Ito *et al. BMC Cancer* (2024) 24:1360
https://doi.org/10.1186/s12885-024-13090-z

BMC Cancer

RESEARCH

Interim analysis of robot-assisted radical hysterectomy in Japan: a multicenter, prospective interventional single-arm clinical trial

Hiroe Ito[1], Yoshihito Yokoyama[2], Satoru Kyo[3], Masaki Mandai[4], Kenzo Kosaka[5], Hiroaki Kobayashi[6], Etsuko Miyagi[7], Mamiko Onuki[8], Koji Matsumoto[8], Noriomi Matsumura[9], Kota Umemura[10], Hideki Ishikawa[11] and Keiichi Isaka[12*]

Abstract

Objective To investigate the efficacy and safety of robot-assisted radical hysterectomy (RARH) as a minimally invasive procedure in patients with cervical cancer that is curable by surgery.

Materials and methods This study was a multicenter, open-label, single-arm clinical trial. The short-term outcome of open radical hysterectomy was used as the historical control. The primary endpoint was successful surgery with minimal blood loss (300 mL or less) and negative surgical margins. Secondary endpoints included surgical outcomes, recurrence-free survival (RFS), and overall survival (OS) rates.

Results Overall, 101 cases were enrolled in this study at 10 participating medical institutions and 100 underwent RARH. Among these cases, 89 met the primary endpoint, exceeding the threshold of 0.75 set by the lower limit. At 2 years postoperatively, 17 cases had recurrences, 4 were classified as International federation of Obstetrics and Gynecology Stage IB1 or lower, while 13 as IB2 or higher. There were three deaths, including one in Stage IB1 and two in Stage IIB in the second postoperative year, all of which had lymph node metastasis. The oncological outcomes for all cases showed RFS and OS rates of 82.7% and 96.9%, respectively, over a median observation period of 37 months. For cases with Stage IB1, RFS and OS were 94.1% and 98.5%, respectively.

Conclusion RARH demonstrated a significant reduction in blood loss while ensuring radicality, indicating the safety and efficacy of this procedure compared to conventional RH. Although it is conceivable that the results of this oncological analysis could change, as the data collection has not been fully completed, we plan to further evaluate the oncologic outcomes of RARH in future studies.

Trial registration UMIN-CTR: UMIN000022278, registered on 11th May 2016.

Keywords Robot-assisted surgery, Radical hysterectomy, Cervical cancer, Oncologic outcome, Clinical trial

*Correspondence:
Keiichi Isaka
isaka@ohori-hosp.jp

Full list of author information is available at the end of the article

Introduction

Hysterectomy is one of the most common non-obstetric gynecological surgical procedures carried out in Western countries, and its surgical approach has recently become more common laparoscopically, in addition to abdominal and vaginal surgery [1].

The da Vinci surgical system (DVSS) is a laparoscopic surgical robot that has been rapidly spreading, especially in the United States. It is reported to compensate for many shortcomings of conventional open and laparoscopic surgery and enable proficiency in a short period of time [2–5]. Since the U.S. Food and Drug Administration's approval of robot-assisted surgery (RAS) for uterine malignancies in 2004, RAS for uterine malignancies has been rapidly outpacing open surgery in the United States [6].

Despite the fact that the standard procedure for cervical cancer in Japan is an open, radical hysterectomy, it is generally performed by a few experienced and skilled surgeons due to its high technical difficulty and high rate of complications, as well as excessive intraoperative blood loss [7]. We conducted a prospective observational study, performing 292 RASs between March 2009 and December 2015. Therefore, we compared 19 cases that underwent robot-assisted radical hysterectomy (RARH) for cervical cancer between January 2011 and April 2014 (robotic group) with 38 cases that underwent RH during the same period (open group) as controls [8] (Additional Table 1). The robotic group exhibited significantly less blood loss, shorter hospital stays, and fewer complications than the open group, which are consistent with previous reports [9–12]. However, the duration of surgery was longer, and the number of lymph nodes removed was fewer.

Accordingly, the purpose of this study was to assess the efficacy and safety of RARH using the DVSS compared to conventional RH. The study was designed as a prospective, multicenter, open-label, single-arm clinical trial (Advanced Medical Care B Study) and was approved by the Minister of Health, Labour and Welfare in Japan (Registry: Tokyo Medical University Hospital, Clinical trial registration ID: UMIN000022278, Registration date: 2016/05/11, Registration title: Robot-assisted laparoscopic radical hysterectomy). As an interim analysis prior to oncological analysis, this study aimed to evaluate the usefulness and safety of RARH as a minimally invasive procedure and to collect comprehensive clinical data to consider insurance coverage for RARH in Japan.

Materials and methods

Technology Description

RARH was conducted following the guidelines set by the Japanese Society of Obstetrics and Gynecology (JSOG). The surgery was performed using the DVSS S, Si, or Xi models. Surgeons participating in the study met the accreditation criteria established by their respective institutions in accordance with the "Guidelines for Robotic-Assisted Laparoscopic Surgery for Gynecologic Malignancies" provided by the JSOG [13]. In this study, the surgeon who performed the surgery served as the responsible physician overseeing the procedure, and it was not permissible for any other physician to conduct the surgery.

All intraabdominal searches were conducted endoscopically, while lymph node dissection, main artery processing, and concurrent surgeries were primarily performed using robot-assisted techniques. For cases with identified risk factors for postoperative recurrence, postoperative treatment was determined based on the risk assessment of postoperative recurrence outlined in the Cervical Cancer Treatment Guidelines 2011 Edition by the JSOG [14].

This study was designed as a single-arm study, and to serve as a historical control, data from 90 cases of RHs were collected. These cases spanned a period of 2–3 years from 2011 to 2014 and were obtained from four institutions: Tokyo Medical University, Kyoto University, Hirosaki University, and Kinki University. These institutions had previously performed at least five RARHs and were participating in the present study. To minimize bias resulting from data collected from a single institution, data from RHs conducted around the same time period were included in the preliminary report [8]. As a result, these four centers accounted for 64% of the total enrollment in this clinical trial.

Target population selection

To be eligible for enrollment in the study, patients had to meet al.l of the specified selection criteria (Additional Table 2) and none of the exclusion criteria (Additional Table 3). The staging and histological classification of the patients were determined according to the Cervical Cancer Treatment Regulations 2012 (3rd Edition) [15].

Evaluation criteria

Primary endpoint

The primary endpoint of the study was defined as a successful surgery with minimal blood loss. In this study, minimal blood loss was specifically defined as a blood loss of 300 mL or less. However, as a main objective of surgery, it was also important to achieve a negative surgical margin in order to correctly assess the radicality of the procedure. Therefore, in order for a procedure to be considered successful, it had to meet both the criteria of minimal blood loss (300 mL or less) and negative vaginal surgical margins.

Rationale for setting the target number of patients

The hypothesis of this study aimed to assess whether the rate of successful RARH with minimal blood loss, the primary endpoint, is significantly higher than the threshold of 75%. This study followed a single-arm design. The threshold for the primary endpoint, which is the success rate of minimal blood loss, was set at 75%, while the expected rate was 90%. The chosen threshold of 75% is based on the fact that RARH using DVSS is anticipated to be less invasive in terms of blood loss than conventional RH. At the same time, the need for minimal invasiveness, even when considering its cost, was taken into account. Relevant data for the study was obtained from a retrospective analysis of 47 cases of RARH and 49 cases of RH performed between 2011 and 2014 at three participating institutions (Tokyo Medical University, Kyoto University, and Hirosaki University). As a result, the target number of patients to be enrolled in the study was set at 100 (details are provided in the Additional material).

Analysis of the primary endpoint

The primary objective of this study was to evaluate the minimally invasive nature of RARH with DVSS in patients with cervical cancer amenable to RH. Analysis of the primary endpoint was performed using an exact method based on a binomial distribution against a predetermined threshold of 75% at a two-sided significance level of 5%. If the test results rejected a statistically significant reduction, the treatment method for this subject was judged to be superior to RH.

The primary analysis of the study was conducted when data could be collected one month after the treatment of the last enrolled patient, following consultation between the Principal Investigator and the Statistical Analyst. The final analysis was performed when all information on postoperative adverse events up to the end of the follow-up period was sent by fax.

Secondary endpoints

Supplementary Table 4 shows the list of secondary endpoints.

Safety evaluation criteria

1) Surgical time, console time, and number of lymph nodes dissected.

   For reference purposes, the analysis was limited to cases of completed RARHs only. For the safety analysis population, surgical time, console time, and number of lymph nodes dissected were summarized using appropriate summary statistics such as median, minimum, and maximum values.

2) Urinary function.

   For the safety analysis population, urinary function tests at each time point were summarized using appropriate summary statistics such as median, minimum, and maximum values.

3) Postoperative recovery (days of oral intake initiation, length of hospital stay, and quality of life [QoL)].

   The number of days of postoperative oral intake and the duration of postoperative hospitalization were summarized using appropriate summary statistics such as frequency, median, minimum, and maximum values for the safety analysis population. Postoperative QoL was assessed using the evaluation of postoperative QoL (EQ-5D) questionnaire at 30, 180, and 365 days postoperatively [16].

4) Adverse events and device failure: For the safety analysis population, adverse events were listed separately for perioperative (intraoperative and early postoperative), postoperative, and late adverse events. Perioperative adverse events were defined from the date of surgery to the 30th postoperative day, while postoperative adverse events were defined from the end of the observation period for perioperative adverse events to 1 year after surgery, and adverse events after that time were considered late adverse events. The data were summarized using appropriate summary statistics, such as frequencies and percentages.

Efficacy criteria

1) Completion of RARH.

   The RARH completion rate was calculated for the Full Analysis Set (FAS).

2) Conversion to laparotomy.

   The rate of conversion to open surgery was calculated for the FAS.

3) Overall survival (OS) and recurrence-free survival (RFS).

   OS and RFS were evaluated for the FAS using the Kaplan–Meier method.

Data management

Details of data management are provided in Additional Table 5.

Statistics

The primary endpoints were analyzed using a two-tailed binomial test. The groups were compared using the Student's t-test, and the association between groups was analyzed using the chi-squared test. RFS and OS survival curves were generated using the Kaplan–Meier method and compared between groups using the log-rank test. A p-value of less than 0.05 was considered statistically significant. Statistical analysis was conducted using the Statistical Package for the Social Sciences version 25 (SPSS 25; SPSS, Inc., Chicago, IL, USA).

Results

A total of 101 cases were enrolled at 10 medical institutions participating in this study between July 2016 and August 2019. However, one case was discontinued, and 100 cases underwent RARH (Additional Fig. 1). The clinical advanced stage (FIGO 2008) of these cases was as follows: IB1 (n=69), IB2 (n=13), IIA1 (n=5), IIA2 (n=2), and IIB (n=11) (Table 1). The mean age and body mass index of the patients were 47 years and 22 kg/m^2, respectively. The American Society of Anesthesiologists physical status (ASA PS) evaluation revealed that 94 patients had ASA PS 1 and 6 patients had ASA PS 2.

Evaluation of the primary endpoint

The primary endpoint results for the 100 patients showed that 89 cases had blood loss of 300 mL or less, while 11 cases had blood loss of 300 mL or more. The mean blood loss was 138 mL. Among these cases, 2 had positive margins and blood loss of 300 mL or less, indicating that 87 patients had negative margins and blood loss of 300 mL or less. The primary endpoint analysis was 0.870, and the lower limit of the 95% confidence interval (CI) was higher than 0.75. Regarding resection margins, 96 cases (96%) had negative margins, 3 (3%) had positive margins, and 1 (1%) had unknown margin status. All cases with positive margins were at clinically advanced stage IIB, but all relapsed, including two patients with tumors more than 4 cm in diameter and positive lymph nodes, who died of recurrence due to pulmonary metastasis. The postoperative histopathologic search revealed 66 cases of squamous cell carcinoma, five cases of adenosquamous carcinoma, 27 cases of adenocarcinoma, and 1 case of segmental endocervical gland hyperplasia.

In terms of the Union for International Cancer Control (UICC) pTNM 2009 classification [17], 3 cases were classified as pTis, 3 cases as pT1a2, 67 cases as pT1b1, 9 cases as pT1b2, 4 cases as pT2a1, 2 cases as pT2a2, and 11 cases as pT2b. In contrast, the new postoperative histopathologic classification (UICC pTNM 2021) [17] classified 3 cases as pTis, 3 cases as pT1a2, 34 cases as pT1b1, 28 cases as pT1b2, 6 cases as pT1b3, 3 cases as pT2a1, 2 cases as pT2a2, 3 cases as pT2b, and 17 cases as pT3c1 (Table 1).

Table 1 Comparison of preoperative clinical stage classification (FIGO*) and postoperative pTNM classification (UICC**)

FIGO stage†	No. of cases	pTNM (UICC 2009) ††	No. of cases	pTNM (UICC 2021) †††	No. of cases
		is	3	is	3
IA1		1a1	0	1a1	0
IA2		1a2	3	1a2	3
IB1	69	1b1	67	1b1	34
				1b2	28
IB2	13	1b2	9	1b3	6
IIA1	5	2a1	4	2a1	3
IIA2	2	2a2	2	2a2	2
IIB	11	2b	11	2b	3
IIIC				3c1	17
	100		99§		99§

* International Federation of Gynecology and Obstetrics ** Union for International Cancer Control

† Clinical stage classification (FIGO 2008)

†† pTNM pathological classification (UICC TNM 2009)

††† pTNM pathological classification (UICC TNM 2021)

§ One case was a postoperative pathological diagnosis of pT2 stage endometrial cancer.

Safety evaluation results

Surgical results

The mean operative time was 446 min, the mean console time was 376 min, and the mean number of lymph nodes removed was 34. Lymph node metastases were found in 18.2%. When classified by clinical stage, the percentages of cases with lymph node metastases were as follows: IB1: 2.9%, IB2: 50%, IIA1: 20%, IIA2: 50%, and IIB: 72.7%. One of the IB2 cases was diagnosed as uterine cancer on postoperative pathology.

Blood transfusions were performed in 13 cases (13%). Among these cases, 1 received an allogeneic blood transfusion, while 12 received an autologous blood transfusion. Autologous blood preparation was performed in 15 cases, 9 of which were performed intraoperatively with dilutional transfusion as routine at one institution.

Urinary function

Regarding the urinary function of the 100 cases who underwent RARH, 49 cases had a residual urine volume of 50 mL or less, 8 cases had a residual urine volume greater than 50 mL but less than 100 mL, 36 cases had a residual urine volume greater than 100 mL, and 7 cases had a residual urine volume unmeasured on the seventh postoperative day. Similarly, when voiding function was measured one and three months postoperatively, 56 and 55 cases had a residual urine volume of 50 mL or less, respectively. Additionally, 8 and 6 cases had a residual urine volume greater than 50 mL and less than 100 mL. Furthermore, 26 and 15 cases had a residual urine volume greater than 100 mL, respectively. Measurements were not performed or were impossible in 10 and 24 cases, respectively (Additional Table 6). Up to 90 days postoperatively, the lowest residual urine volume measured was less than 50 mL in 86 cases, and only 1 case required self-voiding.

Postoperative recovery progress (postoperative oral intake initiation and postoperative hospital stay)

The mean number of days of postoperative oral intake initiation was 2.7±1.2 days, and the mean postoperative hospital stay was 11.5±12.9 days. This includes several patients who required continued hospitalization for postoperative treatment, such as concurrent chemoradiotherapy (CCRT).

Postoperative quality of life assessment using the EuroQol 5 dimension (EQ-5D)

At 30 days postoperatively, more than 70% of patients showed recovery in all categories. Furthermore, there was a noticeable trend toward recovery at 180 and 365 days postoperatively for all of the items. At 365 days, all items except for pain/discomfort (91.3% improvement) and anxiety/blushing (87.0% improvement) showed improvement of 95% or more (Additional Table 7).

Equipment failure

During the observation period, no defects were found in the DVSS itself. However, instrumentation failures were observed in two cases. In one case, the cover of the monopolar scissors fell off, and in another case, the operative field was disturbed due to decreased insufflation pressure caused by organ entrapment in the AirSeal® port of the insufflation device.

Adverse events

During the study, 58 perioperative adverse events were recorded. The incidence of intraoperative adverse events was 8%, while the incidence of early postoperative adverse events was 30%, excluding duplicate cases. Postoperative adverse events occurred in five patients, with an incidence of 5%. No late adverse events were reported.

Among adverse events, serious cases were observed in 4% of intraoperative adverse events, 4% of early postoperative adverse events classified as Clavien–Dindo Grade 3 or higher, and 1% of postoperative adverse events (Table 2). The overall incidence, excluding duplicates, was 8%, of which three early postoperative adverse events and one postoperative adverse event required hospitalization (50%).

Comparing these results to historical controls, there were no significant differences in patient background or bias in the histology of the specimens removed. However, there was a bias in the advanced stage of the disease. In terms of surgical outcomes, the study findings revealed a significant reduction in blood loss and a shorter hospital stay, although the operative time was significantly longer. There was no significant difference in the incidence of serious adverse events classified as Clavien–Dindo Grade 3 or higher (Table 3).

In summary, RARH was found to be comparable to conventional RH in terms of surgical outcomes. The favorable results in terms of postoperative adverse events confirm that RARH is an excellent and safe surgical method.

Efficacy evaluation

RARH completion rates and conversion to open surgery

The RARH completion rate in 100 cases was found to be 100%, and no cases were converted to open surgery.

Oncologic outcomes

One year postoperatively, 13 cases had recurrences. Among these cases, 3 out of 68 cases (4.4%) were classified as IB1 or less, while 10 out of 30 cases (33.3%) were classified as 1B2 or more. At 2 years postoperatively, 17 patients had recurrences. Among these cases, 4 out of 68

Table 2 Perioperative and postoperative adverse events

AE*	Perooperative		Postoperative	Serious AE**
	Intraoperative	Early postoperative		
Subcutaneous emphysema	4			
Urinary tract injury	1			1
Vascular injury	1			1
Intestinal injury	1			1
Nerve injury	1			1
Bladder dysfunction		16		
Edema of the lower extremities or vulva		5		
Pelvic inflammatory disease		4		1
Urinary tract infection		3	1	1
Ileus		2		1
Leg palpation blunting		2		
Drug-induced hepatitis		2		
Vaginal cuff dihiscence		1	1	1
Pulmonary embolism		1		1
Ureteral fistula		1		
Ureteral dysfunction		1		
Hydronephrosis and hydroureteropathy		1	1	
Lymphocyst		1		
Lymph leak		1	1	
Numbness in the lower extremities			1	
Others		9		
Total number	8	50	5	9
Occurrence rate*** (%)	8	30	5	8

* Adverse event ** Serious adverse events include postoperative adverse events of Clavien-Dindo classification 3 or higher.

*** Incidence of cases with overlapping adverse events counted as one case.

Table 3 Comparison of data between robot-assisted radical hysterectomy (RARH) and radical hysterectomy (RH)

operative procesure		RA-RH		RH*		p-value
No. of cases		100		90		
Age, mean ± SD, (range)		46.9 ± 11.3	(29 - 78)	44.8 ± 11.7	(26 - 76)	0.214
BMI, mean ± SD, (range)		21.6 ± 3.4	(16.8 - 33.3)	22.3 ± 4.1	(15.2 - 33.9)	0.872
FIGO stage, No. of cases, %	*IA2*	0	0.0	7	0.8	< 0.001
	IB1	70	70.0	49	54.4	
	IB2	12	12.0	23	25.6	
	IIA	7	7.0	9	1.0	
	IIB	11	11.0	2	2.2	
Histological type, No. of cases, %	*Squamous cell carcinoma*	66	68.0	61	67.8	0.709
	Adenocarcinoma	27	27.0	20	22.2	
	Adenosquamous epithelial	5	5.0	5	5.6	
	others	2	1.0	4	4.4	
Operative time (min), mean ± SD, (range)		421 ±470	(257 - 869)	343 ± 127	(170 - 841)	< 0.001
Blood loss (ml), mean ± SD, (range)		138 ± 135	(0 - 550)	1008 ± 737	(72 - 5689)	< 0.001
Blood transfusion, No. of cases, %	*allogeneic*	1	1.0	10	11.1	0.003
	autologous	12	12.0	64	71.1	< 0.001
No. of lymph nodes removed, mean ± SD, (range)		34.3 ± 15.6	(4 - 80)	42.3 ± 17.8	(9 - 90)	0.059
Hospital stay (days), mean ± SD, (range)		11.5 ± 12.9	(6 - 82)	34.8 ± 23.9	(12 - 112)	< 0.001
Adverse events, No. of cases, %	*intraoperative*	4	4.0	3	3.3	0.808
	*postoperative ** *	5	5.0	11	12.2	0.073
	total	8	8.0	14	15.6	0.104
Self-urination for more than 3 months, No. of cases, %		2	2.0	29	32.2	< 0.001

* Data on RH at 4 institutes used as historical controls ** Clavien-Dindo classification 3 or higher adverse event

cases (5.9%) were classified as IB1 or less, while 13 out of 30 cases (43.3%) were classified as 1B2 or more.

No deaths were reported 1 year postoperatively. However, 2 years postoperatively, there were 3 deaths, including 1 case of IB1 and 2 cases of IIB. All of these cases had lymph node metastases and were classified as Stage 3C1 according to the UICC pTNM 2021 classification [18].

The oncological outcomes for all patients, as analyzed using the Kaplan–Meier method, showed an RFS rate of 82.7% and an OS rate of 96.9% over a median observation period of 37 months. However, for Stages IB1 and IIA1, the RFS and OS rates were 91.8% and 98.6%, respectively. Specifically, for Stage IB1 alone, the RFS and the OS rates were 94.1% and 98.5%, respectively (Fig. 1). A comparative study of 3-year and 2-year survival rates showed no change in overall survival, with one case of recurrence resulting in a slightly lower RFS. In 1B1 with tumor diameters of less than 2 cm, the RFS was 96.7% and OS was 100% (Additional Table 8).

Discussion

The primary endpoint of the study, which aimed to achieve surgical success with minimal blood loss without compromising the radicality of the procedure, surpassing the prespecified threshold of 75% and RARH is deemed superior to open RH. Based on these results, we can conclude that the original plan of this study was achieved. Regarding the secondary outcomes, the number of lymph nodes removed, blood transfusion, and urinary function were either comparable to or better than the historical controls. However, the longer operative and console time can be attributed to the surgeons' relative lack of experience with robotic surgery, which is a new technology, compared to their familiarity with open surgery, which is considered the gold standard.

Urinary function showed early recovery in the postoperative period, with the majority of patients experiencing recovery by three months. The successful completion of all surgeries with minimal blood loss and without the

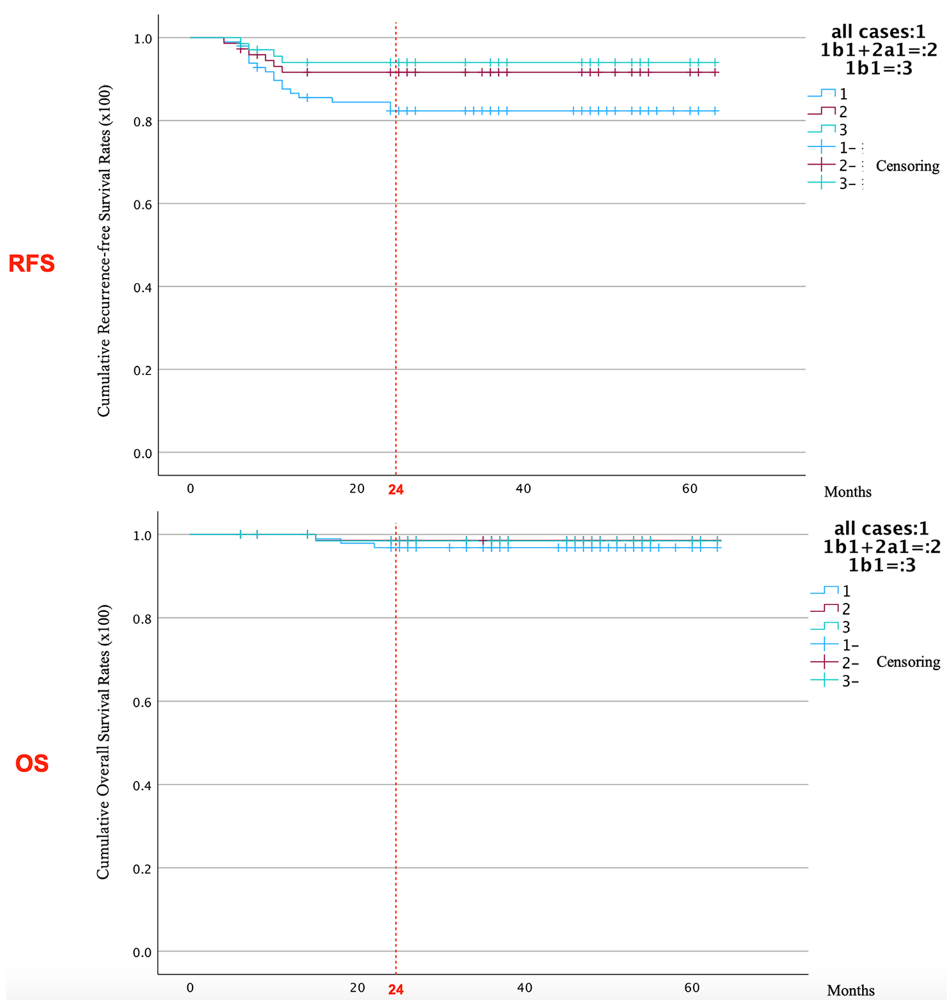

Fig. 1 Comparison of recurrence-free survival (RFS) and overall survival (OS) rates between all cases and cases with Stage 1b1 + 2a1 versus cases with Stage 1b1 RFS, recurrence-free survival; OS, overall survival

need for laparotomy, despite the high surgical difficulty, can be attributed to the seamless implementation of this technique and the effective utilization of the system's capabilities. It allowed sufficient preservation of the pelvic nerves in the enlarged operative field.

Regarding postoperative QoL as assessed by the EQ-5D, the majority of patients had almost returned to their preoperative activity levels by 180 or 365 days postoperatively. However, in terms of anxiety and blockiness, even at 365 days postoperatively, approximately 10% of patients still reported moderate anxiety and blockiness, suggesting that some level of mental anxiety about the disease persists for a long time after surgery.

In addition, there were no deaths due to the treatment protocol in this study, and the incidence of serious adverse events was maintained at a low rate of 8%. RH is a surgical procedure known to carry a higher risk of serious complications due to the complexity of the surgery. However, the incidence of intraoperative adverse events (8%) observed in this study was comparable to that reported in a large study [19] on open surgery (11%) and minimally invasive surgery (11%). Similarly, the rates of perioperative (35%) and serious (8%) adverse events were comparable to those reported for open (38–48% and 11–12%, respectively) and minimally invasive (40–54% and 12–14%, respectively) surgeries [19, 20]. These findings suggest that this technique may have a similar or even better safety profile compared to conventional techniques.

The Okabayashi procedure, established in 1921 [21], has long been the first treatment option in Japan for bulky cancers, including Stages IB2 and IIA2, as well as cancers spreading beyond the uterus, such as Stage IIB. However, due to the high recurrence rate of such cancers even after laparotomy alone, most cases undergo adjuvant radiotherapy after RH. In the present study, although no positive margins were found for stage I, in which the tumor was confined to the cervix, or stage IIA, in which the tumor invaded the vaginal wall, a high percentage of positive margins were found for stage IIB. This is due in part to the fact that in stage IIB, the vaginal wall is often extensively invaded, and adequate vaginal resection is difficult in all cases. On the other hand, the addition of postoperative radiation therapy can cause serious side effects, such as bowel obstruction. Therefore, the current standard treatment for patients with Stages IB2, IIA2, and IIB, as per the National Comprehensive Cancer guidelines, is CCRT rather than RH [22]. In Japan, an increasing number of medical institutions are now adopting CCRT as the first-line treatment for such cases instead of RH. Laparoscopic RH (LRH), currently covered by insurance, follows the guidelines set forth by the JSOG 2022, specifically for stages not exceeding IA2, IB1, and IIA1. Until the issue of the LRH technique's inferiority is addressed based on the results of the LACC trial [19], it is recommended to limit the procedure to cases with tumor diameters of 2 cm or less. This recommendation aligns with patients having Stages IB1 and IIA1 tumors of less than 2 cm in length according to the International federation of Obstetrics and Gynecology (FIGO) stage. By following this recommendation, the recurrence rate in RARH can be further reduced. In other words, we believe that selecting cases with assured safety can consistently improve the recurrence rate. Therefore, we consider the results of this study to provide valuable data for guiding the selection criteria.

It is essential to strive for some degree of standardization when this procedure is covered by insurance, aligning with the current society-led guidelines for LRH. Since the present study achieved safe surgery with minimal complications and an average blood loss of less than 300 mL, we believe it is crucial to establish the aforementioned initiatives and define appropriate surgeon criteria to reduce operating time and improve recurrence rates in the future.

The choice to use open surgery as the historical control in this study rather than laparoscopic surgery is explained in the Introduction section. Also, at the time of the study, there were significant differences between foreign techniques and the Japanese technique, which was based on the Okabayashi technique, despite scattered literature on the subject. However, a recent Japanese Gynecologic Oncology Group (JGOG) study (JGOG1081S) [23, 24] published results on LRH, allowing for a comparison with the results of JGOG1081S. For comparison, patients with the same advanced stage (FIGO 2008) as those undergoing laparoscopic surgery were selected. In the robotic surgery group, both the RFS and OS rates were comparable or better than those in the laparoscopic surgery group for patients with Stage IB1 (less than 2 cm and 2 cm or more) alone, and Stage IB1 plus Stage IIA1 (Table 4). The median observation period for the robotic surgery group was 37.0 months, which is longer than that for the laparoscopic surgery group. The results were also comparable to the 4-year disease-free survival (88.3%) and OS (96.4%) rates reported in a large Japanese retrospective data set of FIGO Stage IB1 and IIA1 patients (91.2% of whom underwent open surgery and 8.8% underwent minimally invasive surgery) [25]. For 3-year survival, the results may change as the data collection at 3 years post-operatively has not been fully completed, but the OS was unchanged from the 2-year survival rate, with only a slightly lower RFS. In addition, in 1B1 with tumor diameters of less than 2 cm, the survival rates were similar to the LACC trail open surgery data [19], which we consider to be promising results for future observational studies. Further long-term observation will clarify the noninferiority or superiority of the robotic surgery group. Even if the

Table 4 Comparison of oncologic outcomes between robot-assisted radical hysterectomy and laparoscopic radical hysterectomy

Operative methods	Median follow-up time (month)	IB1+IIA1		IB1			
				IB1 (< 2cm)		IB1 (2cm ≤)	
		RFS*	OS**	RFS*	OS**	RFS*	OS**
Robotic	37.0	91.8	98.6	100	100	86.7	96.7
Laparoscopic***	15.6	87.4	97.8	95.8	100	80.4	96.1
		RFS†	OS§	RFS†	OS§	RFS†	OS§
Laparoscopic****	42.9	86.9	93.7	91.5	96.0	82.7	91.0

* the 2 year recurrence-free survival ** the 2 year overall survival
† the 5 year recurrence-free survival § the 5 year overall survival

*** Kobayashi E, et al:. A retrospective assessment of the safety and efficacy of laparoscopic radical hysterectomy in Japan during the early years following its introduction: a Japanese Gynecologic Oncology Group study (JGOG1081S). Int J Clin Oncol. 2021 Feb;26(2):417-428.

**** Kobayashi E, et al:. Surgical skill and oncological outcome of laparoscopic radical hysterectomy: JGOG1081s-A1, an ancillary analysis of the Japanese Gynecologic Oncology Group Study JGOG1081. Gynecol Oncol 2022; 165: 293–301

oncological outcomes of the robotic surgery group are comparable to those of the laparoscopic surgery group, the learning curve for RAS is shorter than that for laparoscopic surgery [2, 3], which is a more difficult procedure. Therefore, the safe dissemination and standardization of RARH in Japan, along with its potential contribution to patients with cervical cancer seeking minimally invasive surgery, are highly anticipated. In the future, this technology is expected to be part of the prevention and treatment of cervical cancer, together with an integrated approach based on the synergistic combination of screening strategies, vaccination programs, adoption factor of a healthy lifestyle, and active management of risk factors [26].

There are several limitations to this study. First, it was conducted as a single-arm study, and a historical control was used to evaluate the statistical hypotheses. While the results demonstrated a significant improvement in surgical outcomes, except for operative time, compared to the historical control, the possibility of data bias cannot be completely ruled out. This is due to significant differences observed in the FIGO stage of patients, and therefore, the overall results should be interpreted with caution.

It is worth noting that this study design was chosen instead of a randomized controlled trial, primarily due to budget constraints. Due to the high medical costs associated with RAS, conducting a randomized clinical trial comparing RAS to insurance-covered conventional open surgery or laparoscopic surgery prior to insurance coverage is practically impossible. Therefore, the short-term results of RH were used as the historical control in this study. The rationale behind using historical data on RH as a control is that RH currently serves as the standard treatment for cervical cancer at advanced clinical Stages IA2 to IIB in Japan. Although LRH was approved as an advanced medical treatment A in Japan in 2014 [23], we considered it difficult to evaluate as a control at this stage since it is still in the early stages of investigation.

Conclusion

In this study, the use of minimally invasive surgery with DVSS demonstrated comparable radical cure rates to conventional RH. Specifically, significant reductions in blood loss were observed while maintaining radical cure, indicating the safety and efficacy of this procedure compared to conventional RH. We plan to further evaluate the oncologic outcomes of RARH in future studies.

Abbreviations

RARH	Robot-assisted radical hysterectomy
RFS	Recurrence-free survival
OS	Overall survival
RH	Radical hysterectomy
DVSS	Da Vinci surgical system
RAS	Robot-assisted surgery
JSOG	Japanese Society of Obstetrics and Gynecology
QoL	Quality of life
EQ-5D	EuroQol 5 Dimensions
FAS	Full analysis set
SPSS	Statistical Package for the Social Sciences
FIGO	International Federation of Gynecology and Obstetrics
ASA PS	American Society of Anesthesiologists physical status
CI	Confidence interval
UICC	Union for International Cancer Control
pTNM Classification	pathological tumor nodes metastasis classification
CCRT	Concurrent chemoradiotherapy
LRH	Laparoscopic radical hysterectomy
LACC Trial	Laparoscopic Approach to Cervical Cancer trial
JGOG	Japanese Gynecologic Oncology Group

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-024-13090-z.

Supplementary Material 1: Additional Fig. 1. Flowchart of the clinical trial

Supplementary Material 2: Additional Table 1. Comparison of RARH* and RH** in radical hysterectomy. Case background and data comparison of robotic and open groups. * Robot-assisted radical hysterectomy, ** Open radical hysterectomy, *** International Federation of Gynecology and Obstetrics All surgeries were performed at Tokyo Medical University Hospital between January 2021 and June 2014. This table was taken from Reference 8 in the text and translated into English.

Supplementary Material 3: Additional Table 2. List of selection criteria

Supplementary Material 4: Additional Table 3. List of exclusion criteria.

Supplementary Material 5: Additional Table 4. List of secondary endpoints

Supplementary Material 6: Additional Table 5. Data management The medical institution cooperated with any onsite or written investigation conducted by the Research Secretariat, the Minister of Health, Labour and Welfare, or any other relevant authority.

Supplementary Material 7: Additional Table 6. Results of postoperative residual urine measurements in 100 cases undergoing RARH*. *Robot-assisted radical hysterectomy; **lowest residual urine measured up to 90 days postoperatively; *** cases in which measurement was not performed or not possible

Supplementary Material 8: Additional Table 7. Evaluation of postoperative quality of life using the EQ-5D*. * EuroQol 5 Dimension

Supplementary Material 9: Additional Table 8. Oncologic outcome of robot-assisted radical hysterectomy comparison of 2-year and 3-year survival rates. *recurrence-free survival; **overall survival

Acknowledgements
We sincerely thank Dr. Kenichi Yoshimura, statistician, for drafting the data analysis and providing invaluable advice; Dr. Daijo Hashimoto, Dr. Hisashi Kawashima, and Dr. Osamu Nishii for serving as members of the Independent Monitoring Committee; Ms. Kaori Nakamichi of Tokyo Medical University for serving as the secretariat for the representative institutions; and Ms. Asuka Mizushima of Medical Research Support, data manager of the Data Center.

Author contributions
HI, YY, SK, MM, KK, HK, EM, MO, KM, NM, and KU were responsible for data collection. HI and KI drafted initial versions of the manuscript. HI and KI provided the statistical analyses. HI and KI were involved in data interpretation and manuscript development. All authors approved of the final manuscript version.

Funding
The clinical trial was supported by Intuitive Surgical Sari, Switzerland, which provided financial support for statistical analysis, but not direct research support.

Data availability
Data is provided within the manuscript or supplementary information files. The data presented in this study are also available on request from the corresponding author.

Declarations

Ethics approval and consent to participate
Ethics approval and informed consent for participation were obtained from all participating researchers in this clinical study. In accordance with subsequent amendments to the Clinical Research Act, this study underwent central ethical review (approval number: SH4138), in which Tokyo Medical University Hospital became the principal investigator and collectively reviewed the research plans of multiple research institutions participating in the multicenter collaborative study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Obstetrics and Gynecology, Tokyo Medical University Hospital, Tokyo, Japan
[2]Department of Obstetrics and Gynecology, Hirosaki University Hospital, Hirosaki, Japan
[3]Department of Obstetrics and Gynecology, Shimane University Faculty of Medicine, Izumo, Japan
[4]Department of Obstetrics and Gynecology, Kyoto University Hospital, Kyoto, Japan
[5]Department of Obstetrics and Gynecology, Shizuoka General Hospital, Shizuoka, Japan
[6]Department of Obstetrics and Gynecology, Kagoshima University Hospital, Kagoshima, Japan
[7]Department of Obstetrics and Gynecology, Yokohama City University Hospital, Yokohama, Japan
[8]Department of Obstetrics and Gynecology, Showa University of School of Medicine, Tokyo, Japan
[9]Department of Obstetrics and Gynecology, Kindai University Hospital, Osaka, Japan
[10]Department of Obstetrics and Gynecology, Toyohashi Municipal Hospital, Toyohashi, Japan
[11]Department of Molecular-Targeting Cancer Prevention, Kyoto Prefectural University of Medicine, Kyoto, Japan
[12]The Robot Center, Tokyo International Ohori Hospital, 4-8-40, Shimorenjaku, Mitaka City, Tokyo 181-0013, Japan

Received: 21 April 2024 / Accepted: 23 October 2024
Published online: 07 November 2024

References

1. Giannini A, D'Oria O, Bogani G, Di Donato V, Vizza E, Chiantera V, Laganà AS, Muzii L, Salerno MG, Caserta D, Gerli S, Favilli A. Hysterectomy: Let's step up the ladder of evidence to look over the Horizon. J Clin Med. 2022;11(23):6940. https://doi.org/10.3390/jcm11236940.
2. Lenihan JP Jr, Kovanda C, Seshadri-Kreaden U. What is the learning curve for robotic assisted gynecologic surgery? J Minim Invasive Gynecol. 2008;15:589–94.
3. Lim PC, Kang E, Park DH. Learning curve and surgical outcome for robotic-assisted hysterectomy with lymphadenectomy: Case-matched controlled comparison with laparoscopy and laparotomy for treatment of endometrial cancer. J Minim Invasive Gynecol. 2010;17:739–48.
4. Seamon LG, Fowler JM, Richardson DL, Carlson MJ, Valmadre S, Phillips GS, Cohn DE. A detailed analysis of the learning curve: Robotic hysterectomy and pelvic-aortic lymphadenectomy for endometrial cancer. Gynecol Oncol. 2009;114:162–7.
5. Rocconi RP, Meredith C, Finan MA. Evaluation of the learning curve of total robotic hysterectomy with or without lymphadenectomy for a gynecologic oncology service. J Robot Surg. 2011;5:189–193. https://doi.org/10.1007/s11701-011-0258-7. PMID: 27637706.
6. Casarin J, Song C, Multinu F, Cappuccio S, Liu E, Butler KA, Glaser GE, Cliby WA, Langstraat CL, Ghezzi F, Fu AZ, Mariani A. Implementing robotic surgery for uterine cancer in the United States: Better outcomes without increased costs. Gynecol. Oncol. 2020;156:451–458. https://doi.org/10.1016/j.ygyno.2019.11.016. PMID: 31780236.
7. Yabuki Y. Twenty-first century radical hysterectomy - Journey from descriptive to practical anatomy. Gynecol. Oncol. Rep. 2020;34:100623. https://doi.org/10.1016/j.gore.2020.100623. PMID: 32984492.
8. Isaka K, Kato R, Ito H. [Uterine cancer]. Gan Kagaku Ryoho. 2014;41:1354–7. PMID: 25434437 Japanese.
9. Sert B, Abeler V. Robotic radical hysterectomy in early-stage cervical carcinoma patients, comparing results with total laparoscopic radical hysterectomy cases. The future is now? Int J Med Robot. 2007;3:224–8.
10. Nezhat FR, Datta MS, Liu C, Chuang L, Zakashansky K. Robotic radical hysterectomy versus total laparoscopic radical hysterectomy with pelvic lymphadenectomy for treatment of early cervical cancer. JSLS. 2008;12:227–37.

11. Rocconi RP, Meredith C, Finan MA. Evaluation of the learning curve of total robotic hysterectomy with or without lymphadenectomy for a gynecologic oncology service. J Robot Surg. 2011;5:189–93.
12. Estape R, Lambrou N, Diaz R, Estape E, Dunkin N, Rivera A. A case matched analysis of robotic radical hysterectomy with lymphadenectomy compared with laparoscopy and laparotomy. Gynecol Oncol. 2009;113:357–61.
13. Request for compliance. with the guidelines for robotic-assisted surgery for gynecologic malignancies and cooperation in the registration of institutions and cases. Nihon Sanka Fujinka Gakkai Zasshi. 2014;66(1298):295.
14. Ebina Y, Yaegashi N, Katabuchi H, Nagase S, Udagawa Y, Hachisuga T, Saito T, Mikami M, Aoki Y, Yoshikawa H. Japan Society of Gynecologic Oncology guidelines 2011 for the treatment of uterine cervical cancer. Int J Clin Oncol. 2015;20:240–248. https://doi.org/10.1007/s10147-015-0806-7. PMID: 25800808.
15. Cervical Cancer Treatment Regulations. Japanese Society of Obstetrics and Gynecology, Japanese Society of Pathology, Japanese Society of Radiological Sciences. 3rd ed. Japanese Society of Gynecologic Oncology; Kanehara Publishing Co, editor 2012.
16. Shiroiwa T, Ikeda S, Noto S, Igarashi A, Fukuda T, Saito S, Shimozuma K. Comparison of value set based on DCE and/or TTO Data: Scoring for EQ-5D-5L health States in Japan. Value Health. 2016;19:648–54.
17. Brierley JD, editor. TNM Classification of Malignant Tumours, 8th ed. Wiley-Blackwell. ISBN: 978-1-119-26357-9, Mary K. Gospodarowicz, editor, Christian Wittekind, editor Dec 2016.
18. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri: 2021 update. Int J Gynaecol Obstet. 2021;155(Suppl 1):28–44. https://doi.org/10.1002/ijgo.13865. PMID: 34669203 Supp. l. 1.
19. Ramirez PT, Frumovitz M, Pareja R, Lopez A, Vieira M, Ribeiro R, Buda A, Yan X, Shuzhong Y, Chetty N, Isla D, Tamura M, Zhu T, Robledo KP, Gebski V, Asher R, Behan V, Nicklin JL, Coleman RL, Obermair A. Minimally invasive versus abdominal radical hysterectomy for cervical cancer. N Engl J Med. 2018;379:1895–904.
20. Obermair A, Asher R, Pareja R, Frumovitz M, Lopez A, Moretti-Marques R, Rendon G, Ribeiro R, Tsunoda A, Behan V, Buda A, Bernadini MQ, Zhao H, Vieira M, Walker J, Spirtos NM, Yao S, Chetty N, Zhu T, Isla D, Tamura M, Nicklin J, Robledo KP, Gebski V, Coleman RL, Salvo G, Ramirez PT. Incidence of adverse events in minimally invasive vs open radical hysterectomy in early cervical cancer: Results of a randomized controlled trial. Am J Obstet Gynecol. 2020;222:e2491–24910. https://doi.org/10.1016/j.ajog.2019.09.036.
21. Okabayashi H. Radical abdominal hysterectomy for cancer of the cervix uteri. Surg Gynecol Obstet. 1921;11:335–43.
22. Cervical cancer guideline. (version 1 2021). NCCN Clinical Practice Guidelines in Oncology. https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf
23. Kobayashi E, Kanao H, Takekuma M, Nishio S, Kojima-Chiba A, Tozawa A, Yamaguchi S, Takeshima N, Nakatani E, Mikami M. A retrospective assessment of the safety and efficacy of laparoscopic radical hysterectomy in Japan during the early years following its introduction: A Japanese Gynecologic Oncology Group study (JGOG1081S). Int J Clin Oncol. 2021;26:417–428. https://doi.org/10.1007/s10147-020-01799-3. PMID: 33433752.
24. Kobayashi E, Nakatani E, Tanaka T, Yosuke K, Kanao H, Shiki Y, Kotani Y, Hoshiba T, Minami R, Yoshida H, Kyo S, Yorimitsu M, Yamashita T, Hasegawa T, Matsuura T, Kagami S, Fujioka T, Hirohiko T, Nishio S, Takekuma M, Mikami M, Enomoto T. Surgical skill and oncological outcome of laparoscopic radical hysterectomy: JGOG1081s-A1, an ancillary analysis of the Japanese Gynecologic Oncology Group study JGOG1081. Gynecol Oncol. 2022;165:293–301. https://doi.org/10.1016/j.ygyno.2022.02.005. PMID: 35221133.
25. Ohta T, Nagase S, Okui Y, Enomoto T, Yamagami W, Mikami M, Tokunaga H, Ino K, Ushijima K, Shozu M, Tashiro H, Mandai M, Miyamoto S, Morishige KI, Yoshida Y, Yoshino K, Saito T, Kobayashi E, Kobayashi H, Takekuma M, Terai Y, Fujii T, Kanao H, Aoki D, Katabuchi H, Yaegashi N. Surveillance of radical hysterectomy for early-stage cervical cancer in the early experienced period of minimally invasive surgery in Japan. Int J Clin Oncol. 2021;26:2318–2330. https://doi.org/10.1007/s10147-021-02017-4. PMID: 34435284.
26. Ferrari F, Giannini A. Approaches to prevention of gynecological malignancies. BMC Womens Health. 2024;24(1):254. https://doi.org/10.1186/s12905-024-03100-4.PMID: 38654319.

Publisher's note