Oncologic outcomes of minimally invasive versus open radical hysterectomy for early stage cervical carcinoma and tumor size ≤2 cm: a systematic review and meta-analysis

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/ijgc-2021-002505).

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Received 7 February 2021
Revised 26 April 2021
Accepted 28 April 2021
Published Online First 20 May 2021

To cite: Nasioudis D, Albright BB, Ko EM, *et al. Int J Gynecol Cancer* 2021;**31**:983–990.

HIGHLIGHTS

- Minimally invasive radical hysterectomy for cervical cancer and tumor size ≤2 cm is associated with worse progression-free survival.
- Patterns of relapse appear comparable; rate of distant relapse was comparable between the two groups.
- Minimally invasive radical hysterectomy should be avoided for all patients with cervical cancer despite tumor size.

ABSTRACT

Objective To investigate the oncologic outcomes of patients with early-stage cervical carcinoma and tumor size ≤2 cm who underwent open or minimally invasive radical hysterectomy.

Methods The Pubmed/Medline, Embase, and Web-of-Science databases were queried from inception to January 2021 (PROSPERO CRD 42020207971). Observational studies reporting progression-free survival and/or overall survival for patients who had open or minimally invasive radical hysterectomy for early-stage cervical carcinoma and tumor size ≤2 cm were selected. Level of statistical heterogeneity was evaluated with the I^2 statistic. A random-effects model was used to compare progression and overall survival between the two groups and HR with 95% confidence intervals were calculated with the Der Simonian and Laird approach. Risk of bias and quality of included studies was assessed with the Newcastle-Ottawa scale.

Results A total of 10 studies that met the inclusion criteria were included encompassing 4935 patients. Of these, 2394 (48.5%) patients had minimally invasive and 2541 (51.5%) patients had open radical hysterectomy; respectively. Patients who underwent minimally invasive hysterectomy had worse progression-free survival than those who had open surgery (HR 1.68, 95% CI 1.20, 2.36, I^2 26%). Based on five studies, patients who had minimally invasive (n=1808) hysterectomy had a trend towards worse overall survival than those who had open surgery (n=1853) (HR 1.64, 95% CI 1.00 to 2.68, I^2 15%).

Conclusion Based on a systematic review of the literature and meta-analysis of studies that control for confounders, for patients with cervical cancer and tumor size ≤2 cm, minimally invasive radical hysterectomy was associated with worse progression-free survival than laparotomy.

INTRODUCTION

Cervical cancer is the fourth most common gynecologic malignancy worldwide.[1] For patients with apparent FIGO 2009 stage IA1 with lymphovascular invasion/IA2–IB2 disease, radical hysterectomy with lymphadenectomy or sentinel lymph node biopsy is recommended.[2] Data from retrospective studies show that minimally invasive hysterectomy can be associated with lower blood loss, decreased rate of post=operative complications, faster recovery, and shorter inpatient hospital stay.[3 4] However, the widespread use of minimally invasive surgery for patients with cervical cancer was adopted without evidence from randomized trials and was based on small retrospective studies with a relatively short follow-up.[3] A recent randomized trial demonstrated worse progression-free survival for patients who had minimally invasive radical hysterectomy.[4] In addition, an analysis of the National Cancer Database also revealed inferior overall survival for a similar patient population who underwent minimally invasive radical hysterectomy between 2010 and 2013.[5] It is unclear whether a higher relapse rate is related to the use of uterine manipulator, spread of tumor cells during colpotomy, or inadequate surgical technique.[6 7] A recent meta-analysis of high-quality observational studies also concluded that there is an increased risk of relapse among patients undergoing minimally invasive radical hysterectomy, however a sub-analysis based on tumor size was not performed.[6]

While major organizations such as FIGO, European Society of Gynecological Oncology, Society of Gynecologic Oncology, National Comprehensive Cancer Network guidelines discourage the performance of minimally invasive radical hysterectomy for cervical cancer, for a number of surgeons the question remains whether a minimally invasive approach could potentially be considered for patients with small tumors (<2 cm).[8] Recently, a series of retrospective studies have attempted to answer this question. However,

given the low incidence of cervical cancer, the majority of studies do not have sufficient statistical power to detect a difference in progression-free survival among patients with small tumors, and in many studies follow-up of the minimally invasive group was short.[9–24] The aim of the present systematic review and meta-analysis was to compare the reported oncologic outcomes between open and minimally invasive radical hysterectomy for patients with apparent early-stage cervical carcinoma and tumor size ≤2 cm.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines[25] ; a protocol was determined beforehand by all participating authors and submitted for registration to the PROSPERO Registry (CRD42020207971). A comprehensive electronic search (from conception to end-of-search date January 30, 2021) of the Pubmed/Medline, Embase, and Web of Science databases was performed using the following keywords: (cervical cancer OR cervix) AND (hysterectomy or radical) AND (laparoscopy OR robotic OR minimally invasive OR laparoscopes OR laparotomy OR open); in addition, MESH terms were used. Reference lists of the included studies as well as prior systematic reviews were systematically hand searched. Observational studies published as full papers in English were eligible for inclusion. Inclusion criteria were: patients with invasive squamous, adenosquamous, or adenocarcinoma of the cervix; patients undergoing primary radical hysterectomy with lymphadenectomy for apparent early stage (FIGO 2009 stage IA–IIA) disease; comparison of open and minimally invasive surgical techniques; studies with at least (n=50) patients in each study group; follow-up of at least 24 months; studies reporting the number of patients with tumors <=2 cm in each surgical modality group; studies reporting data on progression-free survival; studies that attempted to control survival for confounders known to be associated with survival, such as lymphovascular invasion, depth of invasion, age, presence of co-morbidities, and histology, with statistical methods such as Cox regression, propensity score matching, or inverse probability weighting. Exclusion criteria were: studies not reporting the number of patients with tumor size ≤2 cm; performance of laparoscopic-assisted vaginal hysterectomy; significant overlapping population; no data on progression-free survival; administration of neo-adjuvant chemotherapy or radiation therapy; follow-up <24 months; not controlling for important confounders; no data on tumor size.

In this study we opted to select as primary outcome progression-free survival while secondary outcomes were overall survival and location of relapse. The methodological quality of observational studies was assessed using the Newcastle-Ottawa Quality Assessment Scale for non-randomized studies.[26] The scale was developed to assess the quality of non-randomized studies directed to the task of incorporating the quality assessments in the interpretation of meta-analytic results. Each study is evaluated on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of outcome of interest. Data extraction from all eligible papers was performed by two authors (DN, BBA) working independently. Any discrepancies were resolved by discussion. From each eligible study the following parameters were extracted when applicable: general study characteristics (author, country of origin, date of publication, years of recruitment), patient demographics, type of minimally invasive surgery (laparoscopic or robotic-assisted), number of relapses and deaths, progression-free (defined as time between diagnosis or surgery until first relapse), and overall survival (time from diagnosis or surgery to death from any cause). If the required data for the primary outcome were not readily available in the published articles or could not be extracted from published tables, online supplemental material or Kaplan-Meier curves, the corresponding authors were contacted. In studies with overlapping populations, the study with the largest number of patients was included.

The level of statistical heterogeneity was evaluated with the X^2 and I^2 statistic; values of 25%, 50%, and 75% were considered low, moderate, and high heterogeneity, respectively A random-effects model was used to compare relapse and death rate between the two groups and OR and 95% confidence intervals were calculated with the Der Simonian and Laird approach. HR and 95% confidence intervals were pooled using the generic inverse variance method as provided by the RevMan software. Forest plots were created for each comparison, while graphical funnel plots were generated to determine the presence of publication bias by visual inspection. P values <0.05 were considered statistically significant. If significant heterogeneity was noted, a sensitivity analysis was performed by a sequential omission algorithm.[27] If HR and 95% confidence intervals were available, validated statistical methodology was used to generate them.[28] Statistical analysis was performed with the Cochrane Review software (Review Manager version 5.2).[29] This study did not require evaluation by an institutional review board.

RESULTS

A total of 10 studies that met the inclusion criteria were identified.[10–13 15 16 20–22 24] The study selection flowchart is depicted in online supplemental Figure 1 while graphical funnel plot is depicted in online supplemental Figure 2. The majority of studies (n=6) originated from Asia[12 13 15 16 21 22] followed by North America (n=2),[10 11] Europe (n=1),[20] and one international study[24] was identified. A total of 4935 patients were included, 2394 (48.5%) patients had minimally invasive and 2541 (51.5%) patients had open radical hysterectomy, respectively, for tumors with size ≤2 cm. Table 1 summarizes the basic characteristics, median follow-up, and method of tumor size assessment in each of the included studies; online supplemental Table 1 summarizes clinicopathological characteristics from studies with available data.[12 15 16 21 22] In nine studies, minimally invasive radical hysterectomy was performed with traditional laparoscopy while in two studies, originating from the United States, the vast majority of patients underwent robotic-assisted radical hysterectomy. The majority of studies (n=8) were deemed of good quality with a total Newcastle-Ottowa score ≥7 (Table 1).

Patients who underwent minimally invasive hysterectomy had worse progression-free survival than those who had open surgery (HR 1.68, 95% CI 1.20 to 2.36, I^2 26%) (Figure 1). Pooled HR following serial exclusion of each study is presented in (online supplemental Table 2). When including studies (n=7)[13 15 16 20–22 24] that reported at least 100 patients in each arm, the minimally invasive (n=2100) group had worse progression-free survival than the open (n=2216)

Table 1 Basic demographic and clinical characteristics of included studies

Author	Year	Country	Institution	Years of enrollment	Follow-up	Type of MIS	Open (n)	MIS (n)	NOS score	Tumor size determination	Stage	Controlling variables
Chen C *et al*[22]	2020	China	Database of 37 hospitals	2004–2016	Median 36 mths	All laparoscopic	926	926	7	pathology, if not available MRI,CT, US	IB1	Age, diagnosis year, histology, vaginal margin, parametrial involvement, LN status, tumor size, depth of invasion, LVSI, and adjuvant treatment
Chen X *et al*[21]	2020	China	First Affiliated Wenzhou, First People's Hosp Foshan, Taizhou Hospital	2010–2018	Open 49.5 mths, MIS 51.8 mths	All laparoscopic	196	129	8	physical examination, MRI or US	IB1	Age, histology, grade, pre-operative conization, depth of invasion, LVSI, adjuvant treatment
Chiva *et al*[20]	2020	Europe	Multicenter	1/2013-12/2014	Median 59 mths	n/a	160	128	7	Pathology	IB1	Tumor size, grade, LVSI, depth of invasion, margins status, LN status, and adjuvant treatment
Hu *et al*[16]	2020	China	Second Uni Hospital of Sichuan	2013–2016	Median 60 mths	All laparoscopic	147	147	6	MRI/CT if not available pelvic examination	IA2–IIA	Age, stage, histology, tumor size, depth of invasion, and adjuvant treatment
Kim *et al*[15]	2019	S.Korea	Seoul National University, Bundang Hospital	2002–2018	Open 133.4 mths MIS 46.8 mths	All laparoscopic	122	122	7	MRI	IB1	Stage, parametrial involvement, and LN status
Nam *et al*[13]	2012	S.Korea	Asan Medical Center	1997–2008	Open 127 mths, MIS 63 mths	All laparoscopic	173	162	7	N/S	IA2–IA	Tumor size, depth of invasion, LVSI, parametrial involvement, LN status, and age
Paik *et al*[12]	2019	S.Korea	Multicenter	2000–2008	Median 63.6 mths	All laparoscopic	186	62	7	Physical examination, if not available CT/ MRI	IB1–IIA	Age, stage, histology, LVSI, depth of invasion, and tumor size
Rodriguez *et al*[24]	2021	International	Multicenter	2006–2017	Open 52.1 mths, MIS 52.6 mths	All laparoscopic	492	486	8	Physical examination	IA1–IB1	Age, year of diagnosis, stage, histology, grade, tumor size, and adjuvant treatment

Continued

Table 1 Continued

Author	Year	Country	Institution	Years of enrollment	Follow-up	Type of MIS	Open (n)	MIS (n)	NOS score	Tumor size determination	Stage	Controlling variables
Uppal *et al*[10]	2020	USA	Multicenter	2010–2017	Open 44.6 mths, MIS 30.7 mths	~80% robotic	82	182	6	Pathology	IA1–IB1	Co-morbidity index, race, BMI, pathology grade, histology, LVSI, and adjuvant treatment
Yang *et al*[11]	2020	USA	Mayo Clinic Registry	2000–2017	Open 130 mths, MIS 53 mths	All robotic	57	50	7	Pathology	IA2–IIA	Age, race, depth of invasion, tumor size, parametrial involvement, positive margins, LN status, stage, grade, and LVSI

LN lymph node, BMI, body mass index; LVSI, lymphovascular space invasion; MIS, minimally invasive surgery; mths, months; n/a, not available; NOS, Newcastle-Ottawa score.;

hysterectomy group (HR 1.50, 95% CI 1.15 to 1.96, I^2 0%). When including studies that determined tumor size based exclusively on pathology (n=4) the minimally invasive (n=1286) group, was associated with worse progression-free survival than the open (n=1225) hysterectomy group (HR 1.66, 95% CI 1.16 to 2.36, I^2 0%). When including studies that determined tumor size based on imaging and/or physical examination (clinical stage) exclusively (n=5), there was no difference in progression-free survival between the minimally invasive (n=946) and open (n=1143) hysterectomy groups (HR 1.70, 95% CI 0.84 to 3.44, I^2 55%). Based on data from studies originating from Asia (n=6),[12 13 15 16 21 22] performance of minimally invasive hysterectomy was not associated with worse progression-free survival (HR 1.73, 95% CI 0.99 to 3.03, I^2 46%). Similarly, based on data from studies originating from Europe and the Americas (n=4),[10 11 20 24] performance of minimally invasive hysterectomy was associated with worse progression-free survival (HR 1.65, 95% CI 1.11 to 2.47, I^2 0%).

Based on data from five studies,[11 16 20 22 24] patients who had minimally invasive (n=1808) hysterectomy had a trend towards worse overall survival compared with those who had open surgery (n=1853) (HR 1.64, 95% CI 1.00 to 2.68) (Figure 2). Table 2 summarizes the outcomes reported in each study. Data on the location of relapse were available from four studies,[12 15 21 22] and included 35 and 59 cases in the open and minimally invasive surgery groups (online supplemental Table 3). Among patients who had open surgery, 51.4% (n=18) experienced an abdominal/distant relapse, 8.6% (n=3) lymph node relapse, and 40% (n=14) a pelvic/vaginal relapse. For patients who had minimally invasive surgery, 64.4% (n=38) had an abdominal/distant relapse, 3.4% (n=2) a lymph node relapse, and 30.5% (n=18) a pelvic/vaginal relapse.

DISCUSSION

Summary of Main Results

Based on a large number of patients, minimally invasive radical hysterectomy was associated with a worse progression-free survival than open surgery. Low heterogeneity was found but a series of sensitivity analyses (mode of tumor size assessment, country of origin, and number of participants) were performed to aid in the interpretation of our results. Patients who underwent minimally invasive radical hysterectomy also had worse overall survival and the difference approached statistical significance. Based on data from four studies, location of tumor relapse did not differ between the minimally invasive and open groups.

Results in the Context of Published Literature

Data on the oncologic safety of minimally invasive surgery for patients with cervical cancer and small tumors are heterogeneous and conflicting. A recent randomized trial did not find a higher relapse rate in the subgroup of patients with tumors,<2 cm, but it was not designed or powered to identify such a difference.[4] In a retrospective study focusing exclusively on patients with tumors <2 cm, Chen et al reported better 5-year progression-free survival for patients who had open surgery (n=196, 97.7%) than for those who had minimally invasive radical hysterectomy (n=129, 90.4%), p=0.016.[21] After controlling for confounders, laparoscopic approach was associated with worse disease-free survival (HR 4.64, 95% CI 1.26 to 17.06).[21] Similarly, Uppal et al performed a multicenter

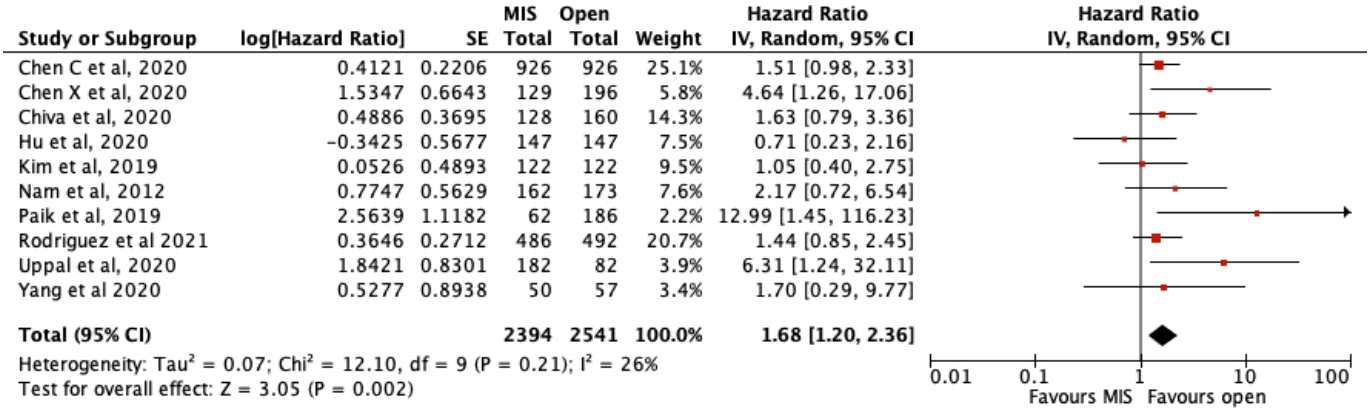

Figure 1 Pooled progression-free survival between minimally invasive and open radical hysterectomy groups. MIS, minimally invasive surgery.

retrospective study among institutions in the United States and Canada and reported inferior progression-free survival among 264 patients with tumors <2 cm who had minimally invasive surgery.[10]

On the other hand, two recent analyses of large European nationwide databases did not find an increased risk of relapse for patients undergoing a minimally invasive approach. Alfonso et al examined the Swedish National Cancer Registry for patients with cervical carcinoma undergoing primary radical hysterectomy at high-volume centers and reported a 5-year progression-free survival rate of 92% in the open (n=150) and 91% in the robotic-assisted (n=460) group.[30] Similarly, in an analysis of the Netherlands Cancer Registry that included 434 patients with tumors of <2 cm who underwent radical hysterectomy between 2010 and 2017, there was no difference in progression-free survival between the open and minimally invasive groups; with 5-year progression-free survival rates of 91.4% and 96.4%, respectively.[9] Nevertheless, in both studies, survival was not controlled for important confounders, exclusively among patients with tumor size <2 cm. Another multicenter European retrospective study (SUCCOR) that recruited patients from 29 countries and 126 institutions, and controlled for important confounders did not find a significantly worse progression-free survival between the minimally invasive (n=126) and open (n=241) groups (HR 1.63, 95% CI 0.79 to 3.40).[20]

A critical point should be underlined; in several studies reported in the literature, patients who underwent open hysterectomy had significantly longer follow-up, while many studies do not control for confounders such as histology, presence of lymphovascular invasion, and post-operative treatment. A shorter follow-up can confound results since late relapses are not captured, while differences in overall survival are not evident. Similar to our results, in a recent analysis of the National Cancer Database, that included 2046 patients with cervical carcinoma and tumor size ≤2 cm who underwent minimally invasive (n=1195) or open (n=851) radical hysterectomy, those who had a minimally invasive approach had a worse overall survival (HR 1.72, 95% CI 1.05 to 2.82) after controlling for confounders.[31] However, that study was limited by the lack of central pathology review, data on surgeon's experience, and cause of death.

The etiology of increased relapse among those receiving minimally invasive surgery is a matter of debate. One theory is that use of an uterine manipulator may be associated with intraperitoneal spread of cancer cells. In a recent multi-institutional study, patients who underwent minimally invasive surgery without the use of an uterine manipulator had similar rate of relapse to those who had an open surgery (HR 1.58; 95% CI 0.79 to 3.15; p=0.20), while within the minimally invasive surgery group use of a uterine manipulator was associated with higher relapse rate.[20] However, in an analysis of 224 patients who underwent minimally invasive radical hysterectomy at two large Canadian centers, after controlling for confounders, use of a uterine manipulator was not associated with recurrence risk.[32] Lack of appropriate surgical expertise may also contribute to worse oncologic outcomes. Chong et al reported the surgical and oncologic outcomes of 100 consecutive patients. With improving surgical experience, operating time and the perioperative complication rate decreased, but overall and progression-free survival remained the same.[33] Kim et al analyzed the learning curve of a single surgeon and reported poorer progression-free survival during the early phase of minimally invasive surgery.[34]

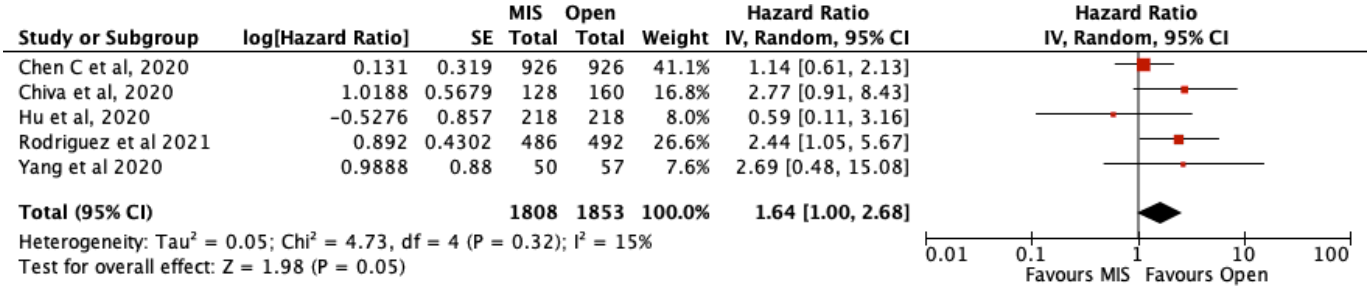

Figure 2 Pooled overall survival between minimally invasive and open radical hysterectomy groups. MIS, minimally invasive surgery.

Table 2 Main outcomes reported in the included studies

Author	Year	Open (n)	MIS (n)	Relapse open	Relapse MIS	Relapse rate open	Relapse rate MIS	Definition OS/PFS	D					
									DFS open	DFS MIS	Death open	Death MIS	OS open	OS MIS
Chen C *et al*[22]	2020	926	926	37	44	4.0%	4.8%	Not provided	5year 94.9%	5year 92.6%	22	18	5year 96.6%	5year 96.3%
Chen X *et al*[21]	2020	196	129	5	11	2.6%	8.5%	Not provided	5year 97.7%	5year 90.4%	3	4	5year 99.4%	5year 96.9%
Chiva *et al*[20]	2020	160	128	15	17	9.4%	13.3%	From surgery	HR 1.63 (95% CI 0.79 to 3.40) favor open		5	8	HR 2.77 (0.91 to 8.47) favor open	
Hu *et al*[16]	2020	147	147	9	5	6.1%	3.4%	From surgery	5year 94.3%	5year 97.3%	2	2	5year 97.6%	5year 99.3%
Kim *et al*[15]	2019	122	122	11	10	9.0%	8.2%	From diagnosis	3year 93.1%	3year 90%	9	2	5year 96.4%	5year 98.6%
Nam *et al*[13]	2012	173	162	5	8	2.9%	4.9%	From surgery	5year 97.4%	5year 94.2%	3	5	n/a	n/a
Paik *et al*[12]	2019	186	62	1	6	0.5%	9.7%	From surgery	HR 12.987 (1.45 to 116.24) favor open		0	1	n/a	n/a
Rodriguez *et al*[24]	2021	492	486	n/a	n/a	n/a	n/a	From surgery	HR 1.44 (0.85 to 2.45)		n/a	n/a	HR 2.44 (1.05 to 5.67)	
Uppal *et al*[10]	2020	82	182	2	16	2.4%	8.8%	From surgery	aHR:6.31 (1.24 to 31.9) favor open		n/a	n/a	n/a	n/a
Yang *et al*[11]	2020	57	50	n/a	n/a	n/a	n/a	From surgery	HR 1.695 (0.29 to 9.77)		n/a	n/a	HR 2.69 (0.48 to 15.07)	

aHR, adjusted hazard ratio; DFS, disease-free survival; MIS, minimally invasive surgery; n/a, not available; OS, overall survival; PFS, progression-free survival.

We should underline that pre-operative tumor size assessment by physical examination and imaging is challenging.[35] The majority of studies included in the present review, determined tumor size based on pathology report and, if not available, imaging or physical examination. Uppal et al reported significant discrepancies between pre-operative and pathologic tumor size; from 291 patients deemed as having no visible disease, 19.9% actually had tumors>2 cm on final pathology while 34.6% of 257 patients with tumors <2 cm based on pre-operative assessment had tumors >2 cm on final pathology.[10] Thus selecting a specific tumor size cut-off point to establish the safety of a minimally invasive approach could be problematic. Nevertheless, a question that merits further investigation is whether a minimally invasive approach is safe for patients with documented microscopic tumors (stage IA2 disease) on physical examination and imaging, or no visible disease following cold knife cone. The number of patients with IA2 disease reported by retrospective studies is very small, while they have a baseline low relapse rate that would require a collaborative effort to obtain a considerable number of patients for a meaningful analysis. For patients who underwent conization and had no residual disease on pre-operative assessment, Uppal et al reported a relapse rate of 1.4% and 2.9% in the open (n=72) and minimally invasive (n=171) groups, p=0.48.[10] Casarin et al also identified 186 stage IA1–IB1 patients who underwent minimally invasive radical hysterectomy and reported that pre-operative conization was associated with a lower risk of relapse (1.1% vs 16.1%, p<0.001) even for patients with stage IB1 disease (1.8% vs 17.2%, p=0.004).[36] Further research, is warranted to investigate whether minimally invasive surgery could be considered for patients with microscopic tumors or no visible disease following cold knife cone.

Strengths and Weaknesses

A major strength of the present study is the inclusion of a large number of patients with tumor size ≤2 cm who underwent minimally invasive or open radical hysterectomy. We performed a thorough review of the literature and a series of sensitivity analyses that can aid readers in the interpretation of our results, while the Newcastle-Ottawa scale was used to evaluate the quality of the included studies. However, certain limitations should be mentioned. First, although all studies controlled for important confounders, post-operative treatment and surveillance might have varied. Only one study reported the performance of protective maneuvers to prevent tumor contamination, and thus its impact on relapse rate could not be assessed in a dedicated sub-analysis.[20] Similarly, evaluation of relapse rate among patients with no residual disease following cone biopsy could not be performed since only two studies reported such an outcome.[10] Moreover, not all studies provided the exact method of tumor size determination while some used a combination of imaging, physical examination, and pathology report. When imaging was used, authors did not clarify how many patients underwent an MRI versus other imaging modalities, such as CT or ultrasound, which may be less sensitive in tumor measurement. In addition, relapse rate in each study varied, probably secondary to patient risk factors, variation in surgical expertise, and post-operative adjuvant treatment. We opted to include studies that had a minimum of 24 months of follow-up in each arm, similar to a recent meta-analysis,[6] though as previously discussed, follow-up might not have captured all relapses, especially in the minimally

invasive hysterectomy groups. Lastly, we excluded studies that did not report any data on tumor size, since we could not request authors to individually collect additional data and re-analyze them. Thus some large retrospective studies did not meet our inclusion criteria.[37 38] Also, only one of the included studies provided data on blood loss, intra-operative and post-operative complications and so we could not compare differences in peri-operative outcomes between the two groups. Since there was a possibility of some minor overlap between two studies,[20 24] we performed a sensitivity analysis excluding serially each study, and our results did not change.

Implications for Practice and Future Research

Given the accumulating evidence demonstrating worse oncologic outcomes for patients undergoing minimally invasive radical hysterectomy, and difficulty in accurately assessing tumor size preoperatively, an open approach should be selected. An international effort to perform individual patient data meta-analysis with information on important confounders and post-operative treatment could aid in further elucidating outcomes of minimally invasive surgery for patients with microscopic or small tumors or no residual disease.

CONCLUSIONS

In this systematic review of literature and meta-analysis that compiled data from a large number of patients who underwent primary radical hysterectomy with tumor size ≤2 cm, minimally invasive radical hysterectomy was associated with worse progression-free survival.

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Acknowledgements We would like to thank Dr Brown, Dr Chiva, Dr Gil-Moreno, and Dr Wenzel for providing additional information from their published papers.

Contributors DN: Conceptualization; data curation; statistical analysis; formal analysis; investigation; methodology; project administration; resources; software; visualization; writing - original draft; writing - review and editing. BBA: Data curation; formal analysis; investigation; methodology; project administration; resources; software; visualization; writing - original draft; writing - review and editing. SK, MM, RLG II, AFH, EMK: Investigation; methodology; writing - original draft; writing - review and editing. NL: Supervision; formal analysis; investigation; methodology; writing - original draft; writing - review and editing.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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