number of peritoneal abnormalities were identified with NBI than with standard WL. However, no statistically significant differences were observed in the identification of histologically confirmed metastatic disease. In fact, of the eight additional suspicious-appearing nodules visualized with NBI, only three were confirmed as malignant on final pathology, and none of the patients had surface

malignancies identified with NBI that were not also seen with WL, even if in a different area (39). Aloisi *et al* (39) pointed out that further exploration of the use of NBI/3D WL imaging is required; this will now be further evaluated in a large randomized clinical trial with clinically relevant endpoints, with adequate power, quality control and measures (44). This will be according to the Idea, Development, Exploration, Assessment and Long-term Study (IDEAL) framework, describing 5 stages of evolution for new surgical therapeutic interventions. IDEAL is an important driver for future incremental and evidence-based modifications (46).

Furthermore, another limitation is the extension of the surgical time, particularly in laparoscopic procedures with the use of NBI. Lier *et al* (30) reported a median extension of surgical time of 30 min with NBI due to thorough inspection of the peritoneum and histological sampling. The clinical question is whether an improved detection of endometriosis with NBI/3D imaging also affects the long-term clinical outcomes after surgery, such as reintervention rates, pain-free interval and quality of life (30).

A shortcoming, particularly with the methodology reported by Barrueto *et al* (34), is the low specificity. This may result in unnecessary resection of healthy tissue, producing postoperative neuropathic pain and adhesion formation.

In the study by Surico *et al* (20), only a small number of patients were recruited, while the study was performed at a single academic institution. Furthermore, the accuracy of NBI hysteroscopy in the prediction of histological findings via analysis of interobserver variability was not assessed (20).

Wang *et al* (37) reported that the physician who performs hysteroscopy must be familiar with endometrial lesions, which are influenced by estrogen and progesterone secretion. Endometrial necrosis may not only be observed in malignant lesions, but also frequently appears in benign hyperplastic lesions associated with abnormal uterine bleeding. These factors increase the difficulty of hysteroscopic diagnosis; therefore, the learning curve for the diagnosis of endometrial neoplasms is relatively long. The authors report that >200 hysteroscopic cases are required to be performed by physicians until proficiency is reached (37).

The drawback of NBI colposcopy is that the system is expensive; thus, widespread use of it is limited and is particularly unsuitable for application in developing countries. It may be appropriate to use for educational purposes in cancer center hospitals or university hospitals (31).

In conclusion, conventional WL imaging in gynecological endoscopy is now well-established as a highly sensitive and specific technique for the diagnosis of intrauterine diseases and the present study clearly indicated that the NBI system, when applied by an expert and experienced surgeon, is capable of enhancing diagnostic accuracy. Furthermore, NBI may increase the diagnostic skills of trainees. Future directions of research should take into consideration the reoperation rates, recurrence and overall cost. Evidence-based frameworks such as IDEAL should be implemented in order to improve clinical practice. Certainly, there is a requirement for large-scale, multicenter, randomized trials to substantiate the present results as to the potential for use of NBI in gynecology, the application of which may improve patients' oncological outcomes and thus their quality of life.

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Authors' contributions

All authors contributed equally to the writing and production of this manuscript. PP and KK extracted information, SS, CK, EA, PT and NA interpreted the extracted information and tabulated the data. NV checked the results and approved the study. PP was the main author that formed the conception of the study. EA checked for the eligibility of the studies. All authors read and approved the final manuscript. PP and NV confirm the authenticity of all the raw data.

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Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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