Cervical conization before primary radical hysterectomy has a protective effect on disease recurrence in early cervical cancer: A two-center matched cohort study according to surgical approach

PRESENTER: R2 王韻涵

SUPERVISOR: VS 江岭諭醫師

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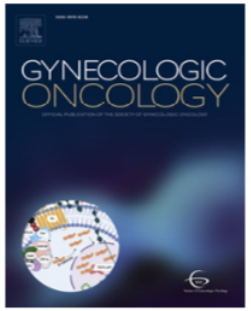

Cervical conization before primary radical hysterectomy has a protective effect on disease recurrence in early cervical cancer: A two-center matched cohort study according to surgical approach

Se Ik Kim [a], Bo Ram Choi [b], Hee Seung Kim [a], Hyun Hoon Chung [a], Jae-Weon Kim [a], Noh Hyun Park [a], Yong-Sang Song [a], Chel Hun Choi [b,*], Maria Lee [a,**]

[a] *Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul 03080, Republic of Korea*
[b] *Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul 06351, Republic of Korea*

Introduction

Cervical cancer is the fourth most frequently occurring cancer and the fourth leading cause of cancer-related deaths in women worldwide. (臺灣子宮頸癌發生率居第9名,2018年)

In developed countries, the incidence and mortality of cervical cancer have decreased steadily owing to well-established screening programs

Introduction

In the United States and Korea, 44% and 56% of cervical cancer patients are diagnosed at the localized stage, respectively, with a 5-year relative survival rate of more than 90%.

For early cervical cancer, the current practice guidelines recommend primary radical hysterectomy (RH) as the standard treatment.

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Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer

Pedro T. Ramirez, M.D., Michael Frumovitz, M.D., Rene Pareja, M.D., Aldo Lopez, M.D., Marcelo Vieira, M.D.,

CONCLUSIONS

In this trial, minimally invasive radical hysterectomy was associated with lower rates of disease-free survival and overall survival than open abdominal radical hysterectomy among women with early-stage cervical cancer. (Funded by the University of Texas M.D. Anderson Cancer Center and Medtronic; LACC ClinicalTrials.gov number, NCT00614211.)

Also, higher disease recurrence and mortality rates

- Tumor spillage during surgery, exacerbated by using a uterine manipulator
- The risk of tumor spillage is associated with cervical mass size at the time of RH.

Aim of this study

Whether cervical conization before RH had a protective effect on survival outcomes in node-negative, margin-negative, parametria-negative, early cervical cancer.

Stratification by surgical approach was also performed.

Materials and methods

Study population

This two-center, matched cohort study was approved by the Institutional Review Boards of Seoul National University Hospital and Samsung Medical Center.

Inclusion criteria

1. 2009 International Federation of Gynecology and Obstetrics (FIGO) stage IB1 disease
2. With squamous cell carcinoma, usual type adenocarcinoma, or adenosquamous carcinoma
3. Underwent Querleu–Morrow Type C RH as primary treatment at either institution between July 2006 and June 2020
4. Did not have any pathologic high-risk factor (involvement of the lymph node, resection margin, and/or parametrium).

Summary of the main landmarks in each type of radical hysterectomy on each part of the parametria

Dimension Type of radical hysterectomy	Paracervix or lateral parametrium	Ventral parametrium	Dorsal parametrium
A	Halfway between the cervix and ureter (medial to the ureter–ureter identified but not mobilized)	Minimal excision	Minimal excision
B1	At the ureter (at the level of the ureteral bed–ureter mobilized from the cervix and lateral parametrium)	Partial excision of the vesicouterine ligament	Partial resection of the rectouterine-rectovaginal ligament and uterosacral peritoneal fold
B2	Identical to B1 plus paracervical lymphadenectomy without resection of vascular/nerve structures	Partial excision of the vesicouterine ligament	Partial resection of the rectouterine-rectovaginal ligament and uterosacral fold
C1	At the iliac vessels transversally, caudal part is preserved	Excision of the vesicouterine ligament at the bladder. Proximal part of the vesicovaginal ligament (bladder nerves are dissected and spared)	At the rectum (hypogastric nerve is dissected and spared)
C2	At the level of the medial aspect of iliac vessels completely (including the caudal part)	At the bladder (bladder nerves are sacrificed)	At the sacrum (hypogastric nerve is sacrificed)
D	At the pelvic wall, including resection of the internal iliac vessels and/or components of the pelvic sidewall	At the bladder. Not applicable if part of exenteration	At the sacrum. Not applicable if part of exenteration

Exclusion criteria

1. Received chemotherapy or radiation therapy (RT) before RH
2. Received cervical polypectomy or excisional biopsy instead of cervical conization
3. Received preoperative cervical conization but lacked invasive cancer tissue (e.g. cervicitis, cervical intraepithelial neoplasia, and carcinoma in situ) or accurate pathologic tumor size (due to split into small pieces, etc.) on conization specimens
4. No relapse, but with follow-up loss within 3 months after RH.

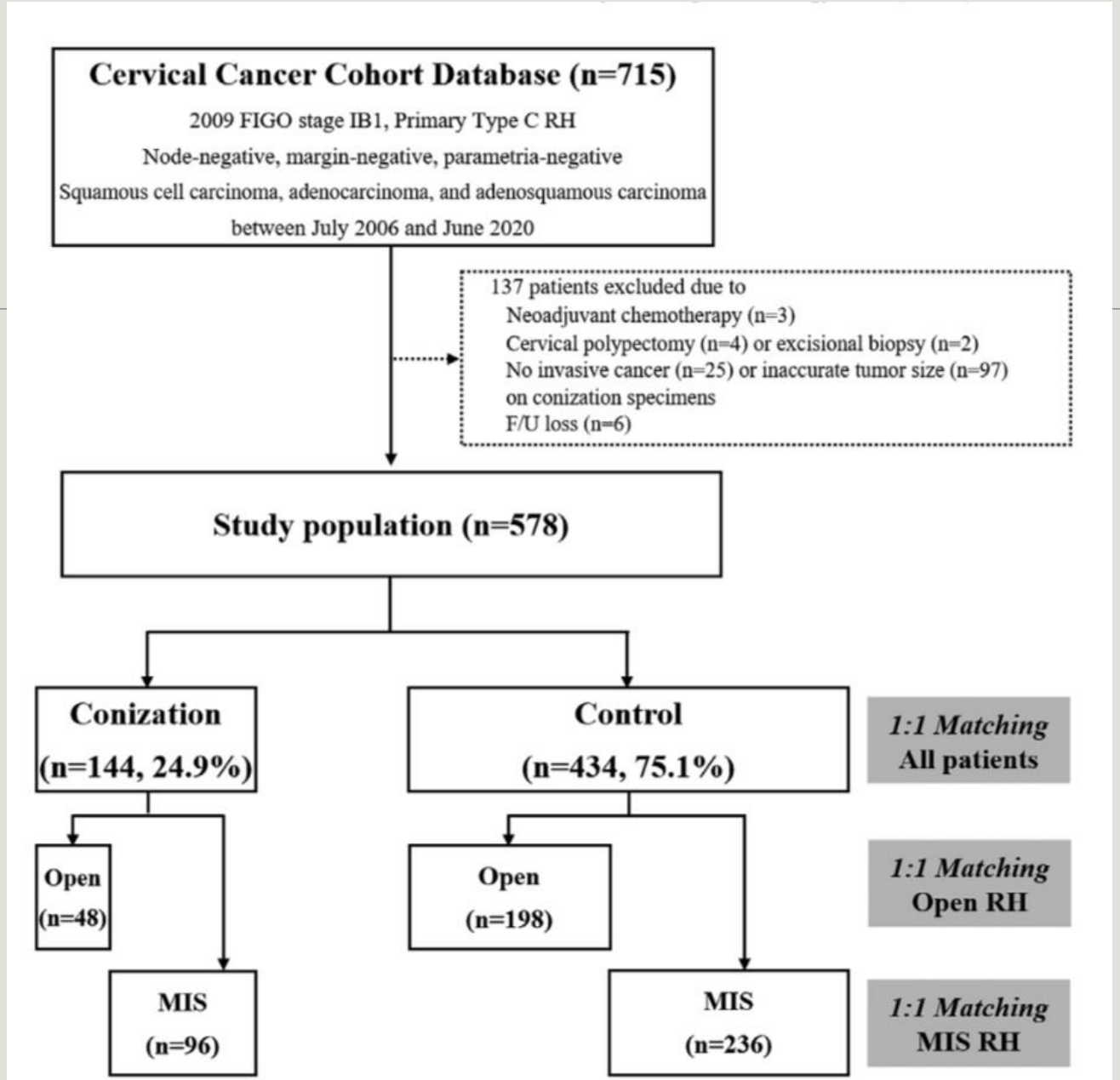


Fig. 1. Flow diagrams depicting the selection of study population and three independent matching processes.

Data collection

- Patient clinicopathologic characteristics, including age, histologic type, surgical approach, pelvic and para-aortic lymphadenectomy, lymphovascular space invasion (LVSI), and adjuvant treatments.
- Initial cervical tumor size by summing the maximum pathologic tumor diameter on the conization specimen and those from the uterine specimen.

Data collection

The loop electrosurgical excision procedure (LEEP) was the preferred method for cervical conization in both institutions.

RH was performed within 2 months after conization.

Data collection

Before the publication of the LACC trial, the surgical approach was mainly determined by the surgeon's preference.

Accordingly, the implementation rate of primary MIS RH significantly decreased after the LACC trial: MIS RH was only considered among 2009 FIGO stage IB1 patients with cervical tumor size ≤2 cm, based on our previous reports

Adjuvant treatment

For intermediate-risk group:

- LVSI
- Depth of stromal invasion
- Tumor size

received adjuvant RT(pelvic external beam RT of 50.4 Gy in 28 fractions, with or without concurrent intravenous administration of cisplatin 40 mg/m2, every week for 4–6 cycles.)

Surveillance methods

- Routine computed tomography (CT) scans every 3–4 months for the first 2 years, every 6 months for the next 3 years
- DFS : the time interval from the date of primary RH to the date of disease recurrence, confirmed by CT scans
- Overall survival (OS) : until the date of cancer-related death or the end of the study.

Sample matching and statistical analyses

- 1:1 propensity score matching : to minimize the effect of covariates on cervical conization.
- Comparisons of continuous variables: Student's t-test and the Mann–Whitney U test
- Comparisons of categorical variables : Pearson's chi-squared test and Fisher's exact test
- Survival outcomes: Kaplan–Meier analysis with the log-rank test
- Multivariate analyses: Cox proportional hazards regression models

Results

Comparisons of the propensity scores within the conization and control groups before and after sample matching

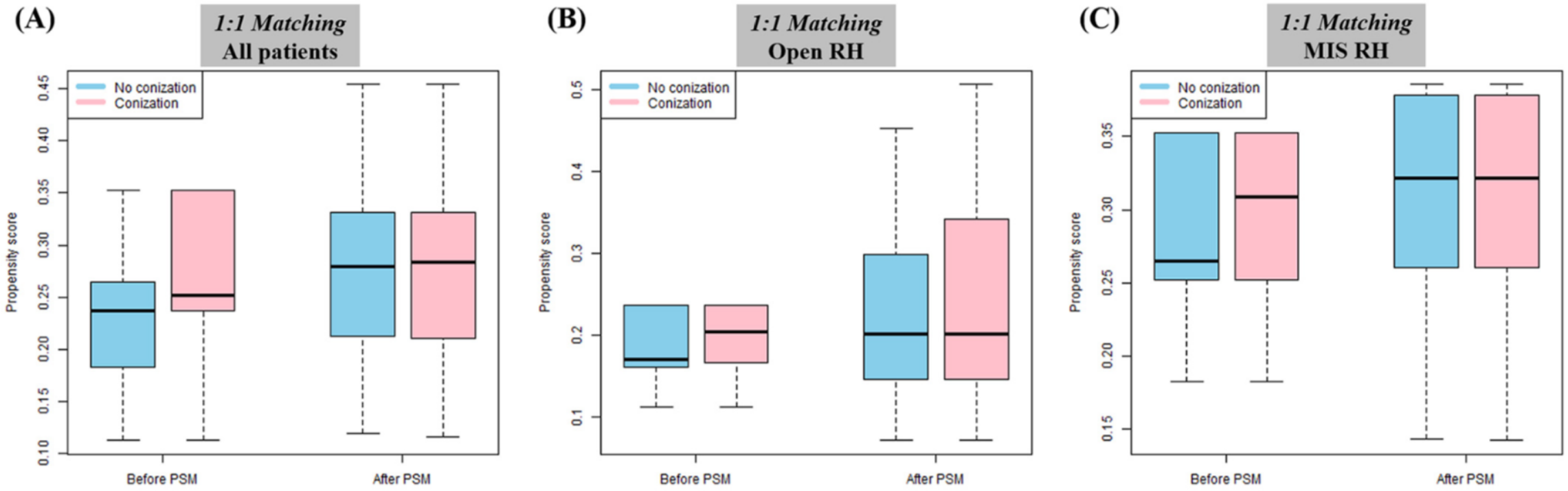


Fig. 2. Comparisons of the propensity scores within the conization and control groups before and after sample matching. (A) Overall matching; (B) Matching in patients with open radical hysterectomy; (C) Matching in patients with minimally invasive radical hysterectomy.

Table 1
Patient characteristics before and after matching.

Characteristics	Before matching			After matching	
	Conization group (n = 144, %)	Control group (n = 434, %)	P	Control group (n = 144, %)	P
Age, years					
Mean ± SD	50.7 ± 10.9	49.3 ± 10.7	0.294	49.7 ± 10.5	0.651
Histologic type, two categories			0.065		0.369
Squamous cell carcinoma	104 (72.2)	277 (63.8)		97 (67.4)	
Non-Squamous cell carcinoma	40 (27.8)	157 (36.2)		47 (32.6)	
Histologic type, three categories			0.183		0.504
Squamous cell carcinoma	104 (72.2)	277 (63.8)		97 (67.4)	
Adenocarcinoma	34 (23.6)	134 (30.9)		37 (25.7)	
Adenosquamous carcinoma	6 (4.2)	23 (5.3)		10 (6.9)	
Pathologic cervical tumor size					
Conization specimen*, mm					
Mean ± SD	16.5 ± 9.8		N/A		N/A
Uterine specimen†, mm					
Mean ± SD	15.4 ± 14.6	29.5 ± 12.0	<0.001	29.7 ± 13.2	<0.001
Initial tumor size‡, mm					
Mean ± SD	31.8 ± 17.0	29.5 ± 12.0	0.424	29.7 ± 13.2	0.479
≤20	43 (29.9)	107 (24.7)	<0.001	42 (29.2)	0.133
>20 and ≤40	62 (43.1)	267 (61.5)		76 (52.8)	
>40	39 (27.1)	60 (13.8)		26 (18.1)	

Before matching, the conization group had a significantly smaller uterine tumor size

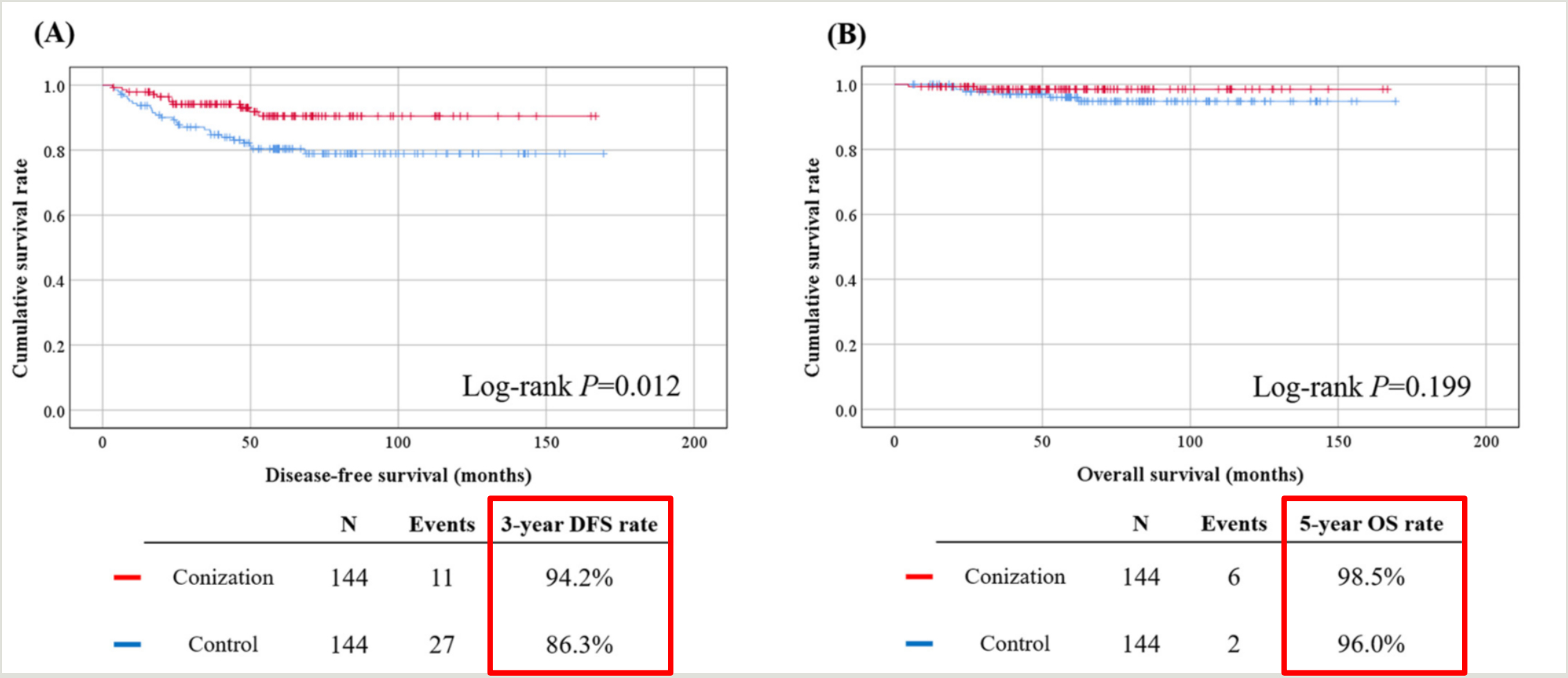
Table 1
Patient characteristics before and after matching.

Characteristics		Before matching		After matching	
	Conization group ($n = 144$, %)	Control group ($n = 434$, %)	*P*	Control group ($n = 144$, %)	*P*
Surgical approach			0.034		0.817
Open surgery	48 (33.3)	198 (45.6)		43 (29.9)	
Laparoscopy	81 (56.3)	202 (46.5)		85 (59.0)	
Robot-assisted surgery	15 (10.4)	34 (7.8)		16 (11.1)	
Lymphadenectomy, two categories			0.167		>0.999
No	3 (2.1)	3 (0.7)		3 (2.1)	
Yes	141 (97.9)	431 (99.3)		141 (97.9)	
Lymphadenectomy, three categories			0.311		0.466
No	3 (2.1)	3 (0.7)		3 (2.1)	
Pelvic LNs only	125 (86.8)	389 (89.6)		131 (91.0)	
Pelvic plus para-aortic LNs	16 (11.1)	42 (9.7)		10 (6.9)	
LVSI	38 (26.4)	140 (32.3)	0.186	29 (20.1)	0.209
Adjuvant treatment					
No	120 (83.3)	296 (68.2)	<0.001	110 (76.4)	0.142
Yes	24 (16.7)	138 (31.8)		34 (23.6)	
RT only	16 (11.1)	99 (22.8)	0.613	26 (18.1)	0.411
CCRT	8 (5.6)	39 (9.0)		8 (5.6)	

- 37 patients received preoperative conization and had no residual tumor in their uterine specimens (14 and 23 for open RH and MIS RH, respectively)

One (2.7%) recurred, involving her pelvic wall 46.6 months after MIS RH.

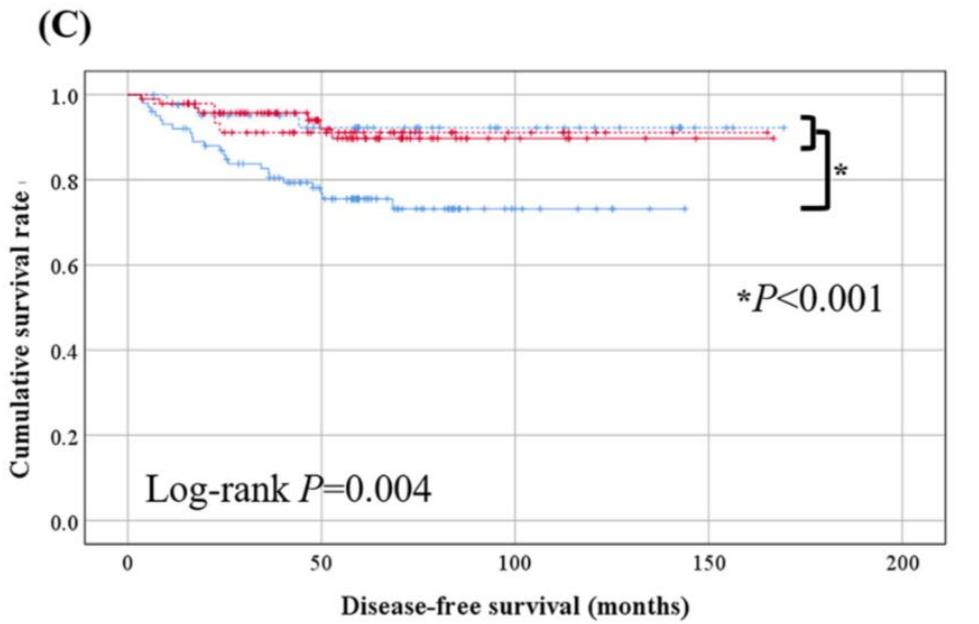
Comparison of the survival outcomes for matched patients

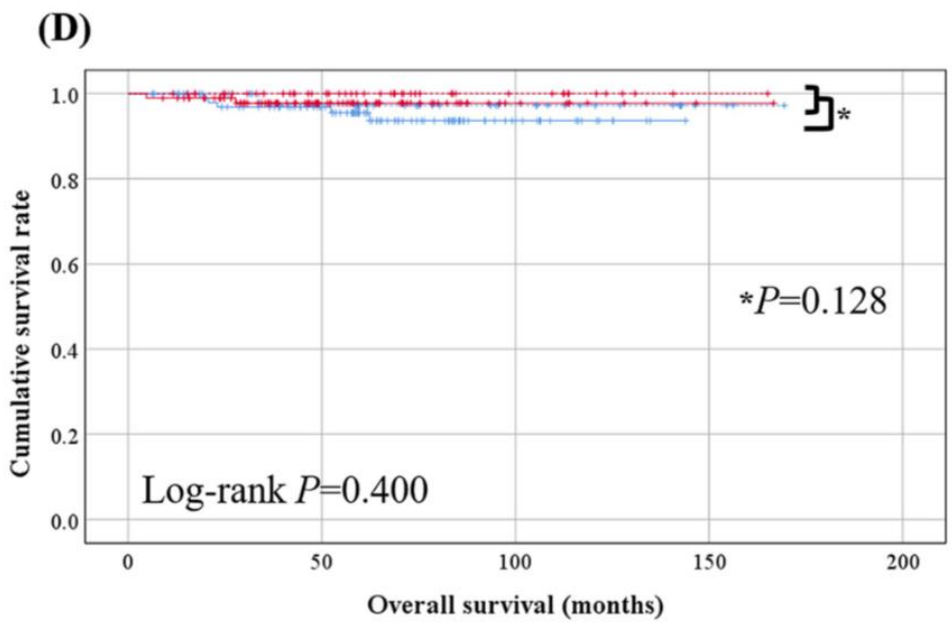


	N	Events	3-year DFS rate
Conization	144	11	94.2%
Control	144	27	86.3%

	N	Events	5-year OS rate
Conization	144	6	98.5%
Control	144	2	96.0%

The conization group showed significantly better DFS versus control (3-year DFS rate, 94.2% vs. 86.3%; P = 0.012), but similar OS (P = 0.199)





	Surgical approach	N	Events	3-year DFS rate	Log-rank P
Conization	Open	48	4	91.1%	0.903
Conization	MIS	96	7	95.7%	
Control	Open	43	3	95.1%	0.022
Control	MIS	101	24	82.7%	

	Surgical approach	N	Events	3-year OS rate	Log-rank P
Conization	Open	48	0	100.0%	0.317
Conization	MIS	96	2	97.8%	
Control	Open	43	1	97.2%	0.473
Control	MIS	101	5	96.9%	

Fig. 3. Comparison of the survival outcomes for matched patients (Upper); and further stratified survival analyses according to the conization and surgical approach (Lower). (A, C) Disease-free survival; (B, D) Overall survival.

Conization group: patients who received open RH (n = 48) and those who received MIS RH (n = 96) showed similar DFS (P = 0.903) and OS (P = 0.317)

Control group: patients who received MIS RH (n = 101) showed significantly worse DFS than those who received open RH (n = 43) (3-year DFS rate, 82.7% vs. 95.1%; P = 0.022), but similar OS (P = 0.473)

Recurrence patterns

The conization group showed a significantly lower incidence rate of pelvic recurrence (4.9% vs. 11.8%; P = 0.033) versus control

similar incidence rates of nodal (P = 0.684), abdominal (P = 0.498), and distant site recurrences (P = 0.238)

Nodal: retroperitoneal LNs

Matched patients by surgical approach

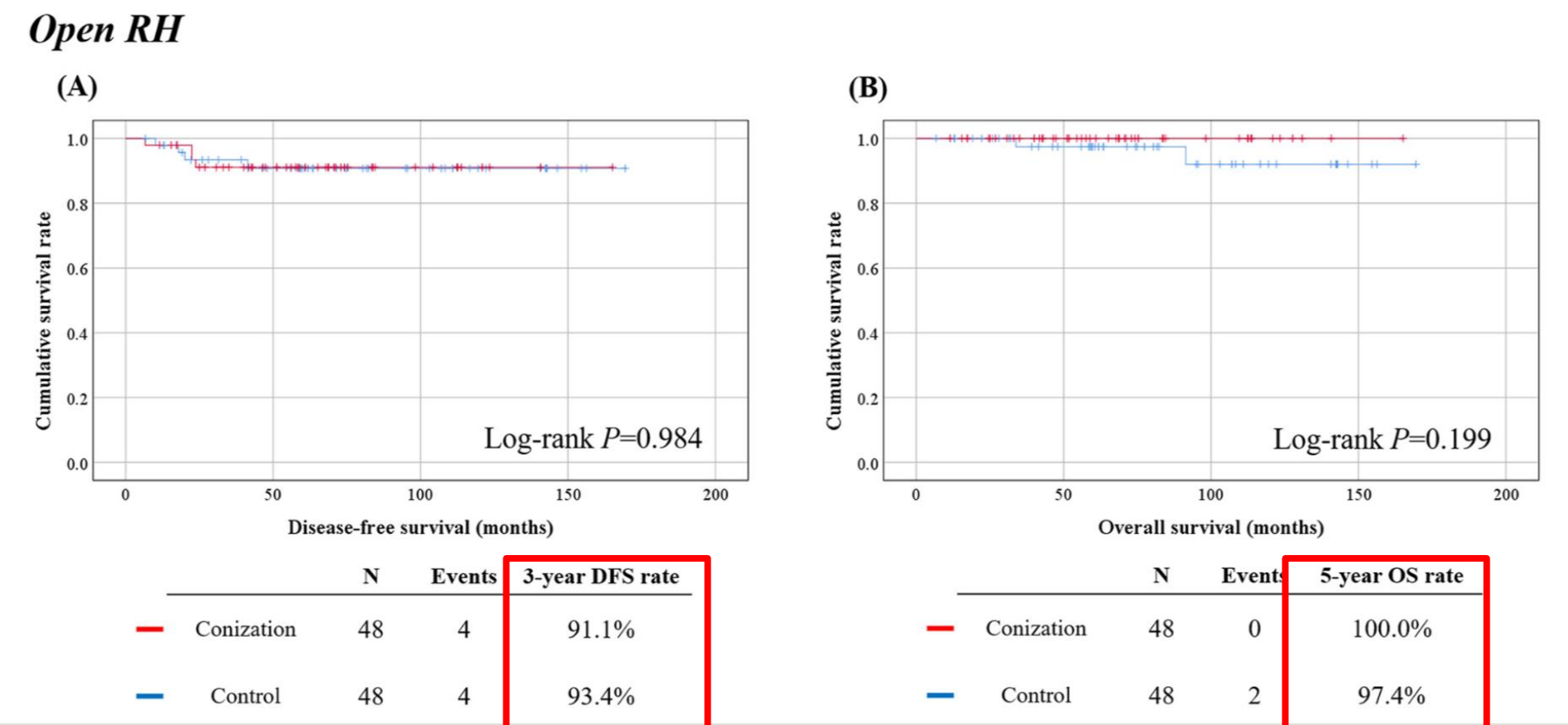
Table 2
Patients' characteristics among the matched patients by surgical approach.

Characteristics	Open RH			MIS RH		
	Conization group (n = 48, %)	Control group (n = 48, %)	P	Conization group (n = 96, %)	Control group (n = 96, %)	P
Age, years						
Mean ± SD	50.8 ± 10.3	49.6 ± 12.3	0.598	50.6 ± 11.3	48.6 ± 10.9	0.208
Histologic type, two categories			0.266			>0.999
Squamous cell carcinoma	36 (75.0)	31 (64.6)		68 (70.8)	68 (70.8)	
Non-Squamous cell carcinoma	12 (25.0)	17 (35.4)		28 (29.2)	28 (29.2)	
Histologic type, three categories			0.398			0.936
Squamous cell carcinoma	36 (75.0)	31 (64.6)		68 (70.8)	68 (70.8)	
Adenocarcinoma	10 (20.8)	12 (25.0)		24 (25.0)	23 (24.0)	
Adenosquamous carcinoma	2 (4.2)	5 (10.4)		4 (4.2)	5 (5.2)	
Pathologic cervical tumor size						
Conization specimen*, mm						
Mean ± SD	18.5 ± 9.9		N/A	15.4 ± 9.6		N/A
Uterine specimen†, mm						
Mean ± SD	18.9 ± 18.0	37.9 ± 18.8	<0.001	13.6 ± 12.3	29.1 ± 13.6	<0.001
Initial tumor size‡, mm						
Mean ± SD	37.5 ± 20.0	37.9 ± 18.8	0.797	29.0 ± 14.6	29.1 ± 13.6	0.982
≤20	14 (29.2)	11 (22.9)	0.781	29(30.2)	32 (33.3)	0.828
>20 and ≤40	16 (33.3)	17 (35.4)		46 (47.9)	46 (47.9)	
>40	18 (37.5)	20 (41.7)		21 (21.9)	18 (18.8)	

Table 2
Patients' characteristics among the matched patients by surgical approach.

Characteristics	Open RH			MIS RH		
	Conization group ($n = 48$, %)	Control group ($n = 48$, %)	*P*	Conization group ($n = 96$, %)	Control group ($n = 96$, %)	*P*
Lymphadenectomy, two categories			>0.999			>0.999
No	0	1 (2.1)		3 (3.1)	2 (2.1)	
Yes	48 (100.0)	47 (97.9)		93 (96.9)	94 (97.9)	
Lymphadenectomy, three categories			0.324			0.861
No	0	1 (2.1)		3 (3.1)	2 (2.1)	
Pelvic LNs only	39 (81.3)	42 (87.5)		86 (89.6)	88 (91.7)	
Pelvic plus para-aortic LNs	9 (18.8)	5 (10.4)		7 (7.3)	6 (6.3)	
LVSI	15 (31.3)	12 (25.0)	0.496	23 (24.0)	23 (24.0)	>0.999
Adjuvant treatment						
No	34 (70.8)	22 (45.8)	0.013	86 (89.6)	72 (75.0)	0.008
Yes	14 (29.2)	26 (54.2)		10 (10.4)	24 (25.0)	
RT only	10 (20.8)	17 (35.4)	0.697	6 (6.3)	19 (19.8)	0.395
CCRT	4 (8.3)	9 (18.8)		4 (4.2)	5 (5.2)	

Comparison of the survival outcomes for matched patients: open RH

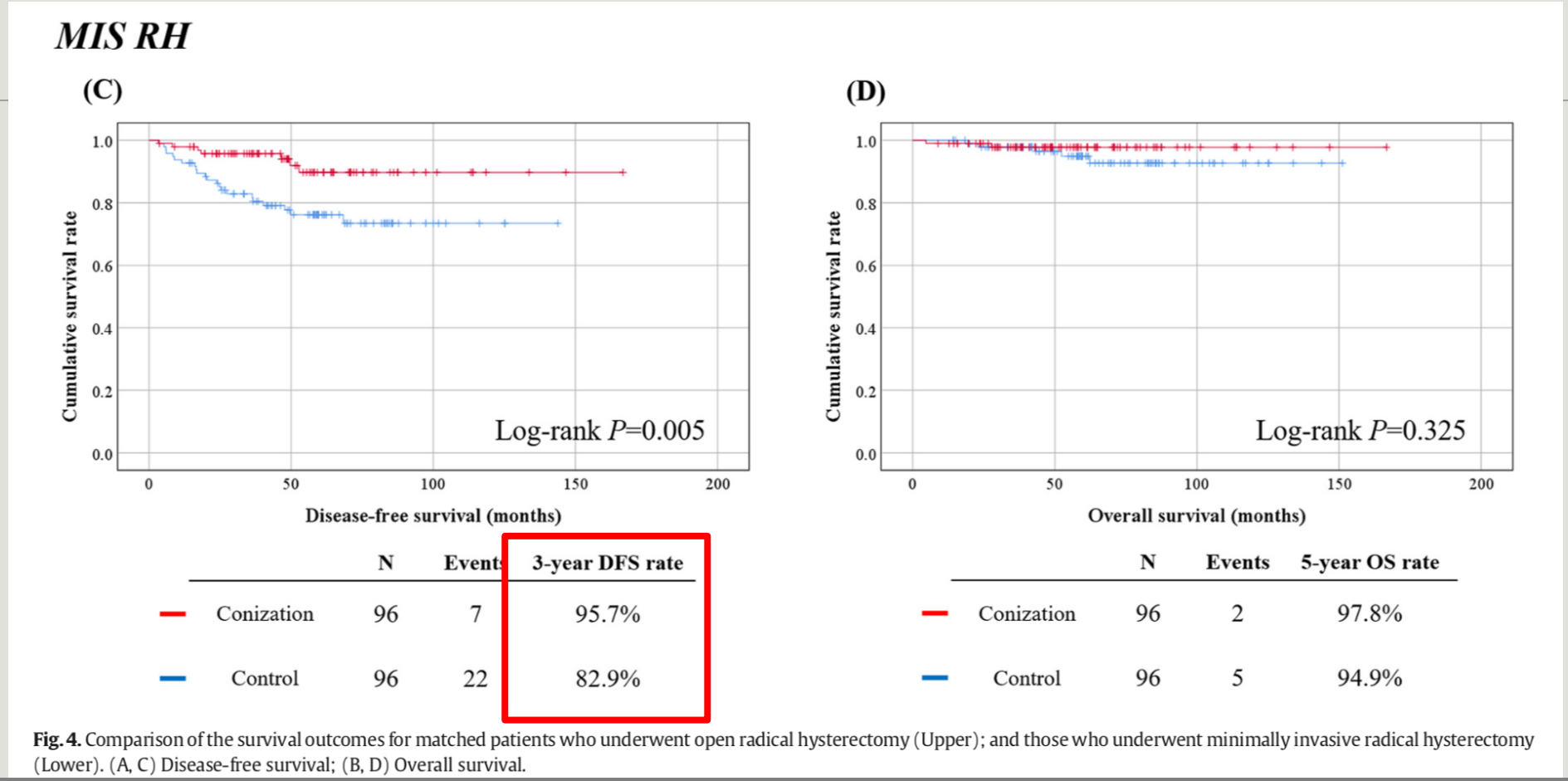


	N	Events	3-year DFS rate
Conization	48	4	91.1%
Control	48	4	93.4%

	N	Events	5-year OS rate
Conization	48	0	100.0%
Control	48	2	97.4%

The median observation period was 66.5 months, during which 8 (8.3%) with disease recurrence and 2 (2.1%) died.
Similar DFS (P = 0.984) and OS (P = 0.199)

Comparison of the survival outcomes for matched patients: MIS RH



	N	Events	3-year DFS rate
Conization	96	7	95.7%
Control	96	22	82.9%

	N	Events	5-year OS rate
Conization	96	2	97.8%
Control	96	5	94.9%

Fig. 4. Comparison of the survival outcomes for matched patients who underwent open radical hysterectomy (Upper); and those who underwent minimally invasive radical hysterectomy (Lower). (A, C) Disease-free survival; (B, D) Overall survival.

During a 57.9 month median observation period, 29 (15.1%) relapsed and 7 (3.6%) died from their disease.

Conization group showed significantly better DFS versus control, but similar OS

Discussion

Discussion

Conization was associated with a significantly lower recurrence rate among matched patients who underwent MIS RH.

However, this association was not observed in cases of open RH.

LACC trial results in real-world clinical practice

- In the United States, the use of MIS RH for cervical cancer decreased after the publication of the LACC trial results: 58% to 42.9%
- A meta-analysis of 15 high-quality observational studies (n = 9499) also reported that MIS RH was associated with worse DFS and OS than open RH in early-stage cervical cancer

LACC trial results in real-world clinical practice

- Quality of life was similar between the open RH and MIS RH groups.
- The trial group insisted that physicians recommend open RH for patients with early-stage cervical cancer.

Robot-assisted approach to cervical cancer (RACC)

- Comparing survival outcomes between robot-assisted RH and open RH is currently ongoing
- Refining optimal candidates

Prevention of tumor spillages

no-look no-touch technique

transvaginal closure of the vaginal cuff

endoscopic stapler

etc.

Compare with other studies

Excluded patients who had any high-risk factors

- we found that preoperative cervical conization did not affect DFS in patients with node-positive cervical cancer who underwent primary RH

Only included those with Type C RH, which is the current standard.

Sample matching differed: tumor size and LVSI, histology and surgical approach.

Tumor size reduction

- The favorable impact of cervical conization before MIS RH on DFS might be explained by a direct size reduction of the cervical tumor.
- Of the 96 patients who received both conization and MIS RH, 23 (24.0%) had no residual tumor in their uterine specimens, with only one patient experiencing disease recurrence.

Tumor size

Clinical using magnetic resonance imaging (MRI), to objectively measure cervical tumor size.

Initial cervical tumor size : maximum pathologic tumor diameter on the conization specimen + uterine specimen

Limitation

1. Biases from the retrospective study design could not be ruled out.
2. Heterogeneity in clinical practice among surgeons between institutions.
3. Study population and death or recurrence events were small, especially for the conization group.
4. We did not investigate intra- and postoperative complications, quality of life issues, and cost-effectiveness in relation to conization.

Conclusions

- Preoperative cervical conization might be preferable for patients with 2009 FIGO stage IB1 cervical cancer who are scheduled to undergo MIS RH.
- For open RH, equivalent survival outcomes were observed regardless of cervical conization.


THANKS
FOR
LISTENING