

*Robotic surgery vs laparoscopic surgery in patients with diagnosis of endometriosis: a systematic review and meta-analysis*

**Stefano Restaino, Liliana Mereu, Angelo Finelli, Maria Roberta Spina, Giulia Marini, Ursula Catena, Luigi Carlo Turco, et al.**

**Journal of Robotic Surgery**

ISSN 1863-2483

J Robotic Surg

DOI 10.1007/s11701-020-01061-y



**Your article is protected by copyright and all rights are held exclusively by Springer-Verlag London Ltd., part of Springer Nature. This e-offprint is for personal use only and shall not be self-archived in electronic repositories. If you wish to self-archive your article, please use the accepted manuscript version for posting on your own website. You may further deposit the accepted manuscript version in any repository, provided it is only made publicly available 12 months after official publication or later and provided acknowledgement is given to the original source of publication and a link is inserted to the published article on Springer's website. The link must be accompanied by the following text: "The final publication is available at [link.springer.com](http://link.springer.com)".**



# Robotic surgery vs laparoscopic surgery in patients with diagnosis of endometriosis: a systematic review and meta-analysis

Stefano Restaino<sup>1,9</sup> · Liliana Mereu<sup>2</sup> · Angelo Finelli<sup>3</sup> · Maria Roberta Spina<sup>3</sup> · Giulia Marini<sup>3</sup> · Ursula Catena<sup>1</sup> · Luigi Carlo Turco<sup>4</sup> · Rossana Moroni<sup>5,6</sup> · Michela Milani<sup>3</sup> · Vito Cela<sup>7</sup> · Giovanni Scambia<sup>1,8</sup> · Francesco Fanfani<sup>1,8</sup>

Received: 18 November 2019 / Accepted: 29 February 2020  
© Springer-Verlag London Ltd., part of Springer Nature 2020

## Abstract

Endometriosis is one of the most common medical conditions affecting the women. The study aimed to evaluate the safety and efficacy of robotic-assisted laparoscopic surgery (RAS) versus conventional laparoscopic surgery (LPS) in the treatment of endometriosis. PubMed, Embase, Cochrane and CINAHL databases were searched from January 1995 to March 2019. According to meta-analysis criteria, five comparative studies were selected. A total of 1527 patients were identified. In the meta-analysis, there were no significant differences in blood loss, complication, and hospital stay between RAS and LPS surgeries in the treatment of patients with endometriosis. However, RAS surgery required a higher weighted mean operating time than LPS surgery, 0.54 (95% confidence interval; 0.37 to 0.70;  $p < 0.00001$ ) min. This meta-analysis confirmed that the robotic surgery is safe and feasible in patients affected by endometriosis. We could suggest that RAS is a valid option and might be considered an alternative to LPS especially in advanced cases.

**Keywords** Robotic surgery · Laparoscopic surgery · Endometriosis

## Introduction

Endometriosis is defined as the presence of endometrial glands and stroma outside the uterine cavity, predominantly, but not exclusively, in the pelvic compartment. It is an oestrogen-dependent chronic inflammatory condition that affects women in their reproductive period and is associated with pelvic pain and infertility [1]. Endometriosis occurs in 6–10% of women of reproductive age, with a prevalence

of 38% (range, 20–50%) in infertile women and in 71–87% of women with chronic pelvic pain [2]. This disease can be asymptomatic or associated with several symptoms such as dysmenorrhea, chronic pelvic pain, dyspareunia, infertility, as well as cyclic urinary and intestinal symptoms according to the location of the disease [3].

For many years, diagnostic laparoscopy with pathological confirmation has been considered to be the gold standard for the diagnosis of endometriosis. However, in symptomatic

✉ Stefano Restaino  
restaino.stefano@gmail.com

<sup>1</sup> Fondazione Policlinico Universitario A. Gemelli IRCCS, UOC di Ginecologia Oncologica, Dipartimento per la Tutela della Salute della Donna e della Vita Nascente, L.go A. Gemelli, 00167 Rome, Italy

<sup>2</sup> Department of Obstetrics and Gynecology, Santa Chiara Hospital, Largo Medaglie d'Oro 9, 38121 Trento, Italy

<sup>3</sup> Department of Medicine and Aging Sciences University "G. d'Annunzio" of Chieti-Pescara, Via dei Vestini 131, 66100 Chieti, CH, Italy

<sup>4</sup> Division of Gynecologic Oncology, Fondazione di ricerca e cura Giovanni Paolo II, Catholic University of Sacred Heart, Campobasso, CB, Italy

<sup>5</sup> Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

<sup>6</sup> Biostatistico Presso Direzione Scientifica, Rome, Italy

<sup>7</sup> Department of Obstetrics and Gynecology, University of Pisa, Pisa, Italy

<sup>8</sup> Università Cattolica del Sacro Cuore, Rome, Italy

<sup>9</sup> Division of Gynecological Oncology, Department of Obstetric and Gynecology, Fondazione Policlinico Universitario A. Gemelli IRCCS, L.go A. Gemelli, 00167 Rome, RM, Italy

women, noninvasive diagnosis with methods such as transvaginal ultrasound (TVUS) with or without bowel preparation and magnetic resonance imaging (MRI) have been gaining a greater role in the diagnosis of endometriosis outside of surgery [2–6].

Endometriosis is classified as superficial (or peritoneal), ovarian (endometrioma), and deep (defined as infiltrating lesions greater than 5 mm in depth) [7, 8]. Deep infiltrating endometriosis (DIE) are nodules that extend deep into the peritoneal surface (> 5mm) and often occur in the uterosacral ligaments, pouch of Douglas, vagina, bowel, bladder, and ureter [9, 10].

Treatment recommendations are generally based according to symptoms, response to medical treatment, and fertility status [3]. Many studies agree that surgical resection of DIE improves pain and quality of life [2–4]. There are no specific guidelines from any society regarding the indication and surgical approach for bladder and bowel DIE. The general recommendation by ACOG, ESHRE, and SOGC for the definitive treatment of pain associated with DIE is still hysterectomy with or without bilateral salpingo-oophorectomy in women with no desire for future fertility, associated intractable pelvic pain, adnexal masses, or multiple previous conservative surgical procedures. In women who desire future fertility, conservative surgical treatment sparing the uterus and adnexa should be offered [2–4]. Limited data are available on reproductive outcomes after treatment of DIE [3].

During the last decades, laparoscopic surgery (LPS) has been accepted as the technique of choice for the treatment of endometriosis, because it provides long-term outcomes comparable to those achieved by laparotomy (LPT), with the established advantages of a minimally invasive technique (MIS), including better visualization, shorter hospital stays, faster recovery and better cosmetic results [7].

More recently, robotic-assisted laparoscopic surgery (RAS) has become available [11]. Proponents argue that increased dexterity, depth perception, and wrist articulation compared with conventional laparoscopy may result in improved outcomes for endometriosis [12].

The aim of this review and meta-analysis is to compare RAS versus LPS in the treatment of endometriosis in terms of operative time, blood loss, intra- and post-operative complication, as well as length of hospital stay.

## Materials and methods

### Search strategy

A systematic literature review was performed using electronic database (PubMed, Embase, Cochrane and CINAHL). All English-language publication comparing RAS versus

LPS surgery in patients affected by endometriosis from January 1995 to March 2019 have been identified. The following key words were used in the search: “robotic surgery” AND “laparoscopy surgery” AND “endometriosis”. Moreover, the related articles offered by database were explored to broaden the search and all abstracts, studies and citations were reviewed. Finally, a manual search for relevant studies was also carried out to identify studies for possible inclusion as a supplement.

### Data extraction

The data were extracted by two researchers (A.F. and M.R.S.) independently for each eligible study comparing RAS versus LPS. Any disagreements were resolved by a third reviewer (S.R.), until a consensus was reached. Full-text copies of those papers were obtained and the same reviewers independently extracted relevant data regarding study characteristics. If more than one study was published on the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations. PRISMA guidelines were followed [13, 14]. Five studies were selected according to the criteria based on the following three items: comparability of RAS and LPS groups, patient selection and exposure. Assessment of the comparability of the study includes the evaluation of the comparability of cohorts based on the design or analysis. Finally, the ascertainment of the outcome of interest includes the evaluation of the type of the assessment of the outcome of interest, length and adequacy of follow-up.

The primary outcome measures including operative time, blood loss, operative complications, and the length of hospitalization. The secondary outcomes included the costs and the learning curve.

### Inclusion criteria

All the selected studies in the meta-analysis adhered to the following inclusion criteria: comparison of outcomes of RAS with LPS in patients affected by endometriosis; evaluation of operative time, blood loss, intra- and post-operative complication, length of hospital stay; patients' medical parameter (age, BMI, endometriosis stage); and cost.

### Exclusion criteria

Only full-text articles were considered eligible for inclusion. The exclusion criteria for this meta-analysis were as follows: review, letters, editorials, case reports; studies not published in English; report only LPS or only RAS; and studies not providing clear outcomes or patients parameters.

## Statistical analysis

The meta-analysis was performed using Revman 5.3 (Review Manager version 5.3). The statistical package of the software was used to analyse the risk ratios (RRs) for dichotomous variable and weighted mean differences (WMDs) for continuous variables. Heterogeneity was evaluated by  $F$  and  $I^2$ . We considered heterogeneity to be present if the  $I^2$  statistic was  $> 50\%$  and the threshold of significance was considered at  $p < 0.05$ . A random effect model was used to compute the pooled data analysis.

## Results

### Study characteristics and study selection

Three hundred and eighty-two articles were identified, 27 were assessed with respect to their eligibility for inclusion (Fig. 1) and five studies were included in the systematic review (Fig. 1) [15–20]. Five studies were retrospective and one was a randomized controlled trial (RCT). A total of 1527 patients were identified: 676 in the RAS group and 851 in

the LPS group. All studies involved RAS versus LPS for the treatment of endometriosis. The first author and year of publication, patient parameters (age, body mass index and endometriosis stage) and study design are summarized in Table 1.

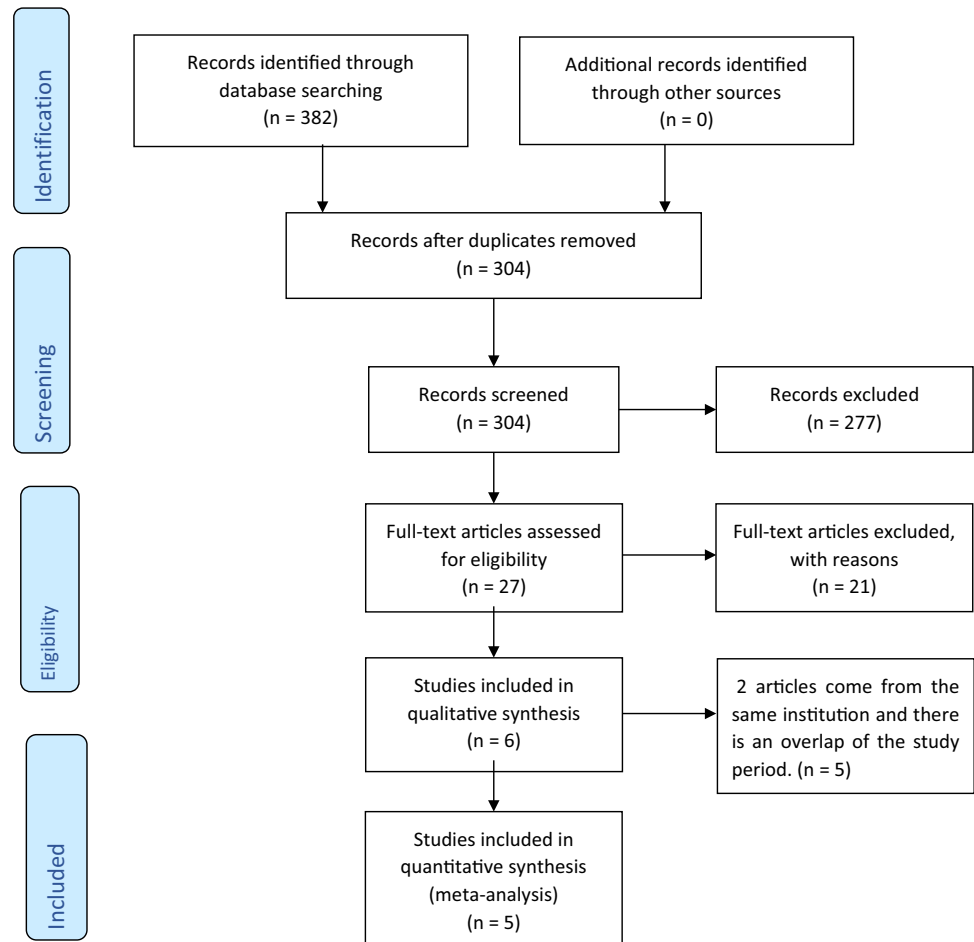
### Synthesis of the results

Four studies assessed the operative time of the two surgical procedures. The weighted mean difference (WMD) of 0.54 (95% confidence interval (CI), 0.37 to 0.70;  $p < 0.00001$ ) min shows that the patients in the RAS group have a longer operative time than those of the laparoscopic group, despite having eliminated the docking time (Fig. 2).

All studies analysed the length of hospitalization in both RAS and LPS groups, but it was not comparable. The pooled estimate showed a WMD of 0.12 (95%CI – 0.05 to 0.29;  $p = 0.17$ ) and it indicated no significant difference between RAS and LPS. The  $I^2$  was 78%, which suggested high statistical heterogeneity (Fig. 3).

With regard to intra- and post-operative complication, conversion rates and blood loss, five studies indicated no significant difference between RAS and LPS (Figs. 4, 5, 6, 7).

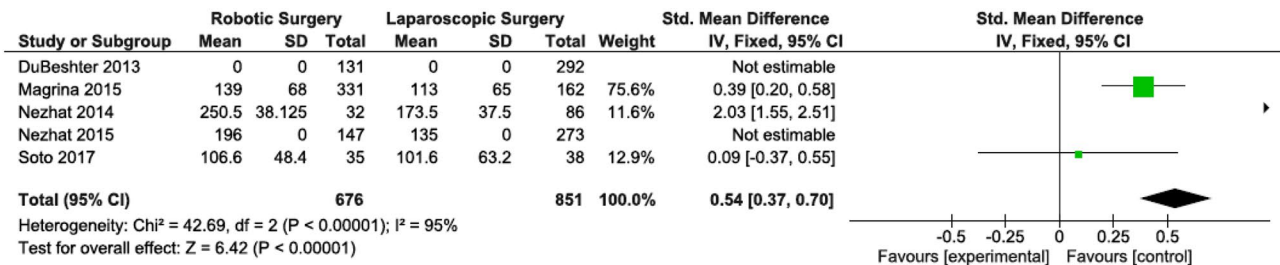
**Fig. 1** PRISMA 2009 flow diagram



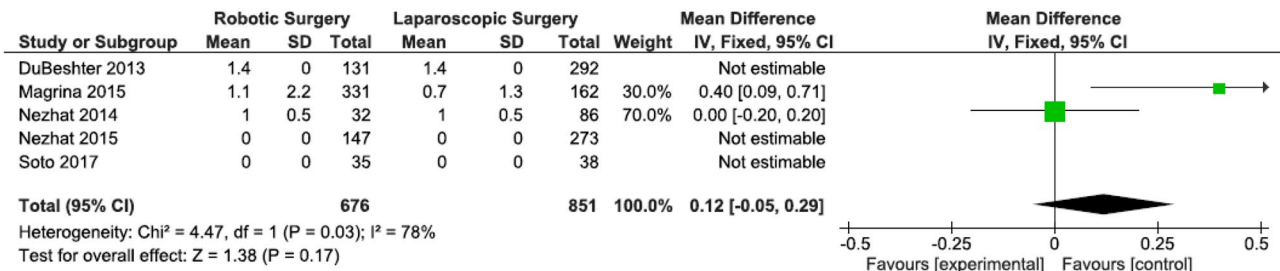


**Table 1** Characteristics of the studies

Author	Year	Study type	Group	Sample size (n)	Age (years ± SD)	BMI	Stage (n)
DuBeshter	2013	Retrospective	RAS	131	44.2	N.A.	N.A.
			LPS	292	41.8		
Magrina	2015	Retrospective	RAS	331	40 ± 10.1	26.1 ± 5.9	III/IV
			LPS	162	38.3 ± 10.7	25.5 ± 5.7	III/IV
Nezhat	2014	Retrospective	RAS	32	42.5 ± 2.2	27.36 ± 2.5	III/IV
			LPS	86	40 ± 4.5	24.53 ± 1.2	III/IV
Nezhat	2015	Retrospective	RAS	147	30 ± 2.5	23 ± 3.2	III/IV
			LPS	273	31 ± 5.7	23 ± 2.5	III/IV
Soto	2017	RTC	RAS	35	34.3 ± 7.2	26.1 ± 5.2	I/II:19 III/IV:10
			LPS	38	34.5 ± 8.5	24.8 ± 5.9	I/II:9 III/IV:14



**Fig. 2** Forest plot for operative time comparing RAS with LPS



**Fig. 3** Forest plot for the length of hospitalization comparing RAS with LPS

The costs and the learning curve were not clearly indicated in all studies. Therefore, it is not possible to make a comparison. In different studies, the common conclusion regarding the costs is that a longer operative time has been correlated with increased costs.

## Discussion

Minimal invasive surgery is considered the gold standard for endometriosis. In this century, the introduction of robotic-assisted laparoscopy has been introduced in several gynaecologic diseases, especially in malignant conditions. More

recently, some authors claimed for the use of RAS also in endometriosis [21, 22].

A meta-analysis on the role of RAS in deep endometriosis already exists [23], but this is the first paper performed on patients with all stages of endometriosis. Moreover, this work could be considered an update of Chen's meta-analysis, because we have included four more articles than the previous one. According to Chen's paper, we found a non-inferiority of robotic surgery compared to laparoscopic surgery. Additionally, our results in this meta-analysis showed that the RAS required a longer mean operating time than LPS, with no significant differences between the two groups in blood loss, complications and hospital stay.

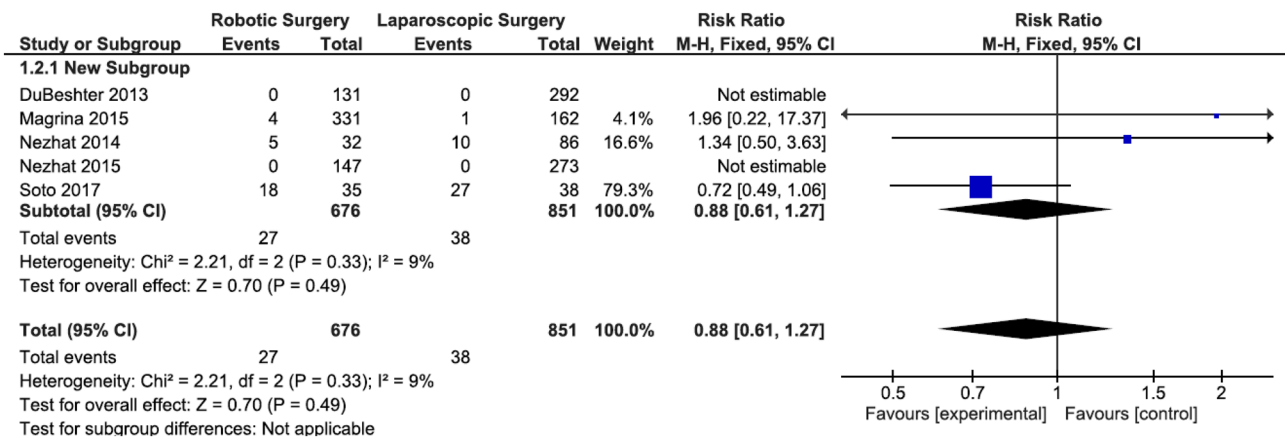


Fig. 4 Forest plot for post-operative complication comparing RAS with LPS

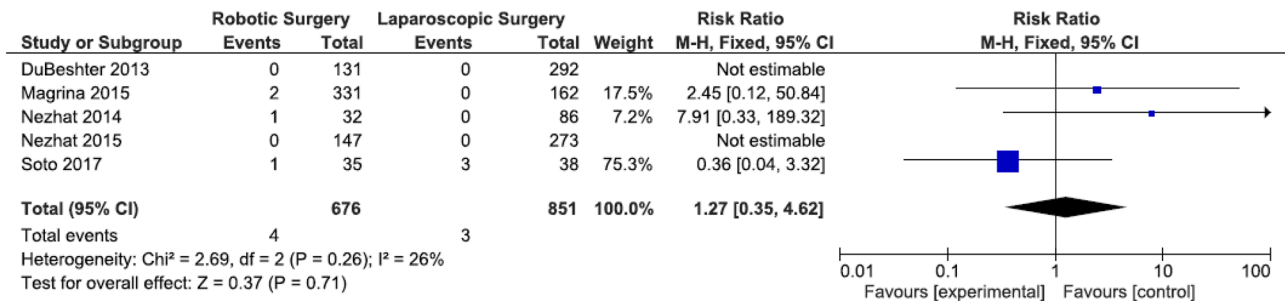


Fig. 5 Forest plot for intra-operative complication comparing RAS with LPS

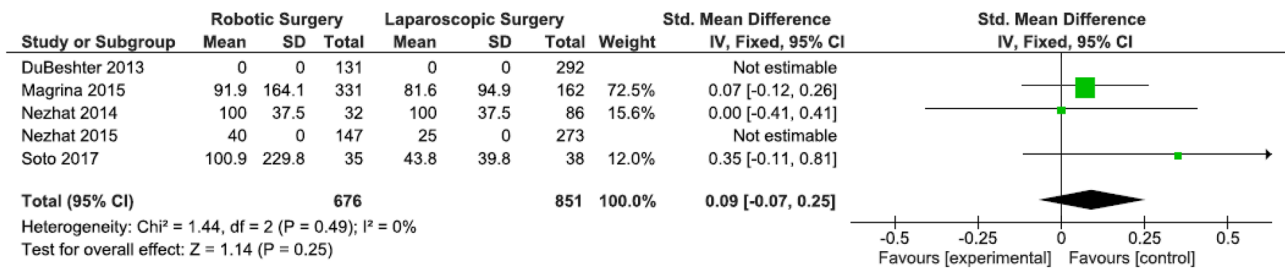


Fig. 6 Forest plot for blood loss comparing RAS with LPS

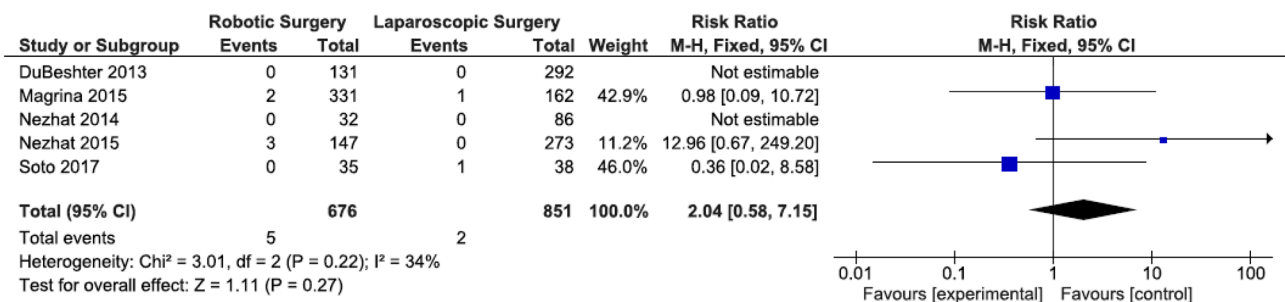


Fig. 7 Forest plot for conversion rates comparing RAS with LPS

Meanwhile, the learning curve for RAS was also a critical factor, which might exert a confounding result. In fact, if more surgical procedures are performed, we could observe less operating times and fewer risk of complications.

Unfortunately, in the studies we have selected, the “learning curve” time was not mentioned. Though improving the learning curve of the different surgeons could be useful, the integration of robotic training in residency and fellowship programs as well as the formation of a structured didactic robotic curriculum continues to be a challenge. A meta-analysis demonstrated that the operative performance is increased and the operating time is decreased by virtual reality training when compared with no supplementary training or with box trainer training [24]. However, conclusions on the benefits and risk of robotic surgery should be made with caution until further high-quality data are available.

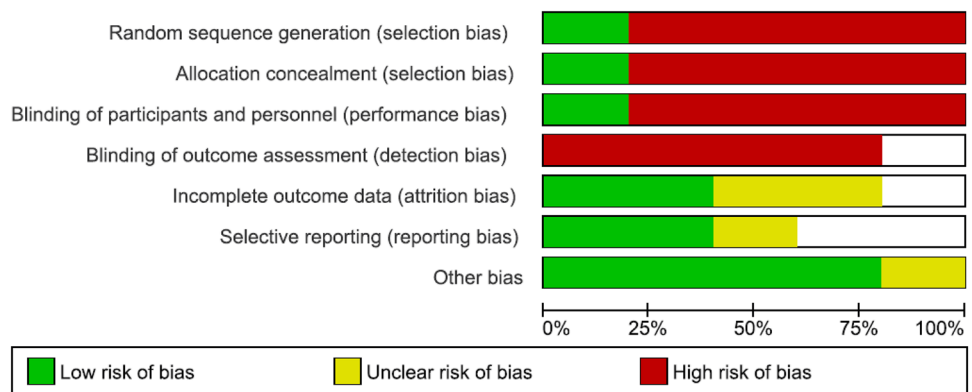
Many studies show that the use of RAS for the treatment of endometriosis is feasible and safe [22, 25–27], but most of them are retrospective. The surgical procedures successfully performed by RAS include radical treatment of the most severe, surgically demanding and painful [28] form of the disease, which is deeply infiltrating endometriosis involving the bowel or the urinary tract. Although these results appear encouraging, RCT studies, including women operated using RAS and patients submitted to LPS by the same surgical team, did not show any substantial advantage of the former over the latter technique. In particular, the only statistically significant differences were in favour of LPS, was a shorter operating time in three studies [16, 17, 29] and a reduced hospital stay in one study [17]. However, comparative studies were all retrospective and they lack an adequate follow-up. Because in these studies the comparison between RAS and LPS has been limited to perioperative outcomes, by no means has it been possible to draw any conclusion about the most important outcomes such as long-term relief of pain, pregnancy rates in infertile women and variation in health-related quality of life. Only adequately designed randomized trials comparing RAS and LPS for the treatment of endometriosis would disentangle these issues.

The main bias of the present meta-analysis was that the overall quality of the studies included was low (Figs. 8, 9). In fact, most data came from retrospective studies. However, they were included because they were the only ones that compared RAS with LPS. Other limitations of this meta-analysis should be taken into account while interpreting

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
DuBeshter 2013	⊖	⊖	⊖	⊖	?	?	+
Magrina 2015	⊖	⊖	⊖		+		+
Nezhat 2014	⊖	⊖	⊖	⊖	+	+	+
Nezhat 2015	⊖	⊖	⊖	⊖			+
Soto 2017	+	+	+	⊖	?	+	?

Fig. 9 Risk of bias: review authors’ judgements about each risk of bias item presented as percentage across all included studies

Fig. 8 Risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all included studies





the results. First, most data were derived from retrospective non-randomized comparisons. Second, we still could not eliminate the differences in patients, as well as the skills and experience of surgeons, between the two groups. There was a lack of consistency in the outcome measures used in trials, which led to difficulties in combining data in a suitable meta-analysis and thus made it difficult to draw clinically relevant conclusions. One of the limitations for this type of comparison is that in case of DIE involving bowel or urinary tract, a general surgeon or urologist may be required. Different specialists do not have the same surgical skills, both laparoscopic and robotic and could modify surgical outcomes. A multidisciplinary team approach involving several professionals with their own expertise is important in attaining an optimal effect. Perhaps, also for this reason the operating times are longer in patients who undergo robotic surgery. Another bias is how the complexity of the surgery for endometriosis varies greatly depending on the deepness and diffusion of the disease. Evaluating the different studies, they are not homogeneous with respect to the enrolled endometriosis stage. Soto 2017 and Nezhat 2015 enrolled both mild and severe endometriosis, while DuBeshter 2013 does not describe the stadium, and the others have enrolled only severe endometriosis. Limiting factor in the operative time of robotic surgery is naturally the docking. This time is not exhaustively characterized in all the papers [15, 17, 18]. No work has taken into consideration the occurrence of interventions on the diaphragm.

Cost is often considered a limitation of robotic surgery [30]. Perhaps an adequate valuation of costs and benefits in patients affected by deep endometriosis and who are submitted to multidisciplinary approach could play an important role also in these cases. More studies are needed to evaluate these aspects.

In conclusion, minimally invasive surgery should be considered the standard for the management of patients with endometriosis. Data from the literature showed that robotic surgery is not inferior to laparoscopy techniques, and it is safe and efficacious. Thanks to the three-dimensional vision with the freeness of movement of robotic instruments, RAS allows to obtain higher surgical precision [22]. We could consider this approach as a valid alternative to standard laparoscopy especially in deep endometriosis with bowel and ureteral involvement, while avoiding it in patients with mild or moderate disease involving the ovaries and with superficial peritoneal involvement.

According to a previous review, there are very few trials in this area and further trials are required focusing on different MIS techniques [31]. This meta-analysis confirmed that the robotic surgery is safe and feasible in patients affected by endometriosis. As reported for specific condition in malignant disease (obese patients with endometrial cancer) and nevertheless the associated costs of the currently available

technology, the potential advantages of the robotic platform are difficult to ignore in specific selected patients with deep infiltrating endometriosis. While waiting for further randomized trials comparing RAS and LPS in endometriosis patients, we could suggest that RAS is a valid option and might be considered an alternative to LPS especially in advanced cases.

## Compliance with ethical standards

**Conflict of interest** Author Stefano Restaino, Author Liliana Mereu, Author Angelo Finelli, Author Maria Roberta Spina, Author Giulia Marini, Author Ursula Catena, Author Luigi Carlo Turco, Author Rossana Moroni, Author Michela Milani, Author Vito Cela, Author Giovanni Scambia and Author Francesco Fanfani declare that they have no conflict of interest.

**Human and animal rights** This article does not contain any studies with human or animal subjects performed by any of the authors.

## References

1. Giudice LC (2010) Clinical practice. Endometriosis. *N Engl J Med* 362:2389–2398
2. (2010) Practice bulletin no. 114: management of endometriosis. *Obstet Gynecol* 116(1):223–236. <https://doi.org/10.1097/AOG.0b013e3181e8b073>
3. Kho RM, Andres MP, Borrelli GM et al (2018) Surgical treatment of different types of endometriosis: comparison of major society guidelines and preferred clinical algorithms. *Best Pract Res Clin Obstet Gynaecol* 51:102–110
4. Dunselman GA, Vermeulen N, Becker C et al (2014) ESHRE guideline: management of women with endometriosis. *Hum Reprod Oxf Engl* 29:400–412
5. Practice Committee of the American Society for Reproductive Medicine (2012) Endometriosis and infertility: a committee opinion. *Fertil Steril* 98:591–598
6. Leyland N, Casper R, Laberge P et al (2010) Endometriosis: diagnosis and management. *J Obstet Gynaecol Can* 32:S1–S3
7. de Paula Andres M, Borrelli GM, Kho RM et al (2017) The current management of deep endometriosis: a systematic review. *Minerva Ginecol* 69:587–596
8. Nisolle M, Donnez J (1997) Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities. *Fertil Steril* 68:585–596
9. Cornillie FJ, Oosterlynck D, Lauweryns JM et al (1990) Deeply infiltrating pelvic endometriosis: histology and clinical significance. *Fertil Steril* 53:978–983
10. Angioni S, Peiretti M, Zirone M et al (2006) Laparoscopic excision of posterior vaginal fornix in the treatment of patients with deep endometriosis without rectum involvement: surgical treatment and long-term follow-up. *Hum Reprod Oxf Engl* 21:1629–1634
11. Berlanda N, Frattaruolo MP, Aimi G et al (2017) Money for nothing. The role of robotic-assisted laparoscopy for the treatment of endometriosis. *Reprod Biomed Online* 35(4):435–444
12. Luu TH, Uy-Kroh MJ (2017) New developments in surgery for endometriosis and pelvic pain. *Clin Obstet Gynecol* 60:245–251

13. Moher D, Liberati A, Tetzlaff J et al (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 151:264–269
14. Zorzela L, Loke YK, Ioannidis JP et al (2016) PRISMA harms checklist: improving harms reporting in systematic reviews. *BMJ* 352:i157
15. Dubeshter B, Angel C, Toy E et al (2013) Current role of robotic hysterectomy. *J Gynecol Surg* 29(4):174–178
16. Nezhat C, Lewis M, Kotikela S et al (2010) Robotic versus standard laparoscopy for the treatment of endometriosis. *Fertil Steril* 94(7):2758–2760
17. Nezhat FR, Sirota I (2014) Perioperative outcomes of robotic assisted laparoscopic surgery versus conventional laparoscopy for advanced-stage endometriosis. *JLS*. 18(4):e2014.00094
18. Nezhat CR, Stevens A, Balassiano E et al (2015) Robotic-assisted laparoscopy vs conventional laparoscopy for the treatment of advanced stage endometriosis. *J Minim Invasive Gynecol* 22(1):40–44
19. Soto E, Luu TH, Liu X et al (2017) Laparoscopy vs robotic surgery for endometriosis (LAROSE): a multicenter, randomized, controlled trial. *Fertil Steril* 107(4):996–1002.e3
20. Magrina JF, Espada M, Kho RM et al (2015) Surgical excision of advanced endometriosis: perioperative outcomes and impacting factors. *J Minim Invasive Gynecol* 22(6):944–950
21. Lawrie TA, Liu H, Lu D et al (2019) Robot-assisted surgery in gynaecology. *Cochrane Database Syst Rev* 4:CD011422
22. Ercoli A, Bassi E, Ferrari S et al (2017) Robotic-assisted conservative excision of retrocervical-rectal deep infiltrating endometriosis: a case series. *J Minim Invasive Gynecol*. 24(5):863–868
23. Chen Y, Wang H, Wang S et al (2019) Efficacy of ten interventions for endometriosis: a network meta-analysis. *J Cell Biochem* 120(8):13076–13084
24. Nagendran M, Gurusamy KS, Aggarwal R et al (2013) Virtual reality training for surgical trainees in laparoscopic surgery. *Cochrane Database Syst Rev*. 27(8):CD006575
25. Luu TH, Uy-Kroh MJ (2017) New developments in surgery for endometriosis and pelvic pain. *Clin Obstet Gynecol* 60(2):245–251
26. Fanfani F, Restaino S, Ercoli A et al (2016) Robotic versus laparoscopic surgery in gynecology: which should we use? *Minerva Ginecol* 68(4):423–430
27. Siesto G, Ieda N, Rosati R et al (2014) Robotic surgery for deep endometriosis: a paradigm shift. *Int J Med Robot*. 10(2):140–146
28. Vercellini P (1997) Endometriosis: what a pain it is. *Semin Reprod Endocrinol*. 15(3):251–261
29. Cassini D, Cerullo G, Miccini M et al (2014) Robotic hybrid technique in rectal surgery for deep pelvic endometriosis. *Surg. Innov*. 21:52–58
30. Turchetti G, Pierotti F, Palla I et al (2017) Comparative health technology assessment of robotic assisted, direct manual laparoscopic and open surgery: a prospective study. *Surg Endosc* 31(2):543–551
31. Duffy JM, Arambage K, Correa FJ et al (2014) Laparoscopic surgery for endometriosis. *Cochrane Database Syst Rev*. 4:CD011031

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.