Novel Imaging Technologies in Laparoscopic Gynecologic Surgery: A Systematic Review

Novel imaging technologies continued to be introduced into the operative setting. In particular, novel image-enhanced laparoscopic techniques are being explored for use in gynecologic operations. This systematic review describes these technologies in four relevant areas of gynecologic surgery. The PubMed database was searched for human, English-language studies, and the reference lists of retrieved articles were reviewed. An analysis of pooled data from 34 studies that met inclusion criteria was performed. The results suggest that image-enhanced technology may be useful in several common gynecologic procedures. Auto- and drug-enhanced fluorescence laparoscopy allow for increased detection of nonpigmented endometriotic lesions. Using these technologies for peritoneal staging of ovarian malignancy is of uncertain benefit. Drug-enhanced fluorescence laparoscopy for sentinel lymph node (SLN) detection in patients with uterine or cervical malignancy is feasible, showing a high rate of SLN detection, but a low sensitivity of identifying metastases. Finally, their use in intra-operative visualization of the ureter is promising. The majority of available data was from feasibility studies with limited sample sizes. Nevertheless, the results described in this systematic review support the expectation that these upcoming image-enhanced laparoscopy techniques will play a more important role in the future care of gynecologic patients. [DOI: 10.1115/1.4038360]

Introduction

The development and use of new imaging techniques have generated novel applications for the intra-operative detection of gynecologic pathologies. These new techniques generally employ optical modalities other than white light to improve the visualization of various diseases at the time of laparoscopy [1]. Clinically, there is a great need for these technologies due to the difficulty of visualizing many diseases through simple gross inspection. These technologies carry the potential to enhance visualization of diseases otherwise too small to detect, better delineate the extent of gross visible disease, and delineate anatomy in an operative field distorted by underlying pathology.

Despite the growing number of publications addressing image-enhanced laparoscopy, none of these techniques are yet considered standard of care. Nevertheless, these publications are generally thought to provide promising results, and enhanced imaging is likely to become an integral part of the future practice of gynecology. This systematic review analyzes the findings of studies that have examined image-enhanced laparoscopic techniques in the four areas of gynecologic surgery where these techniques have most frequently been tested: identification of peritoneal endometriosis, staging of ovarian epithelial carcinoma, detection of sentinel lymph nodes (SLN) in endometrial and cervical cancers, and visualization of the ureter.

Methods

Systematic Literature Search. The PubMed electronic database (National Library of Medicine, Bethesda, MD) was searched for publications describing studies that examined image-enhanced laparoscopic procedures in four areas of gynecologic surgery: detecting occult peritoneal endometriosis, peritoneal staging of ovarian carcinoma, sentinel lymph node detection in endometrial and cervical cancers, and visual identification of the ureter. The last search was performed on Feb. 24, 2017. The following search terms were used: “fluorescence” or “spectral” or “narrow band” in combination with: “laparoscopic” or “laparoscopy” or “robot assisted” or “robotic” and also in combination with: “ovarian” or “endometriosis” or (“sentinel lymph node” and “endometrial”) or “ureter” to identify relevant publications. A publication was considered for inclusion if it provided original data from a study examining an image-enhanced laparoscopic technique in one of the aforementioned areas of gynecologic surgery. The search was limited to English language publications and only studies with human subjects were included. This systematic review was conducted in accordance with the preferred reporting items for systematic review and meta-analyses guidelines.

Data Collection. A total of 98 publications were identified from PubMed (Fig. 1). Of those, 74 publications were excluded as non-English language publications (n = 2), studies with nonhuman subjects (n = 16), unrelated to gynecologic laparoscopic imaging/topic of this review (n = 37), abstract only or study with insufficient data (n = 8), or review articles without primary data.
An additional ten publications were added from the references of included publications for a total of 34 studies meeting inclusion criteria [2–35]. Two investigators independently performed the systematic literature search. These publications mostly utilized narrow band imaging (NBI) and fluorescence imaging; described in more detail later.

**Narrow Band Imaging.** Narrow band imaging, a form of spectral imaging, captures the light reflected from tissue when illuminated with light in the blue and green regions of the visible spectrum. Hemoglobin has maximal light absorption at these specific wavelength bands, and any blood vessels exposed to this light will appear dark, providing a negative contrast to the surroundings [1]. This results in enhanced visualization of superficial blood vessels and, to a lesser extent, the peritoneal architecture.

**Fluorescence Imaging.** Fluorescence imaging visualizes fluorescent light emitted from tissue after illumination with a specific light wavelength or wavelength range. Tissues are most commonly illuminated with blue or near-infrared (NIR) light, which excite fluorophores present in the tissue, resulting in the emission of light of a longer wavelength, i.e., fluorescence. Since fluorescence is usually fairly subtle, reflected light is commonly filtered out leaving an image of mostly fluorescent light only. Fluorescence imaging can be subdivided into autofluorescence imaging and vector-enhanced fluorescence imaging. In autofluorescence imaging, a signal is recorded from the fluorophores naturally present in the tissues, thereby exposing existing differences in biochemical tissue composition. Vector-enhanced fluorescence imaging utilizes an externally administered fluorophore/drug, which accumulates in the target tissue, or a fluorophore linked to certain carriers such as viruses or antibodies [1].

**Statistical Methods.** Pooled results were described as percentages. For combined analysis, each study was weighted according to sample size. For statistical testing, the Fisher’s exact test and McNemar’s chi-square test (for paired data) was used exclusively, reporting two-tailed p values. β values were calculated with a set x value of 0.05. Due to the limited number of articles meeting inclusion criteria, an assessment of the methodological quality analysis or the heterogeneity of the patient cohorts was not performed. The review rather focused on the feasibility of these novel and innovative approaches.

### Results

**Detecting Occult Peritoneal Endometriosis.** Autofluorescence imaging, using blue light autofluorescence laparoscopy, has been tested for the detection of endometriotic lesions in two human studies. Demco [2] performed a feasibility study of 25 women with suspected endometriosis. During autofluorescence laparoscopy, endometrial implants were seen as areas of reduced fluorescence compared to healthy surrounding tissue. This study did not report the rate of detection of endometriosis compared to white light laparoscopy; although additional lesions were detected and the extent of some lesions was better assessed using the autofluorescence imaging technique. A subsequent feasibility study by Buchweitz et al. [3] tested this technique in a cohort of 83 women with clinical symptoms suspicious for endometriosis. All patients underwent laparoscopic evaluation with white light followed by blue light autofluorescence laparoscopy. Of the 83 patients, 73 were found to have biopsy-proven endometriosis. Autofluorescence imaging detected lesions invisible to white light in 16 patients (22%), which were all thought to be nonpigmented lesions. Overall sensitivity increased from 67% to 100% (p < 0.001, β = 1.00) when adding autofluorescence to the laparoscopic procedure (Table 1).

Fig. 1 Selection of articles for inclusion in systematic review
Additional, otherwise occult, lesions (Table 1). Hillemanns et al. [6] recruited 15 women with suspected endometriosis who underwent fluorescence imaging at the time of laparoscopy. Similarly, no fluorescence was seen in pigmented lesions. However, no sensitivity results were reported in this feasibility study and the overall dose of 5-ALA administered was fairly low. Levey [7] published a case report of a patient with endometriosis in whom indocyanine green (ICG) was administered and visualized with NIR imaging successfully identifying occult disease.

Narrow band imaging has also been evaluated for the detection of peritoneal endometriosis in two feasibility trials. Barrueto and Audlin [8] evaluated 21 patients with suspected endometriosis. When comparing NBI to traditional white light laparoscopy, the study showed increased detection rates with NBI. Specifically, endometriotic lesions were only visualized through NBI in four patients; and in 14 patients additional endometriotic lesions were detected through NBI (Fig. 2). However, when Kuroda et al. [9] evaluated 23 patients with endometriosis using NBI laparoscopy, the authors found no difference in the visualized vascular density between NBI and white light imaging. There was also no difference in vascular density upon subgroup analysis evaluating pigmented and nonpigmented lesions. The rate of detected lesions was not provided. The authors did note that NBI appeared to better visualize the extent of lesions. A subsequent trial by Barrueto et al. [10] included 150 patients with suspected endometriosis who were randomized to white light followed by NBI laparoscopy (study group, n = 112) versus white light laparoscopy (control, n = 38). The study group identified 81 patients whose biopsy confirmed endometriosis. In four out of those 81 patients, the endometriosis lesions were only detectable through NBI, while in the remainder of patients endometriosis lesions were equally visualized with both modalities (sensitivity 95% versus 100%, p = 0.125). A follow-up study examining the quality of life of the prior described clinical trial showed no significant difference between the study group and control group in regards to pain reduction and quality of life improvement after the operation [11].

Table 1 Pooled data comparing sensitivity of identifying endometriotic lesions with white light versus fluorescence laparoscopy

<table>
<thead>
<tr>
<th>Image enhanced laparoscopy technique [Reference]</th>
<th>Pigmented lesions</th>
<th>Nonpigmented lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White light</td>
<td>Image-enhanced</td>
</tr>
<tr>
<td>Autofluorescence imaging [3]a</td>
<td>25/25 (100%)</td>
<td>25/25 (100%)</td>
</tr>
<tr>
<td>5-ALA-enhanced fluorescence imaging [4,5]b</td>
<td>36/36 (100%)</td>
<td>0/36 (0%)</td>
</tr>
<tr>
<td>ICG-enhanced near-infrared imaging [7]b</td>
<td>4/4 (100%)</td>
<td>4/4 (100%)</td>
</tr>
</tbody>
</table>

aComparing white light versus white light plus autofluorescence (n = number of patients).
bComparing white light versus autofluorescence (n = number of lesions).

Fig. 2 Endometriotic lesion on uterine fundus and adnexa seen under white light (a) and NBI (b); with permission from Ref. [8]

A total of 14 studies, including three pairs of studies with duplicate patients [16–29], have examined the use of ICG-enhanced NIR fluorescence imaging for the detection of SLN in patients with endometrial and cervical cancers. These studies report on 832 patients who underwent ICG-enhanced NIR fluorescence laparoscopy. The pooled data are shown in Table 2 and excluded patients who underwent an additional different SLN mapping technique at the time of operation, unless the results were stratified according to the technique used. On pooled data

Detection of Sentinel Lymph Nodes in Endometrial and Cervical Cancers. A total of 14 studies, including three pairs of studies with duplicate patients [16–29], have examined the use of ICG-enhanced NIR fluorescence imaging for the detection of SLN in patients with endometrial and cervical cancers. These studies report on 832 patients who underwent ICG-enhanced NIR fluorescence laparoscopy. The pooled data are shown in Table 2 and excluded patients who underwent an additional different SLN mapping technique at the time of operation, unless the results were stratified according to the technique used. On pooled data posit that the NBI system has unique value as a technique that increases the specificity, and therefore predictive value, of lesions identified during laparoscopic procedures.
analysis ICG-enhanced NIR fluorescence laparoscopy was able to identify a sentinel lymph node in 94% of patients (Fig. 3). The total average number of SLNs retrieved could not be determined precisely due to different statistical methods used in each study, but the approximate average was between 2 and 4 SLNs per patient. In 82% of patients, bilateral SLNs were identified. It is expected that almost all patients had at least one pelvic SLN, but most studies did not clarify this finding. Para-aortic SLNs were found in about 23% of patients. The sensitivity of identifying patients with lymph node metastases using this technique was only about 80%. The specificity, as expected, was 100%, since patients without lymph node metastases by definition will also have negative SLNs.

In regards to determining the optimal injection site for the visualization of SLNs using ICG-enhanced NIR fluorescence imaging, Rossi et al. [25] recruited patients with endometrial cancer who received cervical injections of 1 mg of ICG (n = 17) versus hysteroscopic endometrial injections of 0.5 mg ICG (n = 12). SLNs were detected in 82% (n = 17) and 33% (n = 12, p = 0.018, β = 0.98) of patients, respectively. There was no difference in the detection rate of bilateral SLNs (57% (n = 14) versus 50% (n = 4), p = 1.000, β = 0.06) and para-aortic SLNs (71% (n = 14) versus 75% (n = 4), p = 1.000, β = 0.05).

Four studies [16,17,23,24] compared fluorescence imaging to colorimetric imaging using isosulfan blue (ISB) dye for SLN detection. Three of these studies compared both methods separately and found no significant difference in detection rate (ICG 97% (n = 268) versus ISB 94% (n = 215), p = 0.190, β = 0.83 [17,23,24]. The other study compared ICG to a combination of ICG plus ISB and also found no significant difference in detection rate (ICG 95% (n = 197) versus ICG plus ISB 93% (n = 30), p = 0.643, β = 0.10) [16]; suggesting that ICG is not significantly superior to ISB for detection of SLN.

**Visualization of the Ureters.** In three studies [30–32], image-enhanced identification of the ureters was conducted in human subjects taking advantage of the properties of methylene blue as a moderate strength fluorophore that can be visualized through NIR fluorescence imaging. A combined 30 patients who underwent gynecologic and colorectal operations received intravenous administration of methylene blue. In 24 of 30 patients (80%), the target of either one or both ureters (depending on the type of operation performed) was clearly identified using methylene blue-enhanced NIR fluorescence imaging typically within 10 min of dye injection (Fig. 4). Visualization typically persisted up to 1 h. While some of the results of nonvisualization were felt to be due to under-dosing of methylene blue, other concerns are described for this method. One of the studies [31] reported that the fluorescence signal was only picked up after the ureter had been visible in the conventional white light mode. This is consistent with the finding that even with a greater dye dose the average signal-to-background ratios were only around 2:1 and 5:1. In addition, a limitation of one of the studies [30] involved the dissection and exposure of the ureter prior to dye injection. It is expected that true visualization within an intact retroperitoneum would likely be more limited. Furthermore, there is a concern that intravenous methylene blue potentially can interfere with pulse oximetry monitoring during an operation.

Three studies [33–35], including one pair of studies with duplicate patients, using drug-enhanced NIR fluorescence imaging, recruited a combined 35 patients scheduled to undergo robotic-assisted laparoscopic sacrocolpopexy or ureteroureterostomy. Patients were injected intra-ureterally with ICG and visualization of the ureters occurred via NIR fluorescence imaging.

**Table 2** Pooled data evaluating detection rates of sentinel lymph node mapping with fluorescence laparoscopy alone in patients with endometrial and cervical cancers; overlapping studies from the same institution are pooled together avoiding duplicate patient reporting

<table>
<thead>
<tr>
<th>Study</th>
<th>N/A</th>
<th>N/A</th>
<th>N/A</th>
<th>N/A</th>
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<th>N/A</th>
<th>N/A</th>
<th>N/A</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jewel et al. [16]</td>
<td>188/197 (95%)</td>
<td>N/A</td>
<td>N/A</td>
<td>156/188 (83%)</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
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<tr>
<td>Papadia et al. [17,18]</td>
<td>189/195 (97%)</td>
<td>N/A</td>
<td>N/A</td>
<td>164/195 (84%)</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Paley et al. [19]</td>
<td>119/123 (97%)</td>
<td>N/A</td>
<td>N/A</td>
<td>99/123 (80%)</td>
<td>9/9 (100%)</td>
<td>76/76 (100%)</td>
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<td>Hagen et al. [20]</td>
<td>104/108 (96%)</td>
<td>104/104 (100%)</td>
<td>1/104 (1%)</td>
<td>84/108 (78%)</td>
<td>12/13 (92%)</td>
<td>N/A</td>
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<tr>
<td>Martinelli and coworkers [21,22]</td>
<td>51/57 (89%)</td>
<td>51/51 (100%)</td>
<td>24/51 (47%)</td>
<td>38/51 (75%)</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Sinno et al. [23]</td>
<td>34/38 (89%)</td>
<td>N/A</td>
<td>N/A</td>
<td>30/34 (88%)</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Holloway et al. [24]</td>
<td>35/55 (100%)</td>
<td>N/A</td>
<td>2/25 (6%)</td>
<td>34/35 (97%)</td>
<td>9/10 (90%)</td>
<td>25/25 (100%)</td>
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<tr>
<td>Rossi et al. [25]</td>
<td>18/29 (62%)</td>
<td>16/18 (89%)</td>
<td>13/18 (72%)</td>
<td>10/18 (56%)</td>
<td>1/4 (25%)</td>
<td>14/14 (100%)</td>
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<tr>
<td>Rossi et al. [26]</td>
<td>17/20 (85%)</td>
<td>17/17 (100%)</td>
<td>13/17 (76%)</td>
<td>12/17 (71%)</td>
<td>1/2 (50%)</td>
<td>15/15 (100%)</td>
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<tr>
<td>Schaafsma et al. [27,28]</td>
<td>14/18 (78%)</td>
<td>N/A</td>
<td>N/A</td>
<td>11/14 (79%)</td>
<td>3/6 (50%)</td>
<td>12/12 (100%)</td>
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<tr>
<td>Furukawa et al. [29]</td>
<td>10/12 (83%)</td>
<td>10/10 (100%)</td>
<td>0/10 (0%)</td>
<td>10/10 (100%)</td>
<td>2/2 (100%)</td>
<td>8/8 (100%)</td>
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<tr>
<td>Total</td>
<td>779/832 (94%)</td>
<td>198/200 (99%)</td>
<td>53/235 (23%)</td>
<td>648/793 (82%)</td>
<td>37/46 (80%)</td>
<td>150/150 (100%)</td>
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</table>

*a Likelihood of detecting lymph node (LN) metastases by SLN mapping only using data when standard lymphadenectomy was also performed; N/A—not available.
Identification of the ureters occurred for all patients. Both studies using this technique observed that a primary benefit is the clear delineation of the ureters during laparoscopic surgery. However, with ICG the dye has to be injected directly into the ureter compared to the intravenous injection with methylene blue, which fundamentally limits this technique for common use.

Discussion

Currently, none of the imaging-enhanced laparoscopic techniques available have yet been proven to be universally effective for use in the diagnosis and/or treatment of gynecologic diseases. Early results suggest that these techniques improve visualization of certain diseases, and as more information becomes available about their utility and benefits, these techniques will likely play a large role in the future of gynecologic surgery.

In the studies examining the detection of occult peritoneal endometriosis, fluorescence imaging was more commonly studied than narrow-band imaging. Among those that examined fluorescence imaging, it remains unclear whether one particular technique has greater sensitivity than any other. These studies all suggest that drug-enhanced, specifically 5-ALA-enhanced, fluorescence imaging can increase sensitivity in detecting nonpigmented endometriosis lesions otherwise difficult to visualize with white light laparoscopy alone. On the other hand, 5-ALA-enhanced fluorescence imaging was unsuccessful in detecting pigmented lesions, suggesting that a combined approach using white light and fluorescence imaging might be ideal. The potential benefit for drug-enhanced fluorescence imaging is critical, since the identification of small and nonpigmented lesions, which are most likely to be missed during standard diagnostic laparoscopy, contribute to recurrence of disease following surgery [36]. Although NBI is designed to enhance visualization of neovascularization and therefore potentially reveal endometriotic lesions through negative contrast enhancement, early results are controversial and question whether this method is any better than routine white light imaging.

The data reporting on image-enhanced laparoscopy for the staging of ovarian epithelial carcinoma are scarce, limiting any significant conclusions. Though neither fluorescence nor NBI provided conclusive results, there remains promise for the use of these applications. Further research examining these techniques as well as other potential imaging techniques is, however, necessary to determine which technique most effectively improves the visualization of the disease and accuracy of staging.

The use of fluorescence imaging in the detection of sentinel lymph nodes in women with endometrial or cervical cancer is becoming more widely practiced [37]. This novel method was formally included as an appropriate technique in the 2014 National Comprehensive Cancer Network Endometrial Cancer Guidelines. The most recent studies have utilized cervical injections of ICG followed by NIR imaging and have shown that this technique has good detection rates for identifying SLNs. Biopsying sentinel nodes and using their status to guide further removal of nodes has numerous benefits for patients through limiting the extent of nodal removal and thereby avoiding full pelvic and para-aortic lymphadenectomy in many patients. Though 18% of patients have only one sentinel lymph node identified with this method, current clinical use requires bilateral pelvic mapping for adequate surgical staging with performance of full pelvic lymphadenectomy when either the left or right sentinel node is not identified. Of importance, while the detection rates for identifying SLNs is good, it seems that the sensitivity of detecting lymph node metastases is low, and therefore, the technique probably should be limited to low-risk patients.

Only six studies have reported the use of image-enhanced laparoscopy in human subjects for identification of the ureter. These studies used different techniques of fluorescence imaging (methylene blue and ICG); yet both techniques have great limitations. Methylene blue only provides a relatively weak fluorescence signal resulting in low sensitivity. The need to inject ICG directly into the ureter, which obviously occurs after the ureter already has been identified, clearly limits its clinical use. Nevertheless, visualization of ureteral injury during surgery enables immediate repair,
and aids in both the preservation of renal function and reduction in morbidity [38]; making these techniques valuable. Further research directly examining the identification of the ureter is still necessary to determine whether an enhanced imaging technique is beneficial.

Conclusion

The majority of image-enhanced laparoscopic studies were feasibility studies and therefore, as expected, lack the power to determine true sensitivity. Excluding the studies on sentinel lymph nodes, the β values ranged from 0.60 to 1.00 (i.e., power of 0–40%) demonstrating that even with the combined analysis sample sizes were generally not sufficient to make reliable conclusions. Therefore, there is a true need for larger clinical trials following up on these feasibility trials. In the four areas of gynecologic surgery included in this review, fluorescence imaging in particular is becoming more commonly practiced and researched. Despite this trend, more research is still necessary before any of the techniques included here can be considered as a component of the standard of care. Once implemented, these technologies have the potential to significantly improve patient care by providing the surgeon with additional information needed to provide the best available care.

References