Robotic radical hysterectomy for early-stage cervical cancer: A systematic literature review

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Robotic technology has recently come into widespread use to overcome the limitations of laparoscopic radical hysterectomy in the treatment of early-stage cervical cancer. Most comparative studies showed that blood loss and hospital stays for patients undergoing minimally invasive surgery, including robotic procedures, were superior compared to open surgery. Moreover, the survival outcomes of robotic radical hysterectomy were not inferior to open radical hysterectomy. Unexpectedly, the Laparoscopic Approach to Cervical Cancer (LACC) trial, a randomized, open-label, noninferiority study that compared minimally invasive radical hysterectomy with open radical hysterectomy, revealed that minimally invasive surgery was associated with a higher risk of recurrence and death compared with open surgery. Strict guidelines for robotic radical hysterectomy for the treatment of early-stage cervical cancer should be established in accordance with objective Korean data. In addition, it is recommended that further studies should be performed on how to avoid the use of uterine manipulators and the dissemination of cancer cells by ensuring a more effective vaginal closure using a standardized approach.

Key Words: Cervical cancer; Radical hysterectomy; Robot

INTRODUCTION

Radical hysterectomy (RH) is a well-established treatment modality of early-stage cervical cancer. RH is defined as the *en bloc* removal of the uterus and cervix with the surrounding parametrial tissue and upper vagina. Since the introduction of conventional laparoscopy, improvements in gynecologic surgery have been notable. However, laparoscopic RH (LRH) remains a rather unpopular choice among

gynecologic oncologists because of the increased operative time and the steep learning curve required for competency [1]. Robotic technology has recently come into widespread use to overcome the limitations of laparoscopic surgery [2]. This is because robotic surgery provides more surgical options, such as nerve-sparing technique, due to its superior visualization (3-dimensional imaging of the operative field), mechanical improvement (seven degrees of instrument mobility inside the body) and stabilization/tremor filtration

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of the instrument within the surgical field [2].

Unexpectedly, the Laparoscopic Approach to Cervical Cancer (LACC) trial, a randomized, open-label, noninferiority study that compared minimally invasive RH with open RH (ORH), found that minimally invasive surgery (MIS) was associated with a higher risk of recurrence and death compared with open surgery. Female patients randomized to the minimally invasive surgery arm experienced an almost four times greater risk of recurrence and six times greater risk of death compared with female patients that were randomized to laparotomy [3]. In a statement released after the publication of the LACC trial, the Society of Gynecologic Oncology encouraged surgeons to discuss these data with patients undergoing surgery for cervical cancer [4], and the National Comprehensive Cancer Network cervical cancer guidelines were revised accordingly to define the open abdominal approach as the “standard and recommended approach to RH” [5].

Consequently, this study performed a systemic literature review to appraise and synthesize the available real-world evidence on robotic RH (RRH). Moreover, we compared the risk of recurrence and death between patients who underwent MIS vs. ORH for early-stage cervical cancer.

CASE SERIES OF RRH

After Marchal et al. [6] performed RRH in 2005, several case series of RRH were published (Table 1) [7-10]. In Korea, Kim et al. [7] for the first time reported 10 cases of RRH and concluded that RRH for selected patients with IB1 cervical cancer is feasible, promising and related with a low morbidity (Table 1).

MIS (ROBOT AND LAPAROSCOPY) VS. OPEN

Most initial comparative studies between MIS and ORH focused on the respective surgical outcomes [11-14]. Most comparative studies showed that blood loss and hospital stays for the MIS group were superior compared to the open group [11-17]. Furthermore, previous retrospective comparative studies revealed that the survival outcomes of MIS were comparable to the survival outcomes of open surgery [15-17]. In the LACC trial, however, MIS was associated with a lower range of disease-free survival (DFS; 3-year rate, 91.2% vs. 97.1%; hazard ratio [HR], 3.74; 95% confidence interval [CI], 1.63–8.58) and overall survival (OS; 3-year rate, 93.8% vs. 99.0%; HR, 6.00; 95% CI, 1.77–20.30) [3]. Following the LACC trial, several retrospective comparative studies reported on the survival outcomes of MIS and open surgery [18-20]. Cusimano et al. [18] showed that MIS was associated with increased rates of death (HR, 2.20; 95% CI, 1.15–4.19) and recurrence (HR, 1.97; 95% CI, 1.10–3.50) after adjusting for individual patients' factors and surgeon volume. Moreover, an international European cohort observation study (the SUCCOR study) demonstrated that the risk of recurrence for patients who underwent MIS was twice as high compared to the open surgery group (HR, 2.07; 95% CI, 1.35–3.15; $P=0.001$). Similarly, the risk of death was 2.42-times higher than in the open surgery group (HR, 2.45; 95% CI, 1.30–4.60, $P=0.005$) [19]. Finally, Brandt et al. [20] reported that MIS RH did not confer worse oncologic outcomes in a single-center retrospective study (Table 2).

Table 1. Case series of robotic radical hysterectomy

Year	Nation	Number	Design	Stage	Operative time (minutes)	Blood loss (mL)	Hospital stays (days)	Lymph nodes	Complication (%)	Survivals	Reference No.
2008	Korea	10	Single	IA2-IB1	207	355	7.9	27.6	0.0	NA	[7]
2008	USA	20	Singe	IB1-IIA	309	300	1	18	10.0	2-year DFS 90%	[8]
2009	Sweden	80	Single	IA1-IIA	262	150	NA	26	41.0	NA	[9]
2009	USA	42	Multi	IA1-IB2	215	50	1	25	16.8	NA	[10]

NA, not available; DFS, disease-free survival.

Table 2. Comparative studies between minimally invasive and open surgery

Year	Nation	Design	Number robot vs. LSC vs. open	Period	Stage	Operative time	Blood loss	LN	Stay	Cx	Recurrence	Death	Reference No.
2008	USA	Retrospective, single	27 vs. 31 vs. 35	2003 to 2006 1993 to 2006	IA2-IB2	Open robot	MIS	ND	MIS	ND	NA	NA	[11]
2009	USA	Retrospective, single	32 vs. 17 vs. 14	2006 to 2008 2002 to 2006	IA2-IB2	ND	MIS	Robot	MIS	ND	NA	NA	[12]
2011	USA, Brazil	Prospective, multi	34 vs. 31 vs. 30	2007 to 2010	IA2-IIA	Open	MIS	NA	MIS	ND	NA	NA	[13]
2011	Norway	Prospective, single	35 vs. 7 vs. 26	2005 to 2009 2004 to 2005	IA1-IB1	Open	Robot	Open	Robot	NA	5 recurrence in only robot	NA	[14]
2014	Taiwan	Retrospective, single	32 vs. 24 vs. 44	NA	IA-II B	Robot	MIS	ND	MIS	ND	95.8% vs. 90.6% vs. 90.9%	NA	[15]
2016	USA	Retrospective, single	58 vs. 49 vs. 39	2009 to 2013	IA2-II B	LSC	Robot	NA	Robot	Robot	89.7% vs. 89.8% vs. 84.6%	96.6% vs. 95.9% vs. 92.3%	[16]
2018	Italy	Retrospective, multi	88 vs. 152 vs. 101	2001 to 2016	IB1	ND	MIS	Open	MIS	ND	89.5% vs. 87.2% vs. 91.3% (MIS = open)	88.8% vs. 89.7% vs. 88.7% (MIS = open)	[17]
2018	USA et al.	Prospective, RCT	319 (88.4% LSC) vs. 485	2008 to 2017	IA1-IB1	NA	NA	NA	NA	ND	3 years: 91.2% vs. 97.1% (HR, 3.74)	3 years: 93.8% vs. 99.0% (HR, 6.00)	[3]
2019	Canada	Retrospective, multi	473 (89.6% LSC) vs. 485	2006 to 2017	IA-II	NA	NA	NA	Robot	ND	16.2% vs. 8.4% (P=0.008)	12.5% vs. 5.4% (P=0.019)	[18]

Table 2. Continued

Year	Nation	Design	Number robot vs. LSC vs. open	Period	Stage	Operative time	Blood loss	LN	Stay	Cx	Recurrence	Death	Reference No.
2020	EU	Retrospective, multi	291 (78.5% LSC) vs. 402	2013 to 2014	IB1	NA	NA	NA	NA	NA	4.5 years; 79% vs. 89% (P=0.003)	4.5 years; 89% vs. 97% (P=0.003)	[19]
2020	USA	Retrospective, single	117 (90.6% Robot) vs. 79	2007 to 2017	IA1-IB1	NA	NA	NA	NA	MSI	5 years; 87.0% vs. 86.6% (P=0.93)	5 years; 96.5% vs. 87.4% (P=0.15)	[20]

LN, lymph node; Cx, complication; MIS, minimally invasive surgery; ND, no difference; NA, not available; LSC, laparoscopy; RCT, randomized controlled trial; HR, hazard ratio.

ROBOT VS. OPEN SURGERY

Most comparative studies showed that blood loss and hospital stays for the robot group were superior to those of the open group [21-31]. However, the majority of these studies demonstrated that the operative time of ORH was significantly shorter compared to RRH [21,23,26,28,29]. The survival outcomes of RRH and ORH were first reported in 2010, and for a 3-year progression free survival (PFS) were 94% in RRH and 89% in ORH ($P=0.27$) and the 3-year OS were 94% in RRH and 93% in ORH ($P=0.47$), respectively [24]. After this study [24], several retrospective comparative studies showed that survival outcomes were similar between the two groups [28,29,31]. However, Wallin et al. [30] used a multivariate regression analysis and demonstrated that RRH was significantly more associated with tumor recurrence (HR, 2.13; 95% CI, 1.06–4.26; $P<0.05$). Moreover, abdominal radical hysterectomy had a greater PFS advantage over RRH for tumors ≥ 2 cm (HR, 0.31; 95% CI, 0.11–0.90; $P=0.04$) [32]. Furthermore, recent retrospective studies have also reported poor survival outcomes in RRH compared to ORH after propensity score matching (Table 3) [33,34].

ROBOT VS. LAPAROSCOPY

Surgical outcomes, such as the operative time and complication rate were different for different studies [35-45]. However, most studies reported that blood loss of RRH was superior to that of LRH [35,37-39,45]. Finally, several retrospective studies have reported similar survival outcomes between the two groups (Table 4) [36-38,41,42,44,45].

ROBOTIC SINGLE-SITE RH

Sinno and Tanner [46] reported the first surgical film of robotic single-site RH. Recently, Jang et al. [47] compared the surgical outcomes of robotic single-site and multiport RH. Hospital stay and total hospital cost for single-site were significantly shorter and lower, respectively, compared to multiport surgery ($P<0.01$) [47].

Table 3. Comparative studies between robot and open surgery

Year	Nation	Design	Number robot vs. open	Period	Stage	Operative time	Blood loss	LN	Stay	Cx	Recurrence	Death	Reference No.
2008	USA	Retrospective, single	16 vs. 32	2006 to 2007	IA1-IB1	Open	Robot	ND	Robot	ND	NA	NA	[21]
2009	USA	Prospective, single	51 vs. 49	2005 to 2007	IA1-IIA	Robot	Robot	Robot	Robot	ND	NA	NA	[22]
2009	Italy	Prospective, single	40 vs. 40	2007 to 2009	IA2-IIA	Open	Robot	Open	Robot	ND	NA	NA	[23]
2010	USA	Retrospective, single	63 vs. 64	2005 to 2008 1995 to 2007	IA1-IIB	NA	Robot	NA	Robot	ND	3 years; 94% vs. 89% (P=0.27)	3 years; 94% vs. 93% (P=0.47)	[24]
2010	Korea	Prospective, single	32 vs. 32	2005 to 2007 2002 to 2009	IA2-IIB	ND	Robot	ND	Robot	ND	NA	NA	[25]
2010	Canada	Prospective, single	16 vs. 24	2005 to 2007 2002 to 2009	IA1-IIA	Open	Robot	ND	Robot	Robot	NA	NA	[26]
2010	USA	Retrospective, single	15 vs. 30	2007 to 2008	IA2-IB2	ND	Robot	ND	Robot	ND	NA	NA	[27]
2016	USA, Norway	Retrospective, multi	259 vs. 232	2005 to 2011	IA1-IB2	Open	Robot	ND	Robot	Robot	23% vs. 21% (P=1.00)	7% vs. 9% (P=0.48)	[28]
2016	EU	Retrospective, multi	210 vs. 195	2006 to 2014	IA2-IB2	Open	Robot	NA	Robot	ND	5 years; 89% vs. 90% (P=0.917)	5 years; 98% vs. 97% (P=0.626)	[29]
2017	Sweden	Retrospective, single	149 vs. 155	2009 to 2015	IA1-IB1, IIA1	ND	Robot	Robot	Robot	Robot	5 years; 91.1% vs. 95.2% (HR, 2.13; P<0.05)	5 years; 91.1% vs. 92.7%	[30]
2017	USA	Retrospective, multi	109 vs. 202	2001 to 2012	IA1-IB2	NA	Robot	Open	Robot	Robot	3 years; 89.9% vs. 89.1% (P=0.140)	3 years; 97.2% vs. 95% (P=0.960)	[31]
2019	USA	Retrospective, multi	49 vs. 56	2010 to 2016	IB1	NA	NA	NA	NA	ND	24% vs. 14% (P=0.22)	14% vs. 5% (P=0.18)	[32]

Table 3. Continued

Year	Nation	Design	Number robot vs. open	Period	Stage	Operative time	Blood loss	LN	Stay	Cx	Recurrence	Death	Reference No.
2020	USA, China	Retrospective, multi	152 vs. 181	2000 to 2017	IA2-IIA	Open	Robot	NA	Robot	NA	5 years; 91.4% vs. 91.1% (P=0.98) IPTW 5 years; 79% vs. 90.5% (P=0.01)	5 years; 96.7% vs. 96.6% (P=0.98) IPTW 5 years; 85.8% vs. 95.3% (P<0.01)	[33]
2020	China	Retrospective, multi	1,048 vs. 9,266	2004 to 2016	IA-IIA2	NA	NA	NA	NA	NA	3 years; 91.1% vs. 95.4% (P=0.002)	3 years; 94.4% vs. 97.8% (P=0.002)	[34]

LN, lymph node; Cx, complication; ND, no difference; NA, not available; IPTW, inverse probability of weighting using the propensity score.

NATIONWIDE POPULATION-BASED STUDIES

In an epidemiologic study performed in the USA, MIS was associated with shorter OS rates compared to open surgery (HR, 1.65; 95% CI, 1.22–2.22; $P=0.002$) [48]. In contrast, nationwide population-based studies in Scandinavia, reported different outcomes [49,50]. For instance, a Swedish nationwide population-based cohort study showed that the 5-year OS was 94% and 92%, and DFS was 88% and 84% for the robotic and open cohorts, respectively [49]. Moreover, the 5-year OS after propensity score matching was 92% for both cohorts (HR, 1.003; 95% CI, 0.5–2.01; $P=0.99$) [49]. In a Danish nationwide population-based cohort study, adoption of RRH for early-stage cervical cancer was not associated with either an increased risk of recurrence or reduction in survival outcomes [50].

ISSUES OF TUMOR SPILLAGE IN MIS

In the LACC trials, the potential reasons for the inferior oncologic outcomes in the MIS included the routine use of uterine manipulator, effect of the insufflation gas (CO_2) on tumor-cell growth and that spread might increase the propensity for tumor spillage [3]. In the SUCCOR study, the use of uterine manipulator during MIS was associated with worse 4.5-year DFS (82% vs. 93%; HR, 3.48; 95% CI, 1.17–9.48, $P=0.028$) and 4.5-year OS (88% vs. 96%; $P=0.016$) [19]. Klapdor et al. [51] evaluated peritoneal contamination with indocyanine green stained cervical secretion as surrogate for potential cervical cancer cell dissemination during colpotomy. Peritoneal contamination was detected in 75% (9/12) patients during laparoscopic hysterectomy and uterine manipulator contamination was detected in 60% [51]. However, Nica et al. [52], reported that the use of intra-uterine manipulator in patients with early cervical cancer who underwent MIS was not an independent factor with a significant rate of recurrence after controlling for adverse pathological factors (HR, 0.4; 95% CI, 0.2–1.0; $P=0.05$). Kong et al. [53] demonstrated that the rate of disease recurrence was higher in the intracorporeal colpotomy group compared to the vaginal colpotomy group (16% vs. 5%), and among patients with recurrence in the intracorporeal group, 62% had intraperitoneal spread or carcinomatosis.

Table 4. Comparative studies between robot and laparoscopic surgery

Year	Nation	Design	Number robot vs. LSC	Period	Stage	Operative time	Blood loss	LN	Stay	Cx	Recurrence	Death	Reference No.
2007	Norway	Retrospective, single	7 vs. 7	2005 to 2006 2004 to 2005	IA1-IB1	ND	Robot	ND	Robot	ND	NA	NA	[35]
2011	Italy, USA	Retrospective, multi	23 vs. 76	2003 to 2010	IA2-IIA	LSC	ND	ND	ND	ND	4.3% vs. 5.3% (P>0.05)	NA	[36]
2014	Korea	Retrospective, single	23 vs. 69	2008 to 2013	IA1-IB2	LSC	Robot	ND	ND	ND	3 years; 91.3% vs. 89.9% (P=0.778)	NA	[37]
2014	Korea	Retrospective, single	60 vs. 42	2009 to 2013	IA1-IIA1	ND	Robot	NA	ND	ND	3 years; 96.4% vs. 91.9% (P=0.482)	NA	[38]
2017	China	Retrospective, single	100 vs. 833	2009 to 2016	IA2-IIA1	Robot	Robot	ND	Robot	Robot	0.0% vs. 4.2% (P=0.03)	0.0% vs. 2.9% (P=0.07)	[39]
2018	USA	Retrospective, single	13 vs. 30	2006 to 2008 2000 to 2006	IA2-IIA	ND	ND	ND	ND	ND	0% vs. 0%	NA	[40]
2018	Italy	Retrospective, multi	70 vs. 140	2010 to 2016	IA2-IB2	LSC	ND	ND	ND	ND	3 years; 88.0% vs. 84.0% (P=0.866)	3 years; 90.8% vs. 94.0% (P=0.924)	[41]
2018	Korea	Retrospective, multi	65 vs. 60	2008 to 2013	IB1-IIA2	LSC	ND	ND	ND	LSC	20% vs. 13.3% (P=0.3212)	9.2% vs. 3.3% (P=0.2762)	[42]
2019	Japan	Retrospective, single	64 vs. 57	2010 to 2017	IA2-IIB	LSC	LSC	Robot	ND	ND	NA	NA	[43]
2019	China	Retrospective, single	92 vs. 60	2014 to 2017	IA-IIB	ND	ND	Robot	ND	Robot	81.02% vs. 85.67% (P=0.669)	92.13% vs. 94.45% (P=0.292)	[44]
2019	China	Retrospective, single	216 vs. 342	2014 to 2018	IA1-IIB	Robot	Robot	ND	ND	ND	3 years; 89.9% vs. 89.1% (P=0.669)	3 years; 97.2% vs. 95.0% (P=0.292)	[45]

LSC, laparoscopy; LN, lymph node; Cx, complication; ND, no difference; NA, not available.

The author concluded that exposure of cervical cancer to circulating CO₂ may result in tumor spillage into the peritoneal cavity [53]. Furthermore, other previous studies also presented intraperitoneal recurrences only in robot or MIS during RH [33,42].

UPCOMING TRIALS

Two novel noninferiority randomized controlled trials (RCTs) have been launched in terms of evaluating early-stage cervical cancer following the publication of the LACC trial results. The first one is a multicenter Chinese trial that compares RRH or LRH vs. ORH with DFS at 5 years as its primary objective, which has a planned sample size of 1,488 patients from 28 participating centers with an individual surgeon case volume [54]. The second one is performed in an international multicenter RCT (Robot-assisted Approach to Cervical Cancer [RACC] trial), and compares RRH vs. ORH with the 5-year DFS as its primary end-point and a planned sample size of 800 patients [55].

CONCLUSION

The authors of the LACC study and the US Cancer Resist Evaluation stated that MIS RH was associated with a higher rate of recurrence and poorer OS compared to ORH. Previous meta-analysis based on retrospective studies, showed that open surgery had no significant superiority.

The results were not interpreted as the end of MIS in terms of treating cervical cancer; instead, it was recommended that studies should be performed on how to avoid the use of uterine manipulators and the dissemination of cancer cells by ensuring a more effective vaginal closure using a standardized approach.

In agreement with previous nationwide population-based studies, our findings underline a disagreement on survival outcomes according to the specific conditions and parameters of each nation. Therefore, it is necessary to perform a Korean nationwide population-based study that will focus on the respective oncologic outcomes. Furthermore, strict guidelines for MIS in the treatment of early-stage cervical cancer should be implemented which will be consistent with objective data from the Korean population.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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