Journal Pre-proof

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PII: S1553-4650(19)31298-1
DOI: https://doi.org/10.1016/j.jmig.2019.11.010
Reference: JMIG 4008

To appear in: *The Journal of Minimally Invasive Gynecology*

Received date: 22 June 2019
Revised date: 1 November 2019
Accepted date: 18 November 2019

Please cite this article as: Sarah MAHEUX-LACROIX MD, PhD , Mathieu BELANGER MD , Lorence PINARD , Madeleine LEMYRE MD , Philippe LABERGE MD , Amélie BOUTIN PhD , Diagnostic accuracy of intra-operative tools for detecting endometriosis: A systematic review and meta-analysis, *The Journal of Minimally Invasive Gynecology* (2019), doi: https://doi.org/10.1016/j.jmig.2019.11.010

Diagnostic accuracy of intra-operative tools for detecting endometriosis: A systematic review and meta-analysis

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Conflicts of Interest

The authors report no conflict of interest.

Acknowledgments

S.M.-L. is the recipient of a Career Award from the Fonds de Recherche Quebec-Sante.

Registration

The study protocol was registered with Prospero (#CRD42019130331).

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Word count

Abstract: 315 words

Main text: 3710 words

Abstract

Objective: To evaluate the diagnostic accuracy of intra-operative laparoscopic imaging tools in reference to histopathology for detecting endometriotic lesions and to compare them to conventional white light inspection by performing a systematic review with meta-analysis.

Data sources: We searched the databases MEDLINE, EMBASE, and CENTRAL as well as citations and reference lists to the end of February 2019.

Methods of Study Selection: Two authors screened 1038 citations for eligibility. We included randomized controlled trials or prospective cohort studies published in English, assessing the accuracy of intra-operative imaging tools for diagnosing endometriosis during laparoscopy. We considered studies using histopathologic evaluation as standard criterion.

Tabulation, Integration, and Results: Seven studies were eligible, representing 472 women and 1717 histopathology specimens, and studied the use of narrow-band imaging (2 studies), 5-aminolevulinic acid induced fluorescence (2 studies), autofluorescence imaging (1 study), indocyanine green (1 study), and three-dimensional robot (1 study). Two authors extracted data and assessed the validity of included studies. Bivariate random-effects models and McNemar's test were used to compare the tests and evaluate sources of heterogeneity. Four studies were attributed a high risk of bias and biopsies of normal-looking peritoneum were not performed to verify the results in three studies; both factors were identified as significant sources of heterogeneity, leading to overestimation of sensitivity and underestimation of specificity of imaging tools. In all studies, additional endometriotic lesions were diagnosed with the enhanced imaging tool

compared to white light alone. In the four studies that appropriately performed control biopsies (171 women, 448 specimens) enhanced imaging techniques were associated with a higher sensitivity and specificity compared to white light (0.84 and 0.89 compared with 0.75 and 0.76, respectively, P=<.001). Adverse events were uncommon (n=5) and reported only with the use of exogeneous photosensitizers. There are no reports of long-term changes in patient-reported outcomes arising from better detection of endometriosis lesions

Conclusion: Studies report that enhanced imaging allows for the detection of additional endometriotic lesions missed by conventional white-light laparoscopy. The benefits of the finding of these additional lesions compared to white light alone on long-term post-operative outcomes is not yet determined and these tools should be considered in a research context only at this time.

Keywords: Imaging tool; laparoscopy; endometriosis; diagnostic accuracy; 5-aminolevulinic acid; autofluorescence imaging; indocyanine green; three dimension; robot; narrow band imaging; white light; peritoneal biopsy; systematic review.

INTRODUCTION

Compared with diagnostic laparoscopy, the surgical treatment of endometriotic lesions decreases pain and improves fertility[1 2]. Unfortunately, recurrence of symptoms and repeat surgery is common, ranging from 5% to 50% depending on the nature of the intervention, studied populations and length of follow-up[3]. One hypothesis for this wide range is that some 'recurrences' are in fact persistent disease incompletely treated during surgery[4]. In fact, histologically confirmed endometriosis may be found in normal-looking peritoneum and missed with conventional white-light inspection at laparoscopy[5].

Intra-operative imaging tools have been proposed in order to improve the detection of endometriotic lesions using special light sources, filters and/or fluorescence to enhance the contrast of vascularized lesions and thickened endometrium[5]. Similar to the benefits observed for the surgical management of some malignancies[6-9], these tools could allow for a more complete surgical treatment of endometriosis and possibly a more efficient and durable effect on women's symptomatology.

The objective of this systematic review was to evaluate the diagnostic accuracy of intra-operative laparoscopic imaging tools in reference to histopathology for detecting endometriotic lesions and to compare them to conventional white light inspection. We also evaluated the safety and tolerability of each modality.

METHODS

Sources

We performed a systematic review with meta-analysis using an *a priori* protocol registered with Prospero (#CRD42019130331). This study was designed and reported according to approaches outlined in the 'Cochrane Handbook for Systematic Reviews of Diagnostic Accuracy'[10] and 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses'[11]. We searched MEDLINE, EMBASE, and CENTRAL from their inception to February 2019. Our search strategy was revised by a healthcare librarian and all authors, and is presented in a web appendix. We also searched the reference lists and citations of included studies and previous reviews to identify any additional eligible studies.

Study selection and data collection

We included all studies assessing the accuracy of intra-operative imaging tools for diagnosing endometriosis during laparoscopy. Only studies referring to histopathological evaluation of excised specimens to verify the results were considered. Randomized controlled trials (RCT) or prospective cohort studies published in English were included in the review. Case-controlled, case-reports and retrospective cohort studies were excluded.

Study selection and data collection were performed independently by two reviewers, screening titles, abstracts, and full text publications when required. If disagreements were not resolved by consensus, a third reviewer was consulted. We collected reasons for full-text exclusion. To avoid duplication in extracted

data, author names, location of studies and dates were compared. We developed a standardized data abstraction form, pilot-tested on three studies and subsequently refined, to collect the following information:

1) Study characteristics and methods (study design, inclusion and exclusion criteria, participant characteristics, flow diagram, country, and language of publication);
2) Description of the technique used for laparoscopic imaging (laparoscope, source of light, medication);
3) Measures of accuracy of imaging tools in reference to histopathology (number of true positives, false positives, true negatives and false negatives per histopathological specimen for each modality).

Assessment of the validity of individual studies

Two reviewers independently assessed the risk of bias and applicability concerns using a checklist derived from the *Quality Assessment of Diagnostic Accuracy Study 2 (QUADAS-2)* tool[12]. In instances of discrepancy, a third reviewer was consulted. Reviewers' judgement about risk of bias and applicability concern was used in sensitivity analyses to examine the effects of the studies' validity.

Statistical analysis and data synthesis

Meta-analyses were performed by pooling the number of true positives, false positives, true negatives and false negatives (table 2x2) of each study in

bivariate hierarchical random-effects models using using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). The results are presented using Cochrane Review Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2014). Pooled and individual estimates of sensitivity, specificity and 95% confidence intervals (CI) are presented in paired forest plots and point estimates for each study in a summary receiver operating characteristic (SROC) plot.

Comparison of enhanced imaging tools and white light, as well as subgroup and sensitivity analyses, were achieved using bivariate models or McNemar's test when only one study was involved. We planned a priori subgroup analysis to examine the effect of the different techniques used and validity of the included studies. P-values of subgroup analyses were calculated by computing change in the -2Log likelihood when the covariate was added to the model using the chi-squared statistic[10]. A value of $p<0.05$ was considered statistically significant.

RESULTS

We identified 1038 citations with 26 studies further considered after screening titles and abstracts (Fig. 1). A total of seven studies[13-19] were included in the systematic review and meta-analyses, representing 472 women and 1672 histopathological specimens. Table 1 summarises the characteristics of the included studies. Studies were published in peer-reviewed journals between

2000 and 2019 and conducted in women with suspected endometriosis, pelvic pain and/or infertility. The prevalence of endometriosis varied from 73% to 100% across studies, and two studies excluded women without endometriosis from analyses[16 19].

In all studies, the peritoneum was first inspected with conventional white-light laparoscopy and then by the enhanced imaging tool. Suspected lesions of endometriosis were identified and documented at each stage followed by excision and histopathological evaluation. None of the studies reported performing the enhanced imaging tool while blinded to the white light evaluation, but assessors were blinded to the reference standard (histopathology) results in all cases. A total of four studies[13 16 17 19] were attributed a global high risk of bias (Fig.2). Three studies[13 17 19] were attributed a high risk of bias about the reference standard as biopsy of normal-looking peritoneum were not performed, leading to an overestimation of sensitivity and underestimation of specificity (false negative and true negative not being appropriately assessed) as pointed out in our subgroup analysis (Table 2). The other four studies[14-16 18] were attributed an unclear risk of bias, as we could not fully assess to what extent endometriotic lesions could have been found in unbiopsied tissue of the pelvis. Forest plots and SROC plot for included studies are presented in Fig.3.

Narrow-band imaging (NBI)

In two studies (203 women, 553 specimens)[13 17], high definition NBI was found to have a higher sensitivity and lower specificity than white light for detecting endometriosis with pooled sensitivity of 1.00 (95% CI 0.99-1.00) and specificity of 2% (95% CI 2%-4%) compared to 0.82 (95% CI 0.77-0.86; p<0.001) and 0.35 (95% CI 0.29-0.41, p<0.001), respectively. Both studies were attributed a high risk of bias with no biopsies of normal-looking peritoneum. No adverse events were reported.

5-Aminolevulinic acid (5-ALA) induced fluorescence

In two studies (61 women, 190 specimens)[15 18], 5-ALA induced fluorescence was found to have a higher sensitivity and specificity than white light for detecting endometriosis with pooled sensitivity of 0.77 (95% CI 0.68-0.85) and specificity of 0.81 (95% CI 0.71-0.89) compared to 0.73 (95% CI 0.64-0.81, p<0.001) and 0.62 (95% CI 0.50-0.72, p<0.001), respectively. Biopsies of normal-looking peritoneum were performed in both studies but one study excluded pigmented lesions from analysis as they did not show fluorescence but were visible on white light[15]. Between 20 and 30mg/kg of 5-ALA was administered orally (dissolved in apple juice) 5 to 14 hours prior to surgery and participants were told to avoid sunlight for 24 hours. Two cases of nausea and two cases of facial erythema (exposure to sunlight) occurred in the 61 women studied.

Autofluorescence imaging (AFI)

In one study (83 women, 115 specimens)[14], AFI was found to have a higher sensitivity and specificity than white light for detecting endometriosis with pooled

sensitivity of 0.92 (95% CI 0.80-0.98) and specificity of 0.85 (95% CI 0.74-0.92) compared to 0.65 (95% CI 0.50-0.78, p<0.001) and 0.68 (95% CI 0.56-0.79, p<0.001), respectively. Biopsies of normal-looking peritoneum were performed in this study and no adverse events were reported.

Indocyanine green (ICG)

In one study (27 women, 216 specimens)[16], ICG imaging was found to have a lower sensitivity and higher specificity than white light for detecting endometriosis with pooled sensitivity of 0.82 (95% CI 0.74-0.89) and specificity of 0.97 (95% CI 0.92-0.99) compared to 0.86 (95% CI 0.78-0.92, p<0.001) and 0.95 (95% CI 0.89-0.98, p<0.001), respectively. Despite the lower sensitivity observed with ICG, 16 of the 111 endometriotic lesions diagnosed at histopathology were identified with ICG but not with white light. Also, 20 lesions were only identified with white light. Women with adnexal endometriosis were excluded from this study because of the lack of fluorescence of the ovaries and physiological hypervascularization and diffuse fluorescence of the tubes. Biopsies of normal-looking peritoneum were performed. A dose of 0.25 mg/kg of ICG was administered intravenously 5 to 30 minutes prior to surgery and no allergic reactions were noted. One complication was reported, which was a bleeding of colorectal anastomosis on post-operative day 1 managed with intravenous tranexamic acid.

Three-dimensional robotic laparoscopy (3D robot)

In one study (98 women, 598 specimens)[19], 3D high definition robotic laparoscopy was found to have a higher sensitivity and lower specificity than two-dimensional high definition laparoscopy for detecting endometriosis with pooled sensitivity of 1.00 (95% CI 0.99-1.00) and specificity of 0.01 (95% CI 0.00-0.03) compared to 0.78 (95% CI 0.73-0.82, p<0.001) and 0.19 (95% CI 0.23-0.88, p<0.001), respectively. No biopsies of normal-looking peritoneum were taken (high risk of bias). Women with obliterated cul-de-sac were excluded from this study. No adverse events were reported.

Finally, no studies assessing coloration of peritoneum using methylene blue or indigo carmine fulfilled our selection criteria.

Subgroup and sensitivity analyses

As observed on the summary ROC plot (Fig.3), there was substantial heterogeneity between study results. In a subgroup analysis (table 2), the three studies using high definition scopes were associated with a higher sensitivity and lower specificity both with enhanced and white light imaging. However, these studies were also the three in which biopsies of normal-looking peritoneum were not performed. Sensitivity analyses showed that studies with a high risk of bias and in which no biopsies of normal-looking peritoneum were performed were associated with significantly different results with higher sensitivity and lower specificity compared to those with an unclear risk of bias and control biopsies. Overall, estimates of sensitivity and specificity of white light imaging for

detecting endometriosis, pooling the results of the four studies[14-16 18] that appropriately performed control biopsies, was of 0.75 and 0.76, respectively.

DISCUSSION

Based on the results of this review, white-light laparoscopy has a sensitivity of 75% for diagnosing endometriotic lesions, meaning that a quarter of lesions were missed in these studies. Enhanced imaging techniques may improve the detection of endometriotic lesions - all of them allowing for identification and treatment of additional endometriotic lesions compared to white light alone, preventing missed diagnosis in some cases[13 14 16]. Missed lesions at conventional white-light laparoscopy may be responsible for persistence or recurrence of symptoms after surgery and long-term cohort studies using conventional white light surgery only have reported that a more complete surgical resection is associated with better fertility[20] and pain outcomes[21 22]. It is important to note however, that there are few data that demonstrate the superiority of enhanced imaging tools to prevent symptom recurrence, even with increased detection of lesions. Only one RCT of 167 women compares patient outcomes in this setting, and no differences were observed in pain and quality of pain scores at 3 and 6 months after surgical treatment for lesions detected with NBI or white light only[23]. It is essential that the clinical context be considered and the impact on patient outcomes be more thoroughly assessed. Such comparative studies must include longer-term outcomes (pain relief, quality of

life, fertility, reoperation) than 6-months, as recurrence of endometriosis is commonly reported later than six months after surgery[4].

Sensitivities as high as 100% were reported with enhanced imaging tools from studies where no control peritoneal biopsies were taken, preventing any false-negative calculation. With such controlled sampling, the highest sensitivity was 92%, highlighting that enhanced imaging techniques still miss some lesions. Analogous to the treatment of malignancy, the presence of occult microscopic satellite lesions supports wide excision of endometriotic peritoneum and may explain why excision was superior to ablation at pain reduction in a systematic review of three RCTs[24]. The true benefit of these tools may be distinguishing endometriotic lesions from non-endometriotic tissue, which may decrease the risk associated with removing healthy tissue close to the bowel, ureters, bladder, vessels and nerves.

Limitations of these tools is that they seem to perform differently according to the type and localization of disease - pigmented lesions identified with 5-ALA and AFI[15 18], deep-infiltrating endometriosis with AFI[14], endometriomas with AFI and ICG[14 16]and lesions of the fallopian tubes with ICG. NBI, 5-ALA, AFI and 3-D robotic laparoscopy were described as being mostly useful in the detection of superficial lesions[13-15 17-19]. Taken as a group, different techniques appear to be useful in different types of endometriosis expression, yet an individual woman may present with multiple expressions of disease and to utilise these different tools in succession at the same surgery is unlikely to be tenable. In some of the

included studies, some lesions were only identified with white light[15 16], highlighting that white light laparoscopy remains the basis of endometriosis surgery. These technologies all add cost in terms of equipment and some such as 5-ALA and ICG require exogenous photosensitizers that may lead to additional side effect and inconvenience since 5-ALA is administered orally a few hours before the surgery, requiring additional planning and surveillance[13 16 17].

The main limitation of this review is the quality of included studies and histology as a reference standard. Although widely recognized as the criterion standard, there is a reported lack of agreement between pathologists[18] in regards to histopathological diagnosis of endometriosis. Not taking biopsies of normal-looking peritoneum may have led to overestimation of sensitivity and underestimation of specificity, and even where control biopsies were taken, deeper lesions and lesions of unbiopsied peritoneum could have been missed, resulting in biased estimations[25]. We noted substantial heterogeneity between studies due to the number of biopsies taken; the standardization of histopathologic evaluation; inclusion of all stages of disease and all types of endometriotic lesions. Furthermore, our analyses did not consider within-individual correlation, which could have biased the estimates if individual factors influence the accuracy of the imaging techniques. Finally, the use of hormonal suppression therapy by women was not reported in included studies and prevented us from exploring its effect on the performance of intra-operative diagnostic tools.

In conclusion, studies suggest endometriotic lesions may be missed up to 25% of the time using white light surgery, with the addition of different imaging tools decreasing this to a missed lesion rate of 8%. What the impact of these lesions is in terms of patient reported outcomes is essential to understand before making any conclusions. Given the results from this review and meta-analysis, we recommend that these tools should only be used in a research setting before recommending the use of such tools for the surgical treatment of endometriosis given an increase in costs and possible side effects compared to white-light laparoscopy alone.

FIGURE LEGENDS

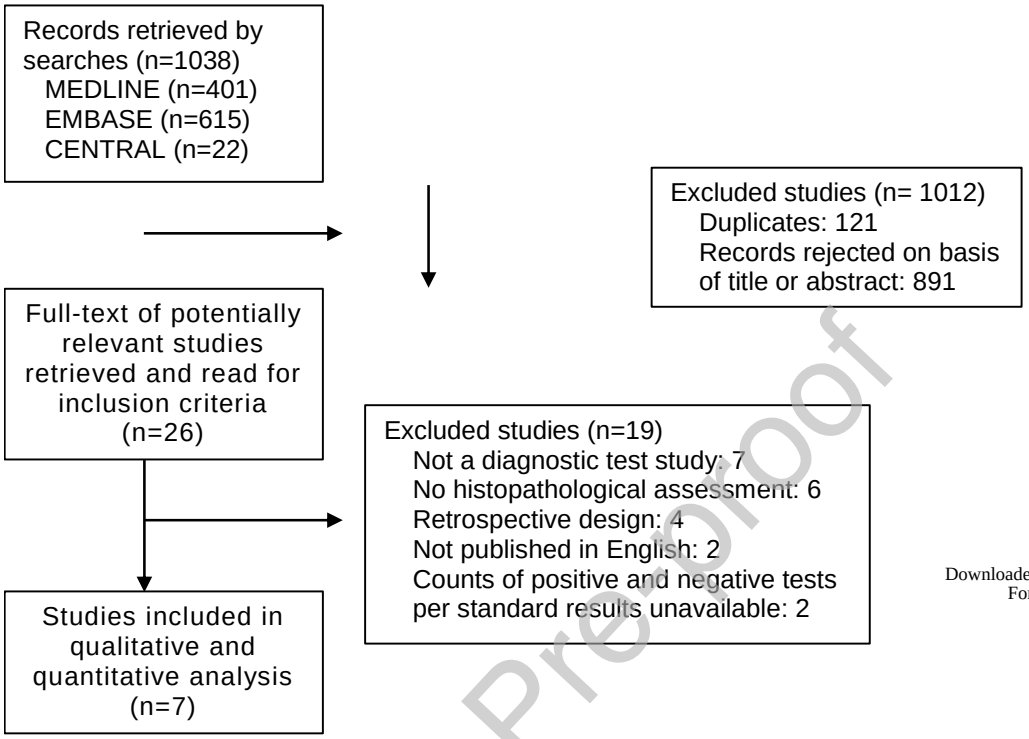


Figure 1. Flowchart of search results

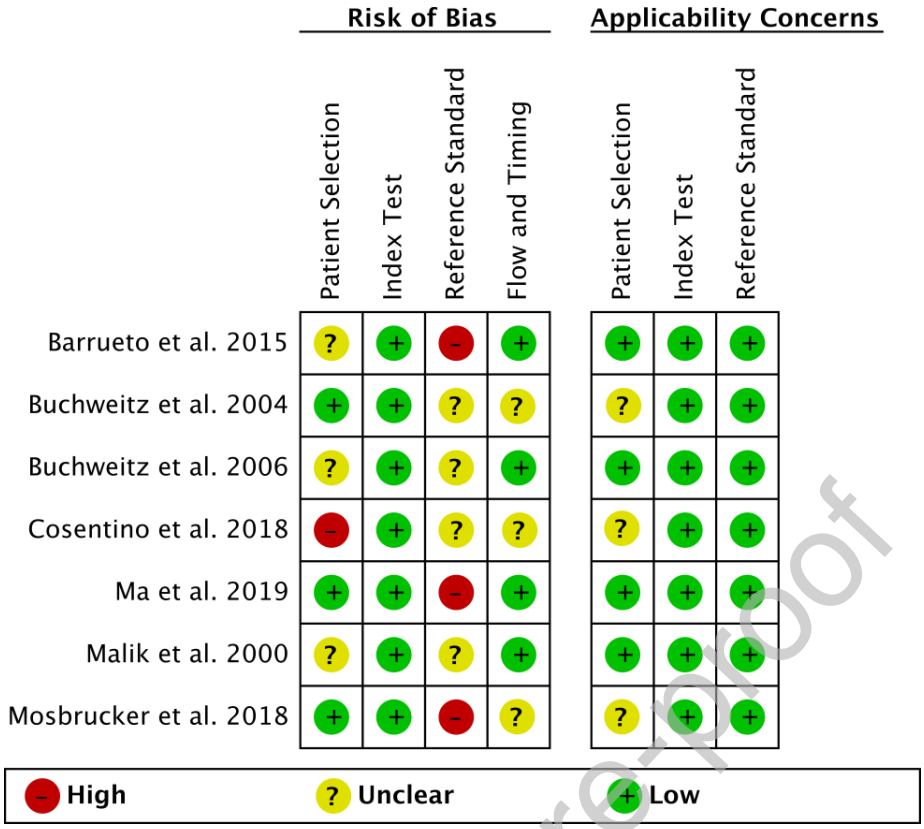


Figure 2. Risk of bias and applicability concerns of included studies based on QUADAS-2

Study

White Light	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Barrueto et al. 2015	202	123	54	74	0.79 [0.73, 0.84]	0.38 [0.31, 0.45]
Buchweitz et al. 2004	14	19	9	36	0.61 [0.39, 0.80]	0.65 [0.51, 0.78]
Buchweitz et al. 2006	32	21	17	45	0.65 [0.50, 0.78]	0.68 [0.56, 0.79]
Cosentino et al. 2018	95	5	16	100	0.86 [0.78, 0.92]	0.95 [0.89, 0.98]
Ma et al. 2019	62	27	6	5	0.91 [0.82, 0.97]	0.16 [0.05, 0.33]
Malik et al. 2000	66	12	20	14	0.77 [0.66, 0.85]	0.54 [0.33, 0.73]
Mosbrucker et al. 2018	272	202	77	47	0.78 [0.73, 0.82]	0.19 [0.14, 0.24]
Total	**743**	**409**	**168**	**352**	**0.80 [0.72, 0.89]**	**0.55 [0.23, 0.88]**

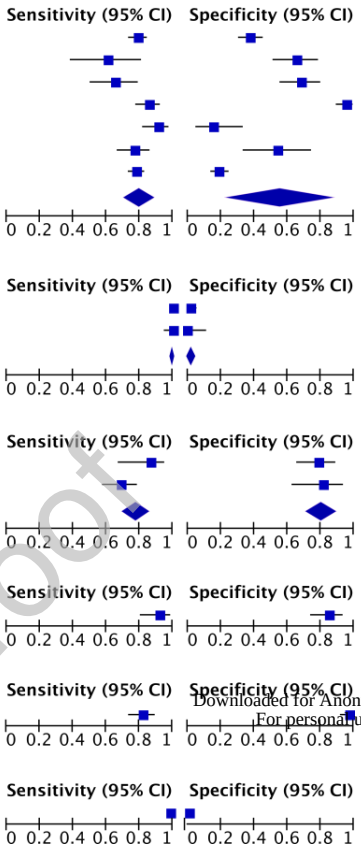
NBI	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Barrueto et al. 2015	256	193	0	4	1.00 [0.99, 1.00]	0.02 [0.01, 0.05]
Ma et al. 2019	68	32	0	0	1.00 [0.95, 1.00]	0.00 [0.00, 0.11]
Total	**324**	**225**	**0**	**4**	**1.00 [0.99, 1.00]**	**0.02 [0.00, 0.04]**

5-ALA	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Buchweitz et al. 2004	21	11	2	44	0.91 [0.72, 0.99]	0.80 [0.67, 0.90]
Malik et al. 2000	61	5	22	24	0.73 [0.63, 0.83]	0.83 [0.64, 0.94]
Total	**82**	**16**	**24**	**68**	**0.77 [0.68, 0.85]**	**0.81 [0.71, 0.89]**

AFI	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Buchweitz et al. 2006	45	10	4	56	0.92 [0.80, 0.98]	0.85 [0.74, 0.92]

ICG	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cosentino et al. 2018	91	3	20	102	0.82 [0.74, 0.89]	0.97 [0.92, 0.99]

3D Robot	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Mosbrucker et al. 2018	349	246	0	3	1.00 [0.99, 1.00]	0.01 [0.00, 0.03]



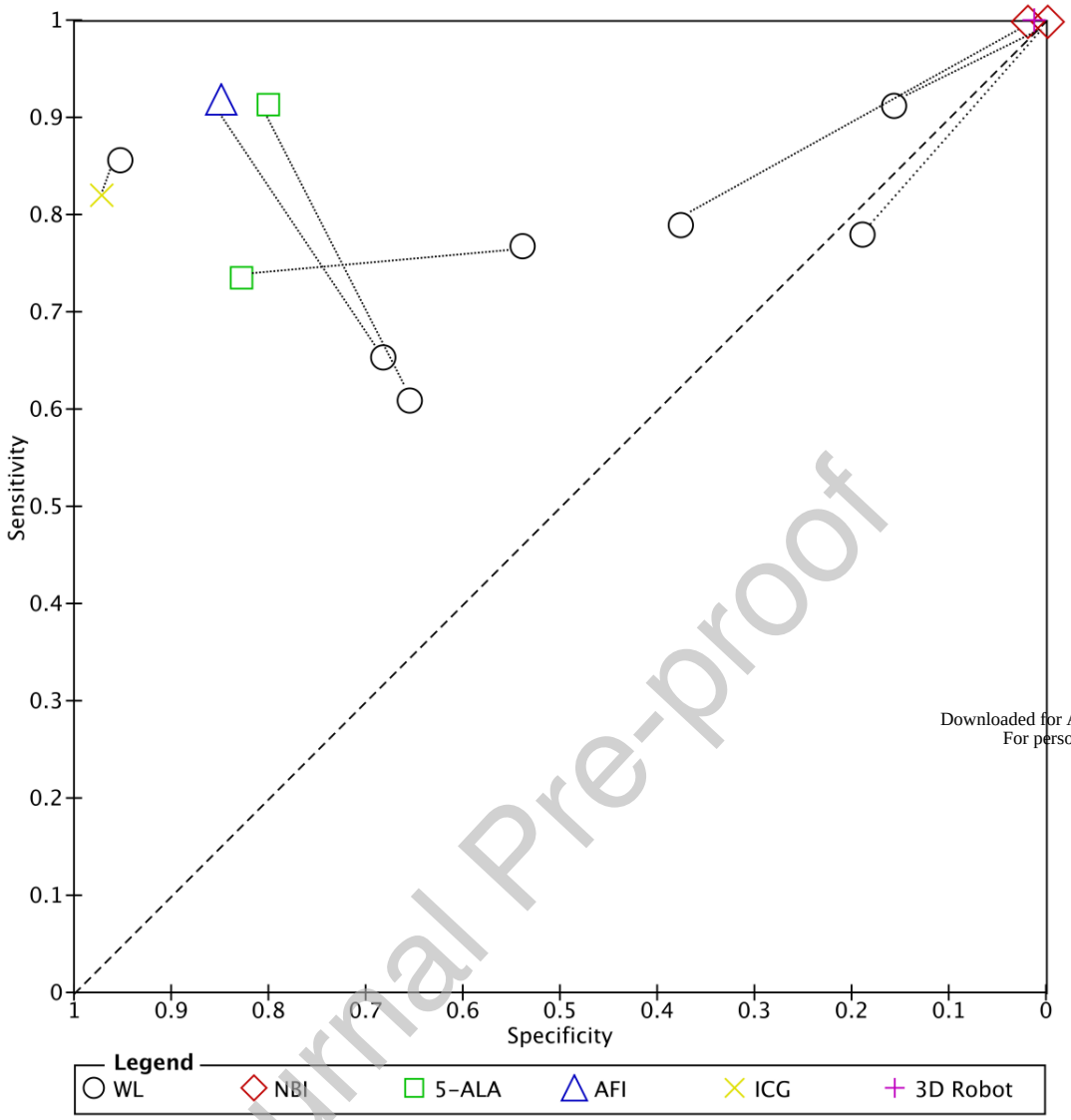


Figure 3. Forest plot (A) and summary ROC plot (B) from direct comparison of white light and ehanced imaging tools for diagnosing endometriotic lesions

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Table 1. Characteristics of included studies

Study	Technique	Design	Laparoscope	No. of women	No. of lesions	Population	Age (y)	Prevalence of endometriosis	Control biopsy*
Barrueto et al. 2015	NBI vs WL	RCT	EXERA II HD Olympus	150	453	Pelvic pain, suspected endometriosis and/or infertility	31 ± 7.2	73%	No
Buchweitz et al. 2004	5-ALA vs WL	PCS	D-LIGHT Storz	24	78	Suspected endometriosis	31 ± 4.5	79%	Yes
Buchweitz et al. 2006	AFI vs WL	PCS	D-LIGHT Storz	83	160	Suspected endometriosis	33 ± 5.4	88%	Yes
Cosentino et al. 2018	ICG vs WL	PCS	ICG imaging Olympus	27	216	Symptomatic endometriosis	37 ± 5.5	100%	Yes
Ma et al. 2019	NBI vs WL	PCS	EXERA II HD Olympus	53	100	Pelvic pain	30	55%	No
Malik et al. 2000	5-ALA vs WL	PCS	D-LIGHT Storz	37	112	Suspected endometriosis	—	86%	Yes
Mosbrucker et al. 2017	3D robot vs 2D WL	RCT	HD da Vinci Surgical	98	598	Symptomatic endometriosis	31	100%	No
Total				**472**	**1717**				

2D: two dimension; *3D*: three dimension; *5-ALA:* 5-aminolevulinc acid; *AFI*: autofluorescence imaging*; ICG:* Indocyanine Green; *NBI:* Narrow Band Imaging; *PCS:* prospective cohort study; *WL:* White Light

Data are presented as mean ± standard deviation (range).
* Biopsies of normal-looking peritoneum

Table 2. Subgroup and sensitivity analyses for enhanced imaging compared to white light

			Enhanced imaging[1]			White light		
Variables	Number of studies	Number of specimens	SE	SP	p	SE	SP	p
High definition								
Yes	3	1151	1.00	0.01	<0.001	0.85	0.28	0.006
No	4	448	0.84	0.89		0.75	0.75	
Control biopsy[2]	4	448	0.84	0.89	<0.001	0.75	0.76	0.006
Yes	3	1151	1.00	0.01		0.85	0.28	
No								
Risk of bias								
Low/Unclear	3	262	0.86	0.84	<0.001	0.70	0.63	0.029
High	4	1357	0.99	0.03		0.85	0.49	

SE: Sensitivity, SP: Specificity

1. Pooling results for narrow-band imaging, 5-aminolevulinic acid induced fluorescence, autofluorescence imaging, indocyanine green and three-dimensional robot

2.Biopsies of normal-looking peritoneum