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Review Article

Minimally invasive radical hysterectomy and the importance of avoiding cancer cell spillage for early-stage cervical cancer: a narrative review

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ABSTRACT

Radical hysterectomy is a standard surgery to treat early-stage uterine cervical cancer. The Laparoscopic Approach to Cervical Cancer (LACC) trial has shown that patients receiving minimally invasive radical hysterectomy have a poorer prognosis than those receiving open radical hysterectomy; however, the reason for this remains unclear. The LACC trial had 2 concerns: the learning curve and the procedural effects. Appropriate management of the learning curve effect, including surgeons' skills, is required to correctly interpret the result of surgical randomized controlled trials. Whether the LACC trial managed the learning curve effect remains controversial, based on the surgeons' inclusion criteria and the distribution of institutions with recurrent cases. An appropriate surgical procedure is also needed, and avoiding intraoperative cancer cell spillage plays an important role during cancer surgery. Cancer cell spillage during minimally invasive surgery to treat cervical cancer is caused by several factors, including 1) exposure of tumor, 2) the use of a uterine manipulator, and 3) direct handling of the uterine cervix. Unfortunately, these issues were not addressed by the LACC trial. We evaluated the results of minimally invasive radical hysterectomy while avoiding cancer cell spillage for early-stage cervical cancer. Our findings show that avoiding cancer cell spillage during minimally invasive radical hysterectomy may ensure an equivalent oncologic outcome, comparable to that of open radical hysterectomy. Therefore, evaluating the importance of avoiding cancer cell spillage during minimally invasive surgery with a better control of the learning curve and procedural effects is needed.

Keywords: Cervical Cancer; Hysterectomy; Laparoscopic Surgery; Minimally Invasive Surgery; Survival

INTRODUCTION

Radical hysterectomy is a standard treatment for early-stage uterine cervical cancer [1-5]. Since the first laparoscopic radical hysterectomy (LRH) was reported in 1992 [6], several studies have indicated minimally invasive radical hysterectomy (MIRH) as a treatment for early-stage cervical cancer. They showed that compared to open radical hysterectomy, MIRH had comparable outcomes regarding 5-year relapse-free and overall survival [7-12]. Moreover,

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although it was shown that MIRH has a prolonged operative time, it has some advantages, including minimal blood loss, reduced length of hospital stay, and fewer perioperative complications. Several meta-analysis studies have shown equivalent outcomes with MIRH than with the open method [13-15]. MIRH had been considered a safer procedure than open surgery with a comparable oncologic outcome.

However, in 2018, the unexpected phase 3 multicenter, randomized trial (the Laparoscopic Approach to Cervical Cancer; LACC trial) results regarding the comparison of oncologic outcomes between open surgery and MIRH (LRH and robot-assisted radical hysterectomy) showed that the prognosis of MIRH for early-stage cervical cancer was incomparable with that of open surgery, increasing the risk of recurrence and death [16]. In this trial, the recurrence risks, locoregional recurrence, all-cause mortality were 3.74, 4.26, and 6.00 times greater, respectively, with MIRH than with open surgery.

Subsequently, many studies were conducted with similar findings, reporting that minimally invasive surgeries had poorer prognoses than open surgeries [17-23], contrasting the retrospective analyses reported before the LACC trial. However, some meta-analyses reported after the publication of the LACC trial have shown conflicting findings [24,25]. At present, open radical hysterectomy is a standard operation, and MIRH is limited to low-risk cervical cancer. However, because the LACC trial was designed not to explore the data that could explain these prognostic differences but to demonstrate the non-inferiority of MIRH, the poor prognostic factors remain unknown.

In 2020, a large cohort observational study, the SUCCOR study, showed that MIRH using a different technique, including avoidance of the uterine manipulator, had a comparable outcome with that of the current techniques [21], consistent with the results of several studies [26-29]. Therefore, cancer cell spillage might result in poorer oncologic outcomes than open surgery.

In this article, we discussed the potential poor prognostic factors of MIRH indicated in the LACC trial. In addition, we evaluated the results of MIRH with avoidance of cancer cell spillage for early-stage cervical cancer.

TWO MAJOR SURGICAL TECHNICAL ISSUES AFFECTING ONCOLOGIC OUTCOMES IN THE LACC TRIAL

Although MIRH for early-stage cervical cancer had a poor prognosis in the LACC trial [16], MIRH, using a surgical technique to prevent cancer cell spillage, may ensure a favorable effect similar to that in open surgery [21,26-29]. Six meta-analyses relating to MIRH in patients with early-stage cervical cancer are presented in **Table 1** [13-15,23-25]. The results were varied, with some studies stating that the prognosis for MIRH was equivalent with that of open surgery [13-15,25], one stating that prognosis was worse [23], and the remaining stating that prognosis was equivalent if a uterine manipulator was not used during MIRH. These findings suggest that the worse outcome in the MIRH group shown in the LACC trial should not be expected with all kinds of MIRH.

Because the LACC trial was not designed to explore poor prognostic factors in MIRH, considering that no one expected MIRH to have a poorer oncologic outcome, the reasons behind the results of the trial remain unclear. In general, when we evaluate the results of

Table 1. Meta-analysis of oncologic outcomes of laparoscopic radical hysterectomy

Authors	Study year	Number of studies	Stage (FIGO 2008)	Control	Experimental	HR of recurrence or death (95% CI)	HR of death (95% CI)	Results
Geetha et al. [13]	2011	47	N/A	ARH (n=1,552)	LRH (n=1,339), RRH (n=327)	N/A	N/A	Recurrence rate was similar among the three RH group
Cao et al. [14]	2007–2014	22	IA1–IIB	ARH (n=1,692)	LRH (n=1,230)	1.01 (0.90–1.11)	0.98 (0.86–1.10)	DFS and OS showed no difference between ARH and LRH
Wang et al. [15]	2007–2014	12	IA1–IIA2	ARH (n=785)	LRH (n=754)	0.97 (0.56–1.68)	0.91 (0.48–1.71)	There were no significant differences in 5-year DFS and OS
Nitecki et al. [23]	2012–2020	15	IA1–IIA	ARH (n=4,815)	LRH (n=2,009), RRH (n=2,675)	1.71 (1.76–2.15)	1.56 (1.16–2.11)	MIRH was associated with an elevated risk of recurrence and death compared with that of ARH
Kampers et al. [24]	2007–2020	30	IA1–IIA	ARH (n=7,701)	LRH (n=7,058)	0.95 (0.93–0.98)	0.97 (0.96–0.98)	DFS and OS in LRH appeared to be dependent on surgical technique
Tantitamit et al. [25]	2000–2018	30	IB–IIA	ARH (n=705)	LRH (n=529)	1.02 (0.97–1.06)	1.00 (0.98–1.03)	LRH was as safe and effective in terms of long-term outcomes as ARH

ARH, abdominal radical hysterectomy; CI, confidence interval; DFS, disease-free survival; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; LRH, laparoscopic radical hysterectomy; MIRH, minimally invasive radical hysterectomy; N/A, not applicable; OS, overall survival; RH, radical hysterectomy; RRH, robot-assisted radical hysterectomy.

surgical randomized controlled trials (RCTs), we have to keep in mind that the internal validity can be compromised by the surgical procedure, surgical skill, perioperative care, and the surgeon's performance bias, which are not present in RCTs of non-skill-dependent interventions, including medications [30-34]. Therefore, the following 2 items related to the LACC trial must be considered: the learning curve (was the skill level of the surgeons eligible for the study appropriate?) and surgical procedural effects (was the surgical procedure performed during the trial reasonable?).

1. MIRH and the learning curve effect

In general, there is a correlation between surgical performance and perioperative outcomes [35]. Regarding open surgery for cervical cancer, it has been reported that an institution highly experienced in surgery had better oncologic outcomes than one with little experience [36]. The learning curve effect in MIRH, including surgical quality, may have impacted the prognosis for the LACC trial, resulting in poor outcomes.

When discussing the learning curve effect in RCTs, the Dutch trial, an RCT for gastric cancer, should be considered [37,38]. In the Dutch trial, the efficacy and safety of D1 lymph node dissection were compared with those of D2 lymph node dissection. At first, there was no significant difference in the 5-year survival rate between the 2 groups; however, the in-hospital mortality rate was higher, (approximately 10%) in the D2 group [37]. This report contradicts the findings of specialist centers in Japan, where D2 gastrectomy could be performed with low morbidity and mortality. However, after 15 years of follow-up, contrasting results indicated that the recurrence rate in the D2 lymph node dissection group was significantly lower than that in the D1 lymph node dissection group [38]. Finally, the European Society for Medical Oncology guidelines recommends D2 lymph node dissection when treating gastric cancer. This result indicated that the excessive morbidity and mortality found in the first report may have occurred under the learning curve of the D2 lymph node dissection procedure; the practice provided to surgeons enrolled in the trial was criticized. This trial is a typical example of results that could be explained by the learning curve effect [39,40]. The fact that the surgeons' skill affected the RCT results should be noted.

Unlike the Dutch trial, the LACC trial did not find any difference in complication rates between the minimally invasive surgery group and the open surgery group. However, the learning curve effect in MIRH was not evaluated in the LACC trial. According to the LACC trial's protocol, MIRH quality control was performed by evaluating an unedited surgical video. However, this video was unavailable; therefore, the evaluation procedure is unclear. Patients were enrolled in the LACC trial starting in 2008, when MIRH had just commenced in the United States. In addition, it was pointed out that this may be due to an underestimation of learning curve effects by inserting manipulators in all patients and allowing type 2 radical hysterectomy (per the Piver-Rutledge-Smith classification). Therefore, we cannot deny the possibility that the surgeons involved in this trial were under the learning curve effect and that the surgical quality of MIRH may have affected the prognosis. Recurrent cases were limited to only fourteen of the thirty-three centers that enrolled in this trial, suggesting that the quality of surgery may have differed among the centers.

Results on the learning curve effect in MIRH on cervical cancer are contradictory. Cusimano et al. [18] showed that despite adjusting the surgeon volume, MIRH was associated with poorer oncologic outcomes than open surgery. In contrast, some studies indicated that the learning curve in MIRH might be associated with cervical cancer recurrence, requiring more cases than open surgery to achieve acceptable oncologic outcomes [41-43]. Currently, the impact of the learning curve on the oncologic outcome for cervical cancer remains controversial. However, we must consider the effect of learning curve to discuss the oncologic outcome of MIRH.

2. MIRH and surgical procedural effect

In the LACC trial, the locoregional recurrence rate was significantly higher in the minimally invasive surgery group than in the open surgery group. In other surgical sites, the locoregional recurrence found during laparoscopic surgery may be related to intraoperative cancer cell spillage. There has been great concern that peritoneal dissemination, including port-site metastases, can result from laparoscopic surgery for malignant tumors in other sites [44-46]. Considering these potential issues relating to cancer cell spillage in MIRH for cervical cancer, the risks are 1) exposure of tumor, 2) the use of a uterine manipulator, and 3) direct handling of the uterine cervix.

Exposure of tumor under minimally invasive surgery

Whether tumors are affected by exposure to carbon dioxide (CO_2) pneumoperitoneum remains unclear. According to basic research, tumor exposure to circulating CO_2 and peritoneal injury from pneumoperitoneum pressure may cause peritoneal dissemination [47-50]. However, recent findings have suggested that this has no impact on prognosis [51,52].

Tumor exposure to the surgical area might have increased the local recurrence rate in the colorectal area [53]. A representative type of colorectal surgery, transanal total mesorectal excision (TaTME), is a surgical procedure in which the rectal mucosa is incised, and the tumor is isolated by wrapping the incised rectal mucosa to prevent cancer cell spillage before the laparoscopy. In Norway, TaTME was discontinued owing to a significantly high local recurrence rate. This report included 157 patients who underwent TaTME for rectal cancer between October 2014 and October 2018. The local recurrence rate was 7.6% (12 out of 157), of which most of the patients had multifocal local recurrence. The hazard ratio (HR) was 6.71 (95% confidence interval [CI]=2.94–15.32; $p<0.001$). The pathophysiological mechanism of the increased local recurrence rate remains unclear; however, anastomotic leakage is associated with a poor prognosis.

In cervical cancer, colpotomy under CO_2 pneumoperitoneum was a risk factor for local recurrence [27]. Cancer cells from an exposed tumor under CO_2 pneumoperitoneum

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disseminate and adhere to the peritoneum, which is damaged by prolonged CO_2 insufflation until vaginal colpotomy, resulting in local recurrence. Although this is a controversial issue, precautions should be taken.

Use of a uterine manipulator

Whether the use of uterine manipulators during LRH contributes to an increased recurrence rates has also been debated for decades. Using uterine manipulators may introduce dysplasic cells into the fallopian tubes, triggering peritoneal dissemination of cervical neoplasms [54]. In contrast, a report suggested that using a uterine manipulator did not affect the pathological findings, including the depth of tumor invasion and the presence of lymphovascular invasion [55]. There is no clear evidence on whether uterine manipulators affect pathological factors.

A large-population observational cohort analysis on endometrial cancer showed that using a uterine manipulator might affect the prognosis of early-stage endometrial cancer [56]. Contrary to previous reports [57-59], using a uterine manipulator was associated with a poorer oncologic outcome in patients with early-stage endometrial cancer. In this study, 2,661 patients were included; 1,756 and 905 underwent a hysterectomy with and without a uterine manipulator, respectively. The recurrence rate was 11.7% in the manipulator group and 7.4% in the non-manipulator group ($p<0.001$). The patients in the manipulator group had a higher risk of recurrence than those in the non-manipulator group (HR=2.31; 95% CI=1.27–4.20; $p<0.006$). Using a uterine manipulator can break a uterus-confined tumor; therefore, the same theory might apply to MIRH.

Several retrospective studies on the comparison of open and minimally invasive surgeries for early-stage cervical cancer suggested that using a uterine manipulator may contribute to local recurrence [21,60]. There are limited data from retrospective analyses indicating whether uterine manipulator use can influence the oncologic outcomes of cervical cancer; therefore, we need to consider and evaluate the possibility that a uterine manipulator may have impacted on the prognosis. We cannot ignore the impact of uterine manipulators because the LACC trial recommended using uterine manipulators in all patients who underwent MIRH.

Based on this information, using uterine manipulators during MIRH should be discouraged, even though there is no clear evidence of its potential to trigger peritoneal dissemination.

Direct handling of the uterine cervix

The importance of tumor manipulation during surgery has been highly concerning. In basic research, applying excessive force to cancerous tissue can induce the dissemination of cancer cells or metastases [61-65]. Only one retrospective study has shown that laparoscopic surgery did not increase the number of circulating tumor cells [66]. In addition, Kong et al. [27] has assessed whether colpotomy (intracorporeal vs vaginal) influenced the oncologic outcome of MIRH, indicating that intracorporeal colpotomy provided poorer oncologic outcome than vaginal colpotomy. However, there are limited data, and minimizing cervical tumor compression during surgery may be necessary.

Regarding the LACC trial protocol, there was no comment on avoiding intraoperative cancer cell spillage, and a uterine manipulator was inserted transvaginally. In addition, type 2 or 3 radical hysterectomies (per the Piver-Rutledge-Smith classification) were permitted, although detailed data are unavailable. Type 3 radical hysterectomy is a standard operation to treat patients with early-stage cervical cancer. In a summary, we cannot deny the possibility that the validity of these procedures was not ensured in the LACC trial, leading to poor oncologic outcomes.

EVIDENCE ON ONCOLOGIC OUTCOMES OF MIRH WITH AVOIDANCE OF CANCER CELL SPILLAGE

We reviewed the medical literature to evaluate the oncologic outcome of MIRH that avoided cancer cell spillage. We searched PubMed and Google Scholar for articles related to MIRH and cancer cell spillage. The search keywords were: “cervical cancer,” “radical hysterectomy,” “minimally invasive surgery,” “laparoscopic surgery,” “cancer cell spillage,” and any other related terms, all of which were combined MeSH terms.

The inclusion criteria of the studies were as follows: studies about MIRH that avoided cancer cell spillage, including vaginal cuff creation; those that included patients with early-stage cervical cancer (International Federation of Gynecology and Obstetrics [FIGO] 2018: IA, IB1, and IIA1); and those that were published original, peer-reviewed articles in English. Study selection was performed independently by ST and AM.

A summary of the previous reports about the oncologic outcomes of MIRH in which cancer cell spillage was avoided is presented in **Table 2** [21,26-29,67-71]. Ten retrospective analyses were included. The researchers of these studies evaluated MIRH oncologic outcomes and reported equivalence between MIRH and open radical hysterectomy. However, 5 were not comparative analyses, and three of the remaining 5 did not include adjusting for confounding factors by propensity scores; therefore, these results should be for reference purposes.

Notably, three articles attracted great interest; one was the SUCCOR study [21], a large observational cohort study that found that the disease-free survival (DFS) in the no-manipulator group was similar to that of the open surgery group (HR=1.58; 95% CI=0.79–3.15), and the DFS in the protective maneuver group was also equivalent to that of the open surgery group (HR=0.63; 95% CI=0.15–2.59). Moreover, the DFS in the MIRH group was worse than that of the open surgery group (HR=2.07; 95% CI=1.35–3.15). The strengths of this study included the large sample size with multiple centers and the use of propensity-adjusted analysis. The limitation of this study was that data were limited because only 43 patients received the protective maneuver technique.

Another study by Kong et al. found that intracorporeal colpotomy was associated with poor prognostic factors (odds ratio=7.038; 95% CI=1.059–15.183), and the DFS rate was higher in the intracorporeal group than in the vaginal group (16.3% vs. 5.1%) [27]. To our knowledge, this report was the only comparative analysis regarding colpotomy during MIRH.

The last studies discussed the “No-Look No-Touch Technique” for preventing cancer cell spillage during LRH [28,29]. This technique has four concepts [72]: 1) Creation of the vaginal cuff before laparoscopy (**Fig. 1A**); 2) Uterine manipulation without the use of a uterine manipulator; 3) Avoidance of direct handling of the uterine cervix by sufficient development of surgical spaces, including paravesical and pararectal spaces; and 4) Bagging the specimen when extracting it outside (**Fig. 1B**).

Table 2. Evidence of laparoscopic radical hysterectomy with avoidance of cancer cell spillage

Author	Study year	Region	Study design	Confounder adjustment	Stage (FIGO 2008)	Control	Experi-mental	Median follow-up (mo)	No. of recurrence	DFS rate	HR of recurrence or death (95% CI)	OS rate	HR of death (95% CI)
Kong et al. [26]	2014	Korea	ARH vs. LRH	-	IB–IIA, tumor diameter ≥3 cm	48	40	46	1 vs. 1	97.9% vs. 97.5%	N/A	No disease-related deaths happened	Could not be calculated
Kong et al. [27]	2016	Korea	MIRH-intracorporeal colpotomy vs. LRH-vaginal colpotomy	-	IB–IIA	49	79	20.5	4 vs. 8	93.7% vs. 80.8% (2 yr)	N/A	N/A	N/A
Chiva et al. [21]	2020	Spain	ARH vs. MIRH	+	IB	402	291	56	60 vs. 47	79% vs. 89% (4.5 yr)	2.07 (1.35–3.15)	89% vs. 97% (4.5 yr)	2.42
			※Subgroup: protective closure				43 (sub)		3 (sub)	93% (sub)	0.63 (0.15–2.59) (sub)	N/A (sub)	N/A (sub)
Kanao et al. [28], Fusegi et al. [29]	2021	Japan	ARH vs. LRH using the no-look no-touch technique	+	IA2–IIA	118	113	38.4	5 vs. 11	91.4% vs. 90.9% (4.5 yr)	1.28 (0.46–3.56)	96.2% vs. 100% (4.5 yr)	Could not be calculated
Gottschalk et al. [67]	2011	Germany	Single-armed: VALRH	-	IA–IIB	N/A	110	19	7	94% (2 yr)	N/A	98% (2 yr)	N/A
Kohler et al. [68]	2019	Germany	Single-armed: VALRH, LAVRH	-	IA–IIA	N/A	389	99	20	95.8 (4.5 yr)	N/A	97.8% (4.5 yr)	N/A
Tanaka et al. [69]	2019	Japan	Single-armed: RH with vaginal closure	-	IA2–IIA	N/A	24	12	1	N/A	N/A	N/A	N/A
Ding et al. [70]	2021	USA	Single-armed: LRH with vaginal cuff with a stapler	-	IB	N/A	8	6	0	N/A	N/A	N/A	N/A
Wang et al. [71]	2021	China	Single-armed: VALRH (gasless)	-	IA2–IIA	N/A	48	11.7	0	N/A	N/A	N/A	N/A

ARH, abdominal radical hysterectomy; CI, confidence interval; DFS, disease-free survival; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; LAVRH, laparoscopy-assisted vaginal radical hysterectomy; LRH, laparoscopic radical hysterectomy; MIRH, minimally invasive radical hysterectomy; N/A, not applicable; OS, overall survival; VALRH, vaginal assisted laparoscopic radical hysterectomy.

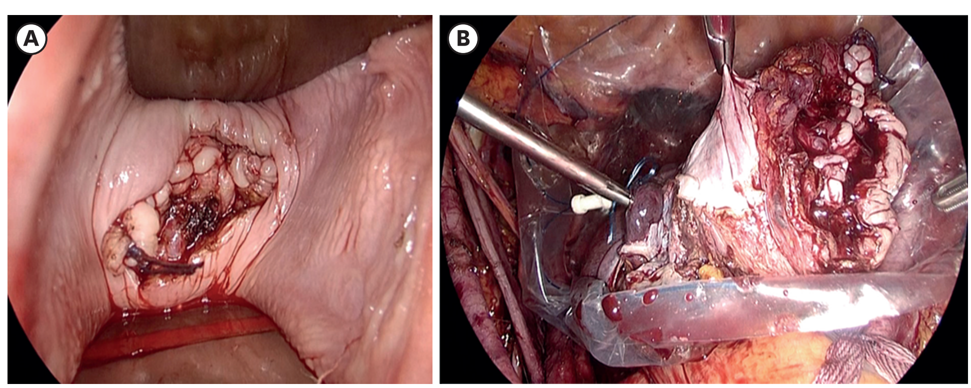

Fig. 1. Laparoscopic radical hysterectomy using the no-look no-touch technique.
(A) Vaginal cuff creation. Before the laparoscopic procedure, we created the vaginal cuff to avoid cancer cell spillage into the operative field. (B) Bagging the specimen. We used the plastic bag to extract the specimen via the vaginal to avoid cancer cell spillage. The vaginal cuff hides the tumor in the picture.

When comparing LRH using the “No-Look No-Touch Technique” with open radical hysterectomy for early-stage cervical cancer, the DFS was not significantly different between the two groups. This study had the following strengths: 1) Quality control of the surgery was ensured, as it was performed by a single surgeon in the same manner; 2) This study included a large sample size with propensity-score adjustment, specializing in a technique that avoids cancer cell spillage; 3) The prognosis was purely a result of the surgical technique because most patients did not receive radiation as an adjuvant therapy, which is effective to control pelvic recurrence. However, as this study implemented a single procedure by a single surgeon, its results are not generalizable.

According to these articles, MIRH, without cancer cell spillage, might be a favorable procedure for treating early-stage cervical cancer. However, data are limited; therefore, the findings should be interpreted cautiously.

FUTURE PERSPECTIVE

This is the first review of MIRH for early-stage cervical cancer focusing on the avoidance of cancer cell spillage. The concerns mentioned above regarding the LACC trial, including the learning curve and procedural effects, are not beyond the scope of the hypothesis and have not been evaluated in clinical comparative studies, although a theory based on basic medicine has been developed. In addition, as the results of the LACC trial have already been reported, it will not be easy to verify these results in the future owing to ethical concerns. Therefore, we believe that this review was warranted.

All the reported studies had a retrospective design, and most did not adjust for confounding factors. High-quality prospective studies confirming the surgeons' skills must be considered in the future. There are 2 ongoing clinical trials, including JGOG1087, a non-randomized controlled LRH trial in Japan whose aim is to prevent cancer cell spillage, and SOLUTION, a phase 2 non-inferiority trial evaluating the oncologic outcomes of MIS using the endoscopic stapler as a tool for preventing cancer cell spillage [73].

We summarized evidence regarding MIRH without intraoperative cancer cell spillage. These techniques are plausible surgical approaches for patients with early-stage cervical cancer. It is necessary to scientifically prove the efficacy of these surgical procedures in high-quality studies. We believe that the results of these studies will be important for the future direction of minimally invasive surgery.

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