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REVIEW ARTICLE

Minimally invasive interval cytoreductive surgery in ovarian cancer: systematic review and meta-analysis

Joel Cardenas-Goicoechea[1] · Yu Wang[2] · Susan McGorray[2] · Mohammed D. Saleem[3] · Semiramis L. Carbajal Mamani[3] · Ariel F. Pomputius[4] · Merry-Jennifer Markham[3] · Jacqueline C. Castagno[1]

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Abstract

The introduction of minimally invasive surgery in other gynecologic cancers has shown benefits with similar oncologic outcomes. However, the biology and complexity of surgery for ovarian cancer may preclude this approach for ovarian cancer patients. Our objective is to assess feasibility to achieve complete cytoreductive surgery after neoadjuvant chemotherapy for stage IIIC–IV ovarian cancer patients via minimally invasive surgery. Our data sources include PubMed, Embase, Scopus, Biosis, Clinicaltrials.gov, and the Cochrane Library. Meta-analysis was performed using the random-effects model with DerSimonian and Laird estimator for the amount of heterogeneity to estimate the pooled outcomes. A funnel plot and Egger's regression test were used to test publication bias. The Newcastle–Ottawa Quality Assessment Scale was used to assess the quality of the studies. There were 6 studies (3 prospective, 3 retrospective) that met the criteria for meta-analysis with a total of 3231 patients, 567 were in the minimally invasive group and 2664 in the laparotomy group. Both groups were similar in stage and serous histology. Complete cytoreductive surgery was achieved in 74.50% (95% CI 40.41–97.65%) and 53.10% (95% CI 4.88–97.75%) of patients in the minimally invasive and laparotomy groups, respectively. There was no statistical significant difference between these 2 pooled proportions ($p=0.52$). Three studies compared minimally invasive surgery vs laparotomy. No significant difference was observed between the 2 groups in obtaining complete cytoreductive surgery [OR = 0.90 (95% CI 0.70–1.16; $p=0.43$)]. A symmetrical funnel plot indicated no publication bias. The pooled proportion for grade > 2 postoperative complications was not significant among the laparoscopy group [3.11% (95% CI 0.00–10.24%; $p=0.15$)]. Complete cytoreductive surgery appears feasible and safe with minimally invasive surgery in selected advanced ovarian cancer patients after neoadjuvant chemotherapy.

Keywords Laparoscopy · Robotic surgery · Ovarian cancer · Cytoreductive surgery · Neoadjuvant chemotherapy

Introduction

Ovarian cancer is the most lethal gynecologic cancer. In 2018, the American Cancer Society estimated 22,240 new ovarian cancer cases and 14,070 ovarian cancer deaths [1]. The treatment and management of advanced stage ovarian cancer involves surgery plus chemotherapy. Traditionally, patients with advanced stage ovarian cancer underwent surgery upfront with maximal cytoreductive surgery via laparotomy (open surgery) followed by adjuvant platinum-based chemotherapy. Another approach that has been emerging recently involves neoadjuvant chemotherapy followed by interval tumor debulking. Phase III clinical trials showed similar progression-free survival and overall survival rates for this emerging modality, but surgery following neoadjuvant chemotherapy had less morbidity and mortality than the

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✉ Joel Cardenas-Goicoechea
joelcardenas@ufl.edu

[1] Division Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Florida College of Medicine, P.O. Box 100294, Gainesville, FL 32610, USA

[2] Department of Biostatistics, University of Florida College of Medicine, Gainesville, FL, USA

[3] Department of Medicine, University of Florida College of Medicine, Gainesville, FL, USA

[4] University of Florida Health Science Center Libraries, Gainesville, FL, USA

traditional method [2–4]. The ultimate goal is to achieve a complete cytoreductive surgery, which has been shown to improve survival [5–7]. A phase II clinical trial by Gueli Alletti et al. [8] showed that minimally invasive surgery is safe and feasible in ovarian cancer patients with complete clinical response to neoadjuvant chemotherapy. Currently, there is no phase III trial that compares standard laparotomy with minimally invasive surgery for ovarian cancer after neoadjuvant chemotherapy.

The latest version of the National Comprehensive Cancer Network's guidelines for ovarian cancer [9] consider that there may be a role for minimally invasive surgical in ovarian cancer. Patients who are unable to be optimally debulked using minimally invasive techniques should be converted to an open procedure, such a procedure should be performed by an experienced surgeon [9]. The purpose of this study is to assess the current literature of minimally invasive surgery after neoadjuvant chemotherapy for ovarian cancer to achieve complete cytoreductive surgery (R0).

Methods

Our review was preceded by a written protocol that was registered in the Prospero International Prospective Register of Systematic Reviews (ID CRD42017070962) and was conducted according to the Meta-analysis of Observational Studies in Epidemiology guidelines [10].

Eligibility criteria, information sources, search strategy

A literature search was performed for articles published from January 1989 to December 2017 using the EMBASE and Scopus library databases and from January 1989 to September 2017 using PubMed, Cochrane, Biosis, and ClinicalTrials.gov. Additionally, a manual search of relevant publications supplemented the database searches. The search terms included the following: ovarian cancer, laparotomy, laparoscopy, robotic surgery, debulking surgery (S1). The primary endpoint was to evaluate complete cytoreductive surgery, defined as resection of all macroscopic disease, after neoadjuvant chemotherapy. The secondary endpoint was perioperative complications.

Study selection

Our inclusion criteria included observational, prospective, and randomized controlled studies with more than 10 cases, female patients diagnosed with advanced ovarian cancer that underwent cytoreductive surgery (tumor debulking) after neoadjuvant chemotherapy. Cytoreductive surgery performed via minimally invasive laparoscopy or robotic surgery, comparative studies with minimally invasive approach (laparoscopy/robotic) vs standard laparotomy group, and perioperative outcomes that included operative time, hospital stay, conversion to laparotomy, estimated blood loss, mortality rate, readmission, intra- and postoperative complications. Survival was not focused in this study due to short follow-up of the studies and limited available data to run a meta-analysis.

We excluded any non-English language publications, conference abstracts, case reports, editorials, commentaries, review articles, incomplete original data, and studies where minimally invasive surgery were performed for diagnostic or resectability purposes, surgical staging, primary debulking, or recurrence of disease. The authors were not contacted because the primary endpoint (complete cytoreductive surgery) was reported by all studies.

Data extraction

Two independent researchers (JCG, JC) screened the identified articles for eligibility based on the title and abstract following the inclusion and exclusion criteria. A library was created using EndNote X8 (Clarivate Analytics). Data were abstracted based on a predetermined data collection established before a literature search. Data included the following information: first author, country, and publication year, study design, surgical procedure [minimally invasive surgery (laparoscopy/robotic) and laparotomy], number of patients, age, body mass index (BMI; Kg/m^2), tumor histology (serous), tumor stage, neoadjuvant chemotherapy received, number of chemotherapy treatments before interval cytoreductive surgery, Response Evaluation Criteria In Solid Tumors response, cytoreductive status at the completion of surgery [Complete (R0, no gross residual disease), optimal cytoreductive surgery (residual disease $\leq$ 1-cm), suboptimal cytoreductive surgery (residual disease $>$ 1-cm)], operative time, length of hospital stay, conversion to laparotomy, estimated blood loss, surgical procedure performed [gynecologic surgery (hysterectomy, bilateral salpingo-oophorectomy), additional cytoreductive surgery (Omentectomy, bowel resection, perinectomy)], 90-day mortality rate, 30-day readmission, intraoperative complication, >grade 2 postoperative complications, early postoperative complication, time to start chemotherapy, recurrence rate during follow-up, survival data, and residual disease on pathology.

Assessment of risk bias

Risk of bias assessment was with the Newcastle–Ottawa Scale [11]. Two authors (JCG and MS) performed it independently and their scores were compared. A third investigator was consulted if agreement could not be reach. In this

study, "high quality" was considered when studies achieved 5 or more stars [12].

Data synthesis

Statistical analysis was performed with R software, version 3.4.1 (The R Foundation for Statistical Computing). A pooled proportion was estimated for both minimally invasive surgery and laparotomy groups. Each study's estimated proportion was transformed using the Freeman–Tukey double arcsine method before it was entered into a model. All pooled proportions were then estimated by random effect models (DerSimonian–Laird estimator). Pooled odds ratios (ORs) were estimated for interested factor between minimally invasive surgery and laparotomy. Each OR was log transformed before it was entered into a model. The pooled OR was then estimated by the random effect model (DerSimonian–Laird estimator). A small constant, ½, was added to each cell counts of those 2×2 tables with at least one cell equal to 0. Cochran's Q test was used for testing (residual) heterogeneity between studies. If p value of the test was smaller than 0.05, we concluded that the outcomes of these studies were heterogeneous. I^2 statistics indicated the percentage of variance in a meta-analysis that is attributable to study heterogeneity was also calculated. Satterthwaite T test for transformed proportions was applied to test the difference between two pooled proportions. A funnel plot and Egger's regression test was used to identify the publication bias.

Results

Study selection

Overall, 2682 abstracts were retrieved in the first screening and were reviewed by 2 board-certified gynecologic oncologists (JCG and JC). Forty-eight studies were considered for full-text reviews, and 41 studies were excluded. Only 6 studies met all of our inclusion criteria, and they were accepted by 3 board-certified physicians [MJM (medical oncologist); JCG and JC (gynecologic oncologists)]. One study that met our inclusion criteria was excluded because the patients were included in the MISSION trial [8, 13]. The selected 6 studies were included in our meta-analysis with a total of 3231 patients. Of these patients, 567 were in the minimally invasive group and 2664 were in the laparotomy group (Fig. 1).

Study characteristics

Of the 6 studies, 3 were prospective [8, 14, 15] and the other 3 were retrospective [16–18]. Three studies compared minimally invasive surgery (laparoscopy/robotic surgery) with laparotomy [14–16] and 3 studies had only a single group [8, 17, 18]. One study had 3 comparative groups but only 2 of these groups (laparoscopy and open) were included for the purpose of our study [15]. All 6 studies scored 5 or more stars on the Newcastle–Ottawa Scale (S2).

A total of 567 patients from all 6 studies underwent minimally invasive surgery (range 10–450 cases) and 2664 underwent laparotomy (range 11–2621 cases). Patient characteristics were similar among the studies. The number of neoadjuvant chemotherapy ranged from 3 to 6 cycles and most studies reported at least a partial response before cytoreductive surgery (Table 1).

Synthesis of results

No statistical analysis for age and body mass index was performed due to inadequate data reporting for continuous variables such as mean, median, standard deviation, and range. Table 2 shows an estimate of the pooled ORs on patients with stage IIIC–IV who underwent minimally invasive surgery and laparotomy. Three studies were included in this analysis with 3142 patients [14–16]. There was no statistical significant heterogeneity in stage ($I^2=0$; $p=0.48$). There was also no significant association observed between the surgery groups (minimally invasive and laparotomy groups) and stage [OR 0.44 (95% CI 0.04–4.35); $p=0.48$].

We compared serous ovarian tumor histology between the minimally invasive surgery and laparotomy group. Three studies were included in this comparison with 2534 patients [13–16]. There was no statistical significant heterogeneity ($I^2=0$; $p=0.42$) and no significant difference was observed between the 2 groups [OR 0.91 (95% CI 0.71–1.16); $p=0.42$] for serous ovarian tumor histology.

Complete cytoreductive surgery via minimally invasive surgery was achieved in 74.50% (95% CI 40.41–97.65%) of the 6 reported studies. Significant heterogeneity was observed ($I^2=96.31\%$; $p<0.0001$) among the 6 studies ($n=394$ patients). There was no significant difference in achieving complete cytoreductive surgery between minimally invasive surgery and laparotomy [pooled proportions, 74.50% (95% CI 40.41–97.65%) vs 53.10% (95% CI 4.88–97.75%); $p=0.52$] (Table 2; Fig. 2) [8, 13–18]. An estimate of the pooled ORs on patients who underwent minimally invasive surgery vs those who underwent laparotomy was based on three studies ($n=1943$ patients). There was no statistical heterogeneity in these studies that compared two groups to achieve complete cytoreductive surgery ($I^2=0$; 0.97). No significant difference was observed between the two groups in obtaining complete cytoreductive surgery [OR = 0.9; 95% CI (0.70–1.16); $p=0.43$] (Table 2; Fig. 3). Complete cytoreductive surgery was selected to analyze publication bias, and a symmetrical funnel plot and the Egger's regression test both indicated no publication bias (Fig. 4).

Fig. 1 Prima flow chart

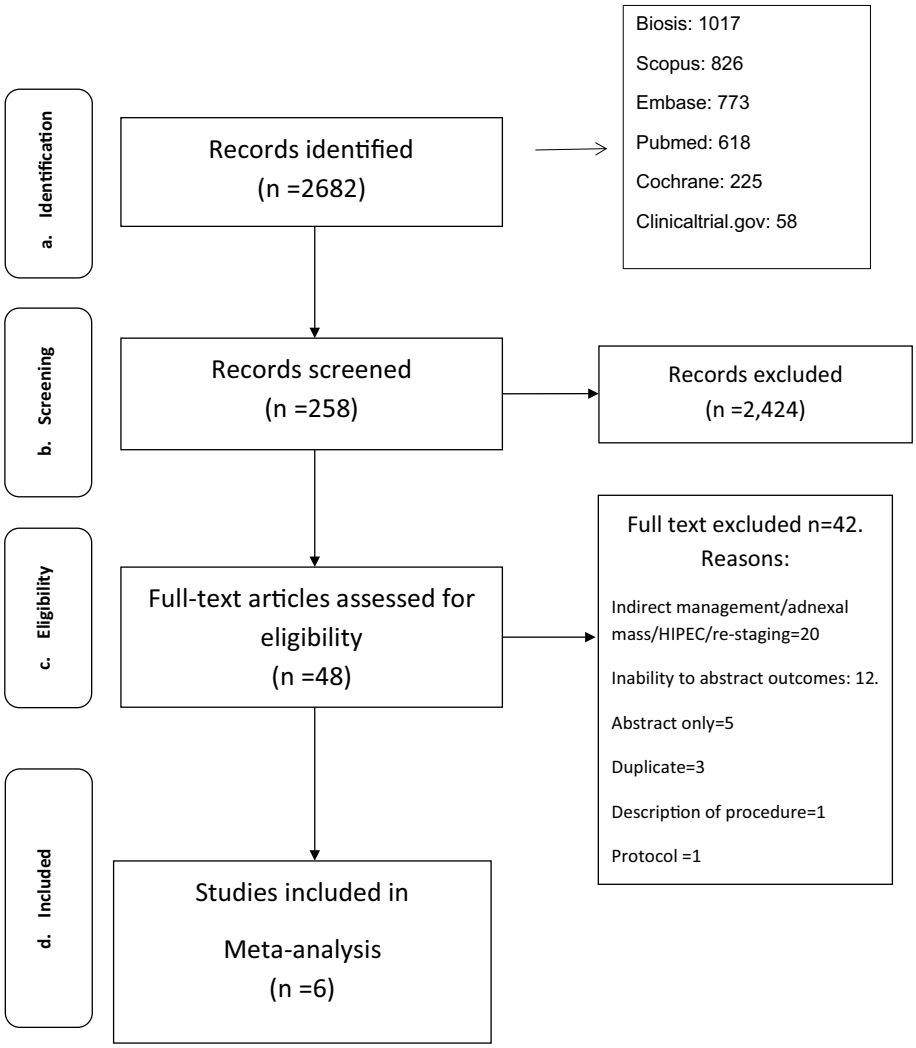

Table 3 shows the perioperative outcomes. All studies reported operative time except Melamed et al. [16]. The operative time for the minimally invasive ranged from 152 to 292 min and for the laparotomy group from 264 to 370 min. Length of hospital stays appeared to be shorter in the laparoscopic group than in the laparotomy group, but we were unable to analyze due to inadequate data reporting among the studies. The length of hospital stays for the laparoscopic group was 2–4 and 5–12 days for the laparotomy group. The conversion rate was 16% in the largest study (range 0–16%). The MISSION trial had a conversion rate of 0% and excluded patients with a BMI > 40 Kg/m^2 and an ASA score between III and IV. Favero's study had a conversion rate of 0% and excluded patients who were older than 70 years and presented disease in critical areas. The reported estimated blood loss appears to favor minimally invasive surgery (range 70–107 mL) over laparotomy (532 mL). Most studies reported that extra-pelvic surgery was needed to accomplished complete cytoreductive surgery [8, 15, 16].

Only one study reported the 90-day mortality rate (2.9 vs 2.8%, $p = 0.93$) [16] and the 30-day readmission rate was reported by 2 studies (3.7 vs 5.3%, $p = 0.26$) [16] and 14% [18]. The highest reported intraoperative complication was 3% for both the minimally invasive and laparotomy groups. Five studies reported early postoperative complications. The non-comparative studies reported an early postoperative complication rate from 0 to 7% [8, 17, 18]. Two comparative studies reported a lower postoperative complication rate in the minimally invasive group (0–1 vs 3–31%) [8, 15]. Favero et al. [14] reported higher rate of complication in the laparoscopic group (9 vs 20%). However, 2 patients received blood transfusion in the laparotomy group, making it a grade 2 complication based on Dindo et al. [19].

The pooled proportion for grade > 2 postoperative complications was not significant among the laparoscopy group [3.11% (95% CI 0.00–10.24%; $p = 0.15$)]. Since there was only 2 studies in the open group, adequate pooled proportion for this outcome was not done. A summary of the selected studies, the postoperative and intraoperative complications

Table 1 Patient demographics of the literature

Literature	Study design	Surgical procedure	No. of patients	Age (years)	Body mass index (Kg/m^2)	Serous histology, no. of patients (%)	Stage IIIC-IV no. of patients (%)	Neoadjuvant chemotherapy with carboplatin + taxol,no. of patients (%)	No. of chemotherapy prior to surgery	RECIST response, no. of patients (%)	
										Complete	Partial
Ackroyd et al. [18] USA	Retrospective	Robotic	29	64.9	29	24 (83)	29 (100)	29 (100)	3.9	N/A	N/A
Melamed et al. [16] USA	Retrospective	Open	2621	63.2	N/A	2114 (81)	2621 (100)	N/A	N/A	N/A	N/A
		Laparoscopy, robotic	450	63.9	N/A	357 (79)	450 (100)	N/A	N/A	N/A	N/A
Tozzi et al. [15] Italy	Prospective	Open	32	65.1	29	28 (88)	32 (100)	N/A	N/A	0	15 (47)
		Laparoscopy	18	62.4	27.2	14 (78)	18 (100)	N/A	N/A	0	15 (83)
Gueli Alletti et al. [8] Italy Mission trial NCT02324595	Prospective, phase II	Laparoscopy, robotic	30	61	24	29 (97)	30 (100)	18 (60)	4	6 (20)	24 (80)
Favero et al. [14] Brazil	Prospective, pilot	Open	11	61.3	27.4	11 (100)	11 (100)	11 (100)	6	N/A	N/A
		Laparoscopy	10	58.3	29.3	10 (100)	10 (100)	10 (100)	6	N/A	N/A
Corrado et al. [17] Italy	Retrospective	Laparoscopy	30	50	24.5	23 (77)	30 (100)	30 (100)	3	N/A	N/A

N/A not available

Table 2 Pooled (a) proportions and (b) odds ratios comparisons between minimally invasive surgery and laparotomy groups

Incidence type	Group	No. of studies	Total no. of events	Total no. of patients	Q stats	Q-*p*-value	I^2	Pooled proportion (95% CI)	DF test *p* value between groups
(a) Pooled proportions									
Stage IIIC–IV	Laparoscopy	6	567	567	2.38	0.794	0	100% (100–100%)	0.22
	Open	3	2664	2664	1.62	0.445	0	100% (100–100%)	
Serous histology	Laparoscopy	6	457	567	11.86	0.037	57.83	85.48% (77.08–92.40%)	0.75
	Open	3	2153	2664	5.13	0.077	60.99	87.47 (76.26–95.76%)	
Grade >2 postoperative complication	Laparoscopy	5	5	117	7.89	0.096	49.29	3.11% (0–10.24%)	0.15
	Open	2	9	43	–	–	–	–	
Optimal cytoreductive surgery (R0)	Laparoscopy	6	335	394	38.12	< 0.0001	86.88	97.25% (86.59–100%)	
	Open	3	1277	1638	26.59	< 0.0001	92.48	95.16% (70.96–100%)	0.82
Complete cytoreductive surgery	Laparoscopy	6	226	394	135.5	< 0.0001	96.31	74.50% (40.41–97.65%)	0.52
	Open	3	821	1638	82.17	< 0.0001	97.57	53.10 (4.88–97.75)	

Incidence type	No. of studies	Total no. of events	Total patients	Q stats	Q-*p*-value	I^2	Pooled odds ratio (95% CI)	*p* value
(b) Pooled odds ratio								
Stage IIIC–IV	3	3142	3142	0.36	0.833	0	0.44 (0.04–4.35)	0.48
Serous histology	3	2534	3142	0.6	0.742	0	0.91 (0.71–1.16)	0.42
Optimal cytoreductive surgery (R1)	3	1525	1943	0.12	0.94	0	1.12 (0.82–1.53)	0.47
Complete cytoreductive surgery (R0)	3	969	1943	0.06	0.97	0	0.90 (0.70–1.16)	0.43
Serous histology	3	2534	3142	0.6	0.742	0	0.91 (0.71–1.16)	0.42

CI confidence interval, *DF* Dickey-Fuller, *Q-stats* the test statistics of Cochran's *Q* test, *Q-p-value* the *p* value of Cochran's *Q* test

DF test *p* value between groups: The *p* value of Satterthwaite *T* test for pooled proportions between Laparoscopy and Open groups

reported, and the conversions are described in the supplemental materials (S3–S6).

The oncologic outcomes are shown in Table 4. Any interpretation of these outcomes, such as recurrence, progression-free survival, and overall survival rates, is limited due to the short follow-up (range 10–32 months). The largest study reported a similar survival rate between the 2 groups with a median follow-up of 32 months [16]. The presence of residual disease was reported in 5 studies. Residual disease was present in 43–100% of cases in the laparoscopic group.

Discussion

Our review evaluated the performance of complete cytoreductive surgery with a fairly new strategy (laparoscopy or robotic) for ovarian cancer after neoadjuvant chemotherapy. We found that complete cytoreduction can be accomplished in highly selected patients, and the procedure appears safe and feasible when compared with standard laparotomy.

All six studies reported cytoreductive status. These studies achieved complete cytoreductive surgery in 74.5% (range 40–97.65%) of patients in the minimally invasive surgery group and 53.10% (range 5–97.75%) in the laparotomy group. All those patients were highly selected for minimally invasive surgery (complete clinical response to chemotherapy, low tumor load on diagnostic laparoscopy). In the CHORUS, and NCT00003636 trial, complete debulking surgery after neoadjuvant chemotherapy was obtained in 39 and 50% [2, 3]. In both trials, patients were randomized and no CT scan or laparoscopic scoring systems were used in the selection of patients. Laparotomy was the standard approach. Our primary end point (complete cytoreductive surgery) was selected to analyze for publication bias, a symmetrical funnel plot and the Egger's test regression test both indicated no

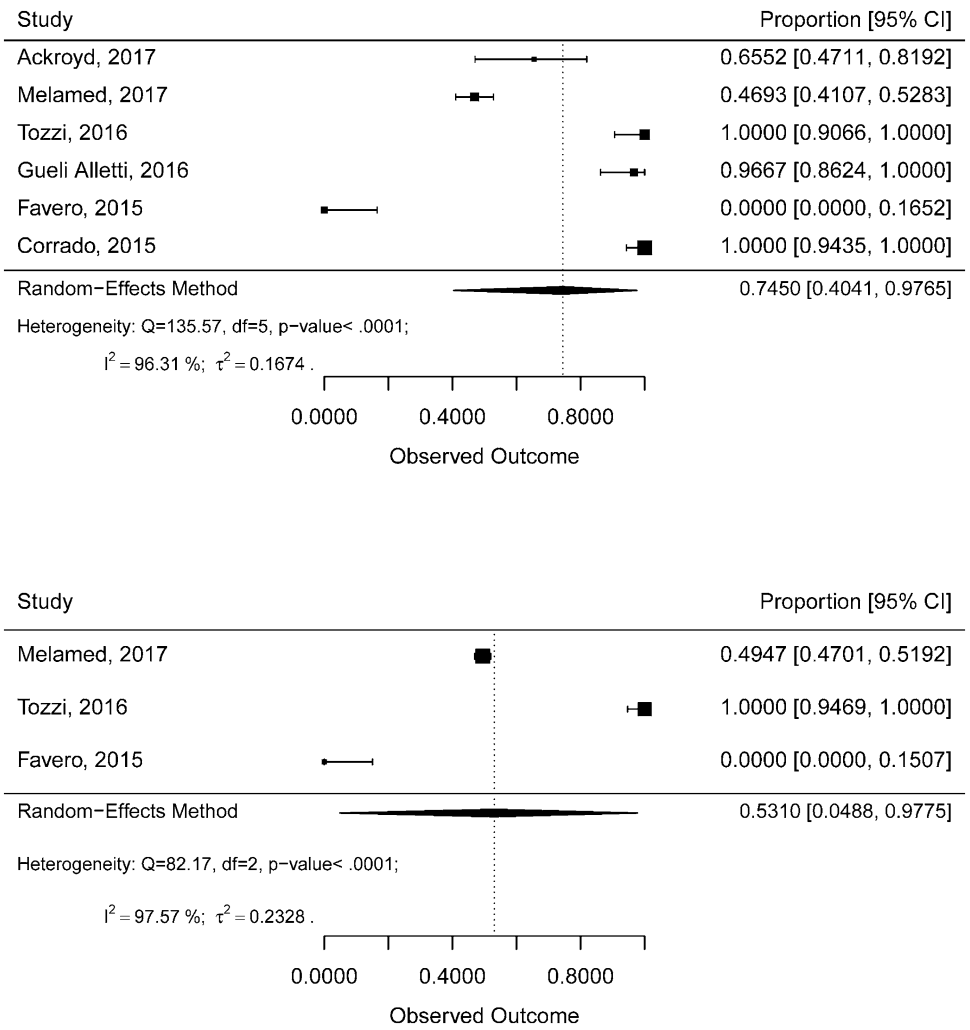

Fig. 2 Forest plot. Pooled proportion comparison between minimally invasive surgery (laparoscopy/robotic) and laparotomy to achieve complete cytoreductive surgery

selection bias. However, the power of this method to detect bias is low due to the inclusion of only 3 studies.

Traditionally, cytoreductive surgery is performed via laparotomy. In certain patient populations, complete resection appears to be achievable with minimally invasive surgery. However, the biology and complexity of ovarian cancer raises oncologic concerns when using the minimally invasive approach. These concerns include inadequate identification of tumor, tumor resection and port-site metastases. Adequate exposure, identification of tumor in the upper abdomen, and location of the residual tumor (i.e., diaphragm, abdominal peritoneum, rectum and sigmoid) is critical. The feasibility to perform complex and widespread surgery, such as resection of the large or small bowel, diaphragm stripping, splenectomy, partial cystectomy, pelvic and para-aortic lymph node dissection, may have some limitations with minimally invasive surgery. Minimally invasive surgery may have some limitations to explore the retroperitoneum, and the roof of the mesentery. Although, preliminary data from the Lion Trial NCT00712218 indicate that systematic lymphadenectomy does not affect survival in patients with clinically negative lymph nodes. On the other hand, patients with a complete response to neoadjuvant chemotherapy may need less invasive surgery to accomplish complete cytoreductive surgery. A phase III trial (JCGO0602) showed that interval cytoreductive surgery was less invasive and required fewer surgeries than the standard treatment [4]. The neoadjuvant group required a lower frequency of abdominal organ resection than the standard (23.7 vs 37.6%; $p=0.012$) or distant metastases resection (3.9 vs 10.7%; $p=0.027$), and 82% of the neoadjuvant group had optimal tumor debulking (0- to 1-cm residual tumors) [4].

Strengths and limitations

To our knowledge, this is the first systematic review that assesses the role of minimally invasive surgery after neoadjuvant chemotherapy in advanced-stage ovarian cancer patients to achieve complete cytoreductive surgery. Our study is the result of a thorough and comprehensive

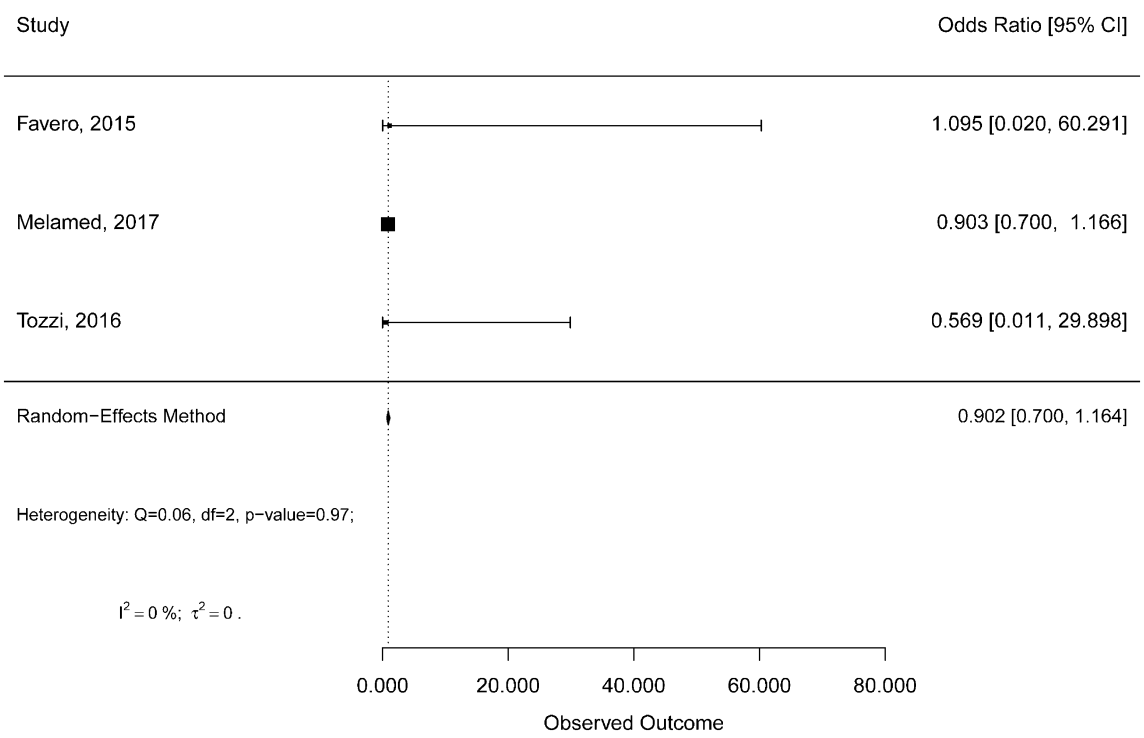

Fig. 3 Forest plot. Pooled odds ratios to achieve complete cytoreductive surgery between minimally invasive surgery and laparotomy

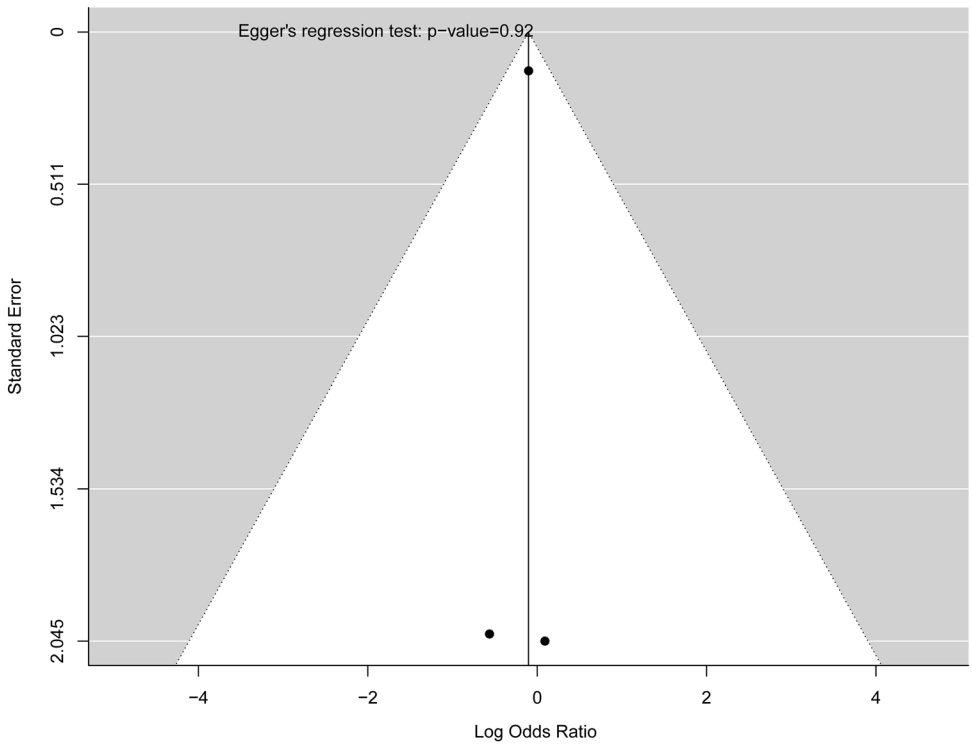

Fig. 4 Funnel plot: Publication bias to achieve complete cytoreductive surgery between minimally invasive surgery and laparotomy

systematic review in various databases. We assessed the outcomes based on strict predetermined criteria and used a funnel plot analysis to assess publication bias. During our study design, we discussed the number of cases to be included due to the learning curve that is required for laparoscopy and robotic surgery. Further analysis of these

Table 3 Perioperative outcomes in the literature

	Ackroyd et al. [18] USA	Melamed et al. [16] USA		Tozzi et al. [15] Italy		Gueli Alletti et al. [8] Italy Mission trial NCT02324595	Favero et al. [14] Brazil		Corrado et al, [17] Italy
Surgical procedure	Robotic	Open	Laparoscopy, robotic	Open	Laparoscopy	Laparoscopy, robotic	Open	Laparoscopy	Laparoscopy
Operative time (mins)	165	N/A	N/A	370	246	285	264	292	152
Hospital stay (days)	2	5	4	11.96	3.2	2	5.3	3.6	4
Conversion to laparotomy, no. of patients (%)	1 (3)	–	72 (16)	–	N/A	0	–	0	2 (7)
Estimated blood lost (mL)	107	N/A	N/A	532	86	100	N/A	180	70
Surgical procedure, no. of patients (%)									
Gynecology surgery only	N/A	266 (10.2)	75 (16.8)	0	0	[a]	N/A	N/A	N/A
Additional cytoreductive surgery	N/A	2338 (89.8)	371 (83.2)	32 (100)	18 (100)	29 (96.6)	N/A	N/A	N/A
Cytoreductive status, no. of patients (%)									
R0	19 (65.5)	789[a] (50)	130 (47)	0	0	29 (97)	0	0	30 (100)
R < 1-cm	8 (27.5)	445 (28)	90 (32)	32 (100)	18 (100)	1 (3)	11 (100)	10 (100)	0
R > 1-cm	2 (6.9)	361 (22)	57 (21)	0	0	0	0	0	0
30-day readmission, no. of patients (%)	4 (13.7)	97 (3.7)	24 (5.3)	N/A	N/A	N/A	N/A	N/A	N/A
Intraoperative complication, no. of patients (%)	0	N/A	N/A	1 (3)	0	0	N/A	0	1 (3.3)
Grade >2 postoperative complication, no. of patients (%)	0	N/A	N/A	6 (18.7)	1 (5.6)	0	3 (27)	2 (20)	2 (7)
Early postoperative complication, no. of patients (%)	0	N/A	N/A	10 (31)	1 (5.6)	0	3 (27)	2 (20)	2 (7)
Time to start chemotherapy (days)	N/A	N/A	N/A	N/A	N/A	20	N/A	N/A	N/A

N/A data not available

[a]Unable to abstract

studies revealed that investigators and surgeons appeared to overcome the learning curve by the time of their publication, so we included studies with at least 10 cases. We excluded studies that focused on open surgical intervention after neoadjuvant chemotherapy and studies that included other treatment characteristics, such as resectability, surgery upfront, recurrence disease, and surgical staging.

Table 4 Oncologic outcomes

Literature	Surgical procedure	Recurrence during study period, no. of patients (%)	Progression-free survival (%)	Overall survival (%)	Follow-up (months)	Residual disease on pathologyno. of patients (%)	No residual disease on pathology, no. of patients (%)
Ackroyd et al. [18] USA	Robotic	12 (41%)	21.2	39.7	NA	25 (86)	4 (14)
Melamed et al. [16] USA	Open	N/A	N/A	37.6	32	N/A	N/A
	Laparoscopy, robotic	N/A	N/A	33.8	32	N/A	N/A
Tozzi et al. 2016 [15] Italy	Open	14 (43.7)	N/A	N/A	16.3	32 (100)	0
	Laparoscopy	4 (22)	N/A	N/A	16.3	18 (100)	0
Gueli Alletti et al. [8] Italy Mission trial NCT02324595	Laparoscopy, robotic	7 (23)	N/A	N/A	10.5	27 (90)	3 (10)
Favero et al. [14] Brazil	Open	10 (90)	20.5	N/A	36	10 (91)	1 (9)
	Laparoscopy	8 (80)	13.3	N/A	20	9 (90)	1 (10)
Corrado et al. [17] Italy	Laparoscopy	4 (13)	N/A	N/A	15	13 (43)	17 (57)

N/A not available

The limitations of our study are inherent to the studies we included. Consistent and reasonable outcomes may promote further prospective and randomized studies. Second, the patient population was highly selected, which may limit the extrapolation to the general population. The common exclusion criteria were as follows: residual tumor in critical area such as the porta hepatis and bowel serosa, patients aged > 70 years, elevated tumor marker, BMI > 40 Kg/m^2, and ASA scores of III or IV [8, 13–15]. The conversion rate from laparoscopy to laparotomy appears to increase with obesity, so weight may limit the efficacy of its role. The robotic platform may need to be explored. Magrina et al. [20] reported a comparison study with robotic surgery for primary or secondary surgery for stage I–IV ovarian cancer patients. A comparison was made between laparoscopy and laparotomy. The researchers concluded that the type of surgery did not influence survival [20, 21].The largest study reported by Melamed et al. [16] had a higher conversion rate with traditional laparoscopy than robotic (20 vs 5%, $p < 0.001$).

Third, there are insufficient data to evaluate the chemotherapy response, operative outcomes, and readmission rates. Only 2 studies reported tumor response with the Response Evaluation Criteria In Solid Tumors criteria [8, 15].

Fourth, the primary endpoint of complete cytoreductive surgery appears to be subjectively decided by the surgeon. Almost all studies included in this review had patients undergo CT scan before surgery. However, only one study performed a CT scan after surgery and before chemotherapy [15]. An ideal study that avoids subjective impression of residual disease at the end of surgery should include both CT scans after surgery and before chemotherapy. The subjective measuring of residual disease by surgeons has been recently studied by Eskander et al. [22].

Finally, the most challenging part of our study was performing a meta-analysis with only a few published studies that had a small number of patients using laparoscopy in a robotic platform. Larger prospective studies are needed to further assess the feasibility and safety of minimally invasive surgery for interval cytoreductive surgery. A clinical trial titled "Minimally Invasive Interval Debulking Surgery in Ovarian Cancer" (NCT03378128) opened on January 12, 2018 and is currently recruiting. The results of a phase II trial titled "Feasibility of Interval Debulking Surgery by Laparoscopy for Peritoneal Carcinosis in Chemosensitive patients" (NCT01905163) are pending.

The purpose of our study is not to assess survival given the paucity of studies and limited follow-up (range 10–32 months). The main objective of our review was feasibility. With the issues of performing a successful randomized trial in mind [23], our review attempts to assess the safety and efficacy of the laparoscopy and the robotic platform in the short term. The theoretical benefits of such intervention need to be confirmed with survival.

Conclusions

Complete cytoreductive surgery after neoadjuvant chemotherapy via minimally invasive surgery appears feasible and safe in selected patients with advanced ovarian cancer. Collaborative, prospective and randomized trials are needed to determine whether overall survival is non-inferior to laparotomy.

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Compliance with ethical standards

Conflict of interest Dr. Merry Markham reports research funding from Aduro Biotech and Astex Pharmaceuticals outside the submitted work. All other authors have no conflicts of interest to disclose.

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