



Peritoneal carcinomatosis after minimally invasive surgery versus open radical hysterectomy: systematic review and meta-analysis

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ABSTRACT

Objective To assess the incidence of peritoneal carcinomatosis in patients undergoing minimally invasive or open radical hysterectomy for cervical cancer. **Methods** The MEDLINE (accessed through Ovid), Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Clinical Trials, and Scopus databases were searched for articles published from inception up to April 2022. Articles published in English were considered. The included studies reported on patients with International Federation of Gynecology and Obstetrics (FIGO) 2009 stage IA-IIA squamous cell carcinoma, adenocarcinoma, and/or adenosquamous carcinoma of the cervix who underwent primary surgery. Studies had to report at least one case of peritoneal carcinomatosis as a recurrence pattern, and only studies comparing recurrence after minimally invasive surgery versus open surgery were considered. Variables of interest were manually extracted into a standardized electronic database. This study was registered in PROSPERO (CRD42022325068).

Results The initial search identified 518 articles. After the removal of the duplicate entries from the initial search, two authors independently reviewed the titles and abstracts of the remaining 453 articles. Finally, 78 articles were selected for full-text evaluation; 22 articles (a total of 7626 patients) were included in the analysis—one randomized controlled trial and 21 observational retrospective studies. The most common histology was squamous cell carcinoma in 60.9%, and the tumor size was <4 cm in 92.8% of patients. Peritoneal carcinomatosis pattern represented 22.2% of recurrences in the minimally invasive surgery approach versus 8.8% in open surgery, accounting for 15.5% of all recurrences. The meta-analysis of observational studies revealed a statistically significant higher risk of peritoneal carcinomatosis after minimally invasive surgery (OR 1.90, 95% CI 1.32 to 2.74, $p < 0.05$). **Conclusion** Minimally invasive surgery is associated with a statistically significant higher risk of peritoneal carcinomatosis after radical hysterectomy for cervical cancer compared with open surgery.

INTRODUCTION

The preferred treatment for early-stage cervical cancer is radical hysterectomy with lymph node

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Peritoneal carcinomatosis after radical surgery in cervical cancer has been described for over two decades. Although reports have increased after the Laparoscopic Approach to Cervical Cancer (LACC) trial, the incidence of peritoneal carcinomatosis after minimally invasive versus open surgery is unknown.

WHAT THIS STUDY ADDS

⇒ Peritoneal carcinomatosis following radical hysterectomy for cervical cancer represents a rate of 22.2% versus 8.8% of recurrences when a minimally invasive approach is compared with open surgery. There is a statistically significant 1.9-fold higher risk of peritoneal carcinomatosis as a recurrence pattern after minimally invasive surgery.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The rate of peritoneal carcinomatosis and its possible association with worse oncologic outcomes in this systematic review highlights the importance of reporting carcinomatosis as an individual recurrence pattern. As the risk is higher with minimally invasive surgery compared with open surgery, these data should be considered for patient counseling. Ongoing randomized controlled trials could provide additional information on the prognosis of peritoneal carcinomatosis after radical hysterectomy and the differences between minimally invasive and open surgery.

assessment.¹ The Laparoscopic Approach to Cervical Cancer (LACC) trial² showed that women who underwent a minimally invasive radical hysterectomy had worse oncologic outcomes than those who underwent open surgery. Other meta-analyses and observational studies have reproduced those results.^{3–6} Therefore, according to most guidelines, the standard approach for radical hysterectomy is the open approach.^{1,7–9}

Forty-four percent of cervical cancer patients are diagnosed with early-stage disease, for which the 5-year overall survival rate is 91.9%.¹⁰ Recurrence

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rates after radical hysterectomy range from 5% to 26%; 48.4% of recurrences are diagnosed within 2 years, while 77.7% are diagnosed within 5 years after treatment.^{11–14} Most recurrences are local,¹⁵ and the most common sites of distant recurrences are the liver (16%), lungs (14%), bones (9.2%), and large bowel (7.2%).¹⁶

A different pattern of recurrence after radical hysterectomy for cervical cancer is peritoneal carcinomatosis,^{16–17} and the mechanism by which it occurs is unclear. The first reported case in 1997 occurred in a patient after a minimally invasive radical hysterectomy whose early recurrence was associated with ascites, multiple peritoneal tumors, and superficial liver and bowel implants.¹⁸ The rate of peritoneal carcinomatosis as a recurrence pattern among patients after radical hysterectomy for cervical cancer is unknown. The aim of this systematic review and meta-analysis was to compare the incidence of peritoneal carcinomatosis between patients undergoing minimally invasive (laparoscopic and robotic) hysterectomy or open radical hysterectomy for cervical cancer.

METHODS

A systematic literature review was conducted following the Meta-Analysis of Observational Studies in Epidemiology¹⁹ and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)²⁰ guidelines. Articles published from inception up to April 2022 were identified through a search of MEDLINE (accessed through Ovid), Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Clinical Trials, and Scopus databases. Search structures, subject headings, and keywords were tailored to each database by a medical research librarian (KJK) specializing in systematic reviews. The overall search strategy is provided in online supplemental material 1. In addition, references cited in the included studies were manually assessed for inclusion. Abstracts and unpublished studies were excluded. This study was registered in PROSPERO (CRD42022325068).

Eligible articles for the study were original research studies published in English that compared the use of minimally invasive surgery and open radical hysterectomy and reported at least one case of peritoneal carcinomatosis as a recurrence pattern (as defined by the authors; including carcinomatosis, peritoneal recurrences, and port-site or scar metastasis). Inclusion criteria were patients who underwent primary surgery for International Federation of Gynecology and Obstetrics (FIGO) 2009 stage IA–IIA cervical cancer (squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma). Studies were excluded if they had only one cohort of patients, included patients under 18 years of age, neoadjuvant chemotherapy or radiotherapy, pregnancy, FIGO 2009 stage IIB or higher disease, or fertility-sparing disease management. If two or more articles were published by the same author or institution or used the same primary data source, only the most recent article was included in the review.

Study Selection, Data Extraction, and Assessment of Study Quality

Covidence software (Melbourne, Australia) was used for study selection and data extraction. After the removal of the duplicate entries from the initial search, two authors (JH and DV-C) independently assessed all the titles and abstracts of the studies retrieved from the search. The final selection of studies for inclusion

was undertaken independently by three authors (JH, FN, and DV-C), and any disagreement was resolved through discussion.

For the studies included in the final analysis, two authors (ATP and EE) independently and manually extracted data on the variables of interest, including the year of publication, study type, number of patients, patient ages, surgical approach (open surgery, laparoscopic and robotic-assisted procedures), FIGO 2009 stage, histology, number of recurrences, and number of recurrences as peritoneal carcinomatosis. Any disagreement about the extracted data was resolved through discussion until a consensus was reached. To get complete data on peritoneal carcinomatosis recurrences, we requested additional information or clarified data from the authors of five studies^{21–25} by mail. The quality of the observational studies was assessed using the Newcastle-Ottawa assessment scale, and the randomized controlled trial was assessed with the Rob2 tool (online supplemental material 2).

Statistical Analysis

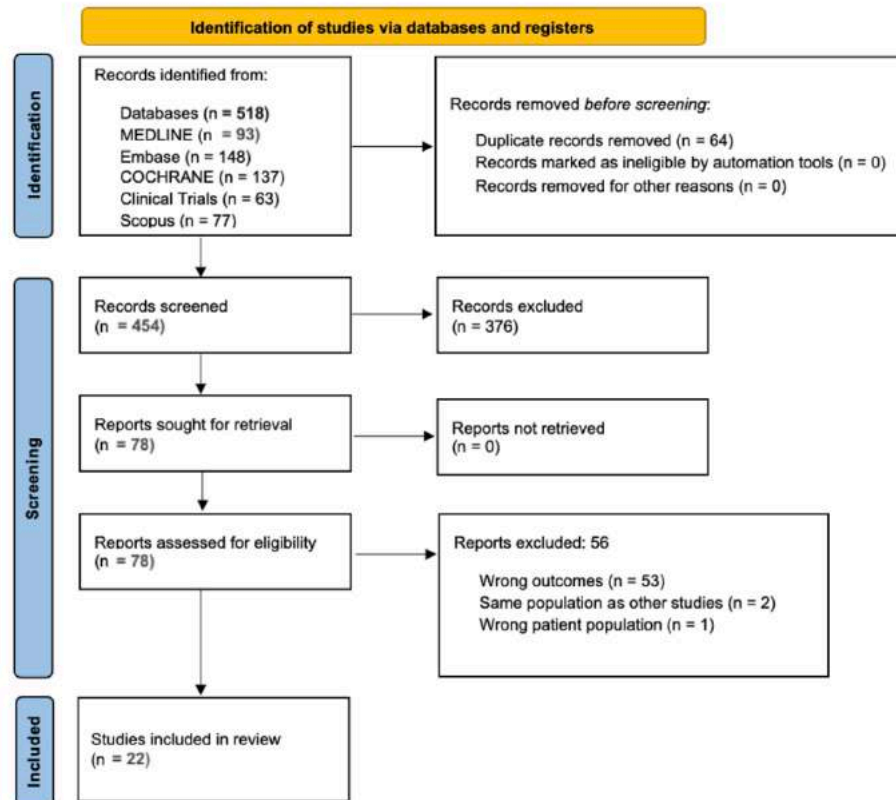
We assessed the overall recurrence incidence, defined as the number of patients with any recurrence divided by the number of patients who underwent a radical hysterectomy, as well as the incidence of carcinomatosis among the patients with recurrence and the incidence of carcinomatosis for each surgical approach.

We conducted a meta-analysis in which the primary outcome was recurrence as peritoneal carcinomatosis. To display the individual study and the pooled effects of the surgical approach on the incidence of peritoneal carcinomatosis, we generated forest plots using RevMan software, version 5.4.1. Statistical heterogeneity was assessed using graphical presentations of the confidence intervals on forest plots and by performing I^2 and χ^2 tests. In the meta-analysis, odds ratio and fixed-effects models were used to generate all statistical estimates. Publication bias was assessed using funnel plots.²⁶

RESULTS

The initial search identified 518 articles. After removing the duplicate entries, the titles and abstracts of the remaining 453 articles were reviewed, and 78 articles were selected for detailed, full-text evaluation. Fifty-three studies were excluded because they did not report the outcome of interest, two because of duplicated information from another study, and one study was left out because it included a population that did not meet the inclusion criteria (online supplemental material 3). Twenty-two studies were included in the final analysis. The PRISMA²⁴ guidelines flow diagram is shown in [Figure 1](#). All but one included studies were retrospective comparative cohort studies. The only randomized controlled trial was considered at low risk of bias according to the Rob 2 tool, and overall Newcastle-Ottawa Scale scores ranged from 5 to 9 points, for the 21 retrospective included studies (online supplemental material 2).

Of the 7626 patients in the 22 studies included^{21–25 27–42} in the final analysis, 3766 (49.4%) underwent minimally invasive surgery, and 3860 (50.6%) underwent open surgery (online supplemental material 4). The most common histology was squamous cell carcinoma (60.9%). Tumor size was reported for 6699 patients (87.8%) and 6220 of these (92.8%) had tumors smaller than 4 cm.



Adapted:: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: <http://www.prisma-statement.org/>

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

The studies' follow-up periods ranged from 25.4 to 112.4 months. In total, 865 (11.3%) of the 7626 included patients had a recurrence. Among the 3766 patients who underwent minimally invasive surgery, 432 (11.5%) had a recurrence, and among the 3860 patients who underwent open surgery, 433 (11.2%) had a recurrence (online supplemental material 5). Of the 865 patients who recurred, 134 (15.5%) had peritoneal carcinomatosis (Table 1). This recurrence pattern was more often seen in patients who underwent minimally invasive surgery (22.2%; $n=96/432$) than in those who underwent open surgery (8.8%; $n=38/433$) (Table 2). For patients who underwent minimally invasive surgery and those who underwent open surgery, the overall rates of peritoneal carcinomatosis were 2.6% and 1%, respectively.

We performed a meta-analysis for the 21 observational studies that revealed a statistically significant higher risk of peritoneal carcinomatosis as a recurrence pattern for patients who underwent minimally invasive hysterectomy compared with those who underwent open surgery (OR 1.90, 95% CI 1.32 to 2.74, $p<0.05$) (Figure 2). There was moderate statistical heterogeneity. This result was concordant with a higher risk reported in the only published randomized controlled trial, even when there was a different magnitude of effect (Figure 2). Assessment of the funnel plots comparing the risk of recurrence presenting as peritoneal carcinomatosis

revealed relative symmetry, suggesting the absence of publication bias (online supplemental material 6).

DISCUSSION

Summary of Main Results

In this systematic literature review and meta-analysis, the risk of recurrence as peritoneal carcinomatosis after radical hysterectomy for cervical cancer was 1.9-fold higher after minimally invasive surgery compared with open surgery. Peritoneal carcinomatosis represented 15.5% of all recurrences, with a recurrence rate of 22.2% in minimally invasive surgery and 8.8% in open surgery.

Results in the Context of Published Literature

The mechanism underlying this pattern of cervical cancer recurrence has not yet been elucidated. Some authors suggest that the high carbon dioxide (CO₂) pressure used during CO₂ pneumoperitoneum alters the superficial mesothelial layer of the peritoneum,⁴³ which could cause intraperitoneal tumor dissemination and a significant increase in the transition of tumorous cells from the G1 to the S phase.^{43 44} However, other authors have found an association between peritoneal carcinomatosis and intracorporeal colpotomy performed under pneumoperitoneum pressure.^{23 45 46}

Original research

Table 1 Carcinomatosis recurrence by surgical approach

Study	N	Carcinomatosis recurrences (N)	Carcinomatosis recurrences by hysterectomy technique*				
			Open surgery	Minimally invasive surgery		Laparotomy scar metastasis	Port-site metastasis
				Laparoscopic	Robotic		
Sobiczewski et al, 2009 ²⁷	80	2	0	2	NA	0	0
Toptas et al, 2014 ²⁸	68	2	1	1	NA	0	1
Mendivil et al, 2016 ²⁹	146	2	0	1	1	0	0
Park et al, 2016 ³⁰	293	11	5	6	NA	0	0
Zanagnolo et al, 2016† ²¹	307	9	2	NA	7	0	2
Ramirez et al, 2018‡ ²	631	9	0	9		0	0
Matanes et al, 2019 ³²	98	2	1	NA	1	0	0
Gil-Moreno et al, 2019 ³¹	188	4	2	2	0	0	1
Alfonzo et al, 2019 ⁴⁰	864	19	6	NA	13	0	7
Kim et al, 2019 ³³	565	7	1	6	NA	0	0
Doo et al, 2019 ³⁴	105	2	1	NA	1	0	0
Kanao et al, 2019 ³⁵	163	1	1	0	NA	0	0
Brandt et al, 2019† ²⁴	196	3	1	2	NA	1	1
Lim et al, 2019 ³⁶	136	1	0	1	NA	0	0
Yang et al, 2020† ²²	333	7	0	NA	7	0	1
Anchora et al, 2020 ³⁹	286	7	2	5	NA	0	0
Bogani et al, 2020† ²³	1058	7	1	6	NA	0	0
Kwon et al, 2020 ⁴¹	510	16	9	7	NA	0	0
Zaccarini et al, 2021 ³⁷	93	2	1	1		0	0
Kim et al, 2021 ³⁸	148	1	0	1	NA	0	0
Sert et al, 2021 ⁴²	582	12	0	12		0	0
Baiocchi et al, 2022† ²⁵	776	8	4	4		0	0
Total	7626	134	38	96		1	13

Zaccarini et al 2021, Sert et al 2021, and Baiocchi et al 2022 did not specify the surgical approach.

*Port-site or scar metastasis included.

†Requested additional information from the authors of the original publication.

‡Additional information from SGO 2022 Annual Meeting on Women’s Cancer. Outcomes by received treatment.

NA, not available; SGO, Society of Gynecologic Oncology.

One of the aims of the retrospective SUCCOR study was to evaluate the impact of the use of a uterine manipulator and protective maneuvers during colpotomy in minimally invasive surgery.⁶

The authors found that the use of uterine manipulators in patients undergoing minimally invasive radical hysterectomy for stage IB1 cervical cancer was associated with a 2.76-fold increased risk of

Table 2 Recurrence rates by surgical approach

	Open surgery (n=3860)	Minimally invasive surgery (n=3766)	Total (n=7626)
Total number of recurrences	433 (11.2%)	432 (11.5%)	865 (11.3%)
Number of carcinomatosis recurrences	38 (1%)	96 (2.6%)	134 (1.8%)
Rate of carcinomatosis*	8.8%	22.2%	15.5%

*Among patients with recurrence.

recurrence (95% CI 1.75 to 4.33, $p < 0.001$). Other patients who had undergone minimally invasive surgery and in whom protective maneuvers were applied had similar oncologic outcomes compared with the open surgery approach. In one retrospective multicenter study, Anchora et al⁴⁷ demonstrated that the 4.5-year disease-free survival rate of patients who underwent minimally invasive radical hysterectomy without intraperitoneal exposure protection maneuvers (86.6%) was significantly lower than that of patients who underwent surgery with protection maneuvers (95.9%, $p = 0.005$). Similar findings were reported in a retrospective study by Kohler et al,⁴⁸ using a combined laparoscopic and vaginal approach following tumor isolation to perform a vaginal colpotomy without the use of a uterine manipulator. They reported 4.5-year disease-free survival and an overall survival rate of 95.8% and 97.8%, respectively.

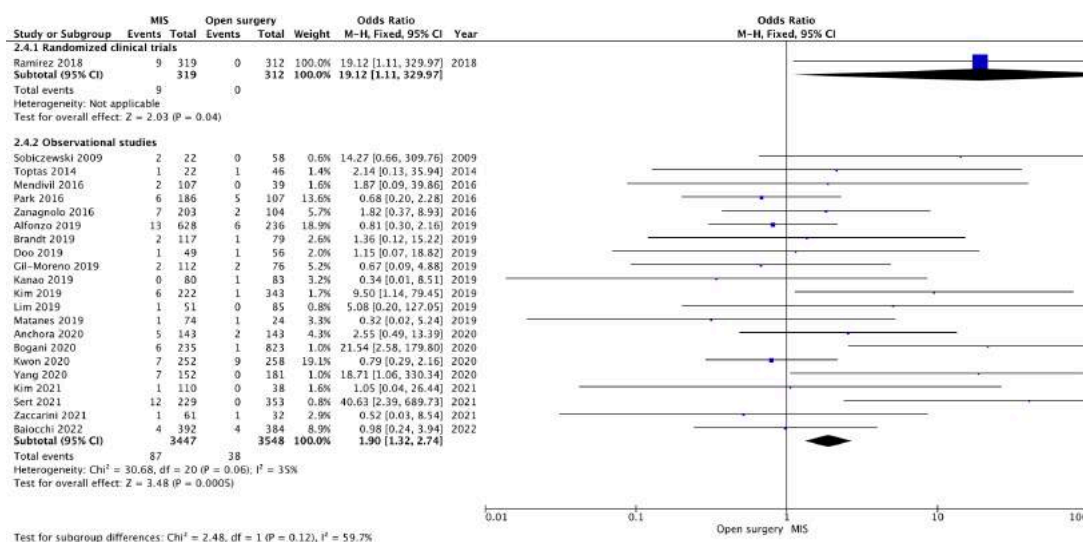
Although cases of peritoneal carcinomatosis as a pattern of recurrence have been reported for more than 20 years, peritoneal carcinomatosis has been underestimated because it is usually categorized into other recurrence patterns, rather than individually.^{24 25 49} Since the publication of the LACC trial,² the reported frequency of peritoneal carcinomatosis as a pattern of recurrence after different surgical approaches for early-stage cervical cancer has increased.^{39–42 46 50} Among studies comparing surgical approaches, the incidence of peritoneal carcinomatosis ranges from 17% to 58% for minimally invasive surgery^{23 49} and from 12.8% to 23.7% for open surgery.^{40 41} In a retrospective analysis of 128 patients who underwent radical hysterectomy with minimally invasive surgery and different colpotomy techniques, 50%

of recurrences were related to peritoneal carcinomatosis, after intracorporeal colpotomy. These recurrences were characterized by ascites; paracolic gutter implants; involvement of the intestinal serosa, duodenum, subhepatic spaces, and splenic areas; and diffuse peritoneal disease.⁴⁵

It seems that oncologic outcomes after peritoneal carcinomatosis relapse are worse. In a retrospective study of 112 robotic radical hysterectomies, Fitzsimmons et al⁵⁰ reported a carcinomatosis recurrence rate of 45%. The authors also found that the overall survival duration of patients with peritoneal carcinomatosis (22 months) was significantly shorter than that of patients with other recurrence patterns (90 months, $p < 0.05$).

The only randomized controlled trial comparing minimally invasive with open surgery in patients undergoing radical hysterectomy for cervical cancer did not report peritoneal carcinomatosis as an independent outcome in the original publication.² However, recently at the Society of Gynecologic Oncology annual meeting in 2022, an update was presented, showing that peritoneal carcinomatosis occurred in 24% of patients undergoing minimally invasive surgery, compared with zero cases in the open surgery arm.^{51 52}

Ongoing randomized controlled trials comparing the oncologic outcomes of minimally invasive versus open surgery for early-stage cervical cancer, such as the Robot-assisted Approach to Cervical Cancer (RACC),⁵³ the Robotic vs Open Hysterectomy Surgery in Cervix Cancer (ROCC),⁵⁴ the LAUNCH 1⁵⁵ and LAUNCH 2⁵⁶ trials, could clarify whether patients who undergo open or minimally

**Figure 2** Forest plot of comparison. Minimally invasive surgery (MIS) versus open surgery, outcome: peritoneal carcinomatosis recurrence.

Original research

invasive surgery have higher rates of peritoneal carcinomatosis, if they investigate that outcome specifically.

Strengths and Weaknesses

Among the strengths of our study are the fact that it has a registered protocol with specified selection criteria, a rigorous process for data analysis, and that it adhered to standardized guidelines for reporting systematic reviews and data collection. Lastly, we used a published tool to assess the quality of the included studies in the review. However, the study has some weaknesses, such as the retrospective nature of all but one of the included studies, potential selection and publication biases, and restriction to data published in English. Also, the included studies were clinically heterogeneous, and an imbalance among the patient's characteristics—between minimally invasive surgery and open surgery favoring minimally invasive surgery—was evident for observational studies. The descriptions of clinical factors such as tumor size, lymph node metastasis, the recurrence location, patient follow-up, surgical details such as colpotomy route, the use of uterine manipulators, and protected specimen extraction, and information about adjuvant treatments were lacking in many studies. We were also unable to describe the treatment and the mortality rate of patients with peritoneal carcinomatosis recurrence pattern. Finally, peritoneal carcinomatosis could have been interpreted differently in the studies included in our analysis because of their retrospective nature.

Implications for Practice and Future Research

This review provides additional information that may be helpful when counseling patients regarding the safety of the surgical approach in early-stage cervical cancer. Also, because patients with peritoneal carcinomatosis could have worse clinical outcomes than patients with other recurrence patterns, our study highlights the importance of individually reporting peritoneal carcinomatosis. We encourage the authors of ongoing randomized controlled trials to report on the related clinical factors and oncologic outcomes of this recurrence pattern.

CONCLUSIONS

In this systematic review, minimally invasive radical hysterectomy was associated with a statistically significant higher risk of peritoneal carcinomatosis recurrence compared with open radical hysterectomy for early-stage cervical cancer.

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