

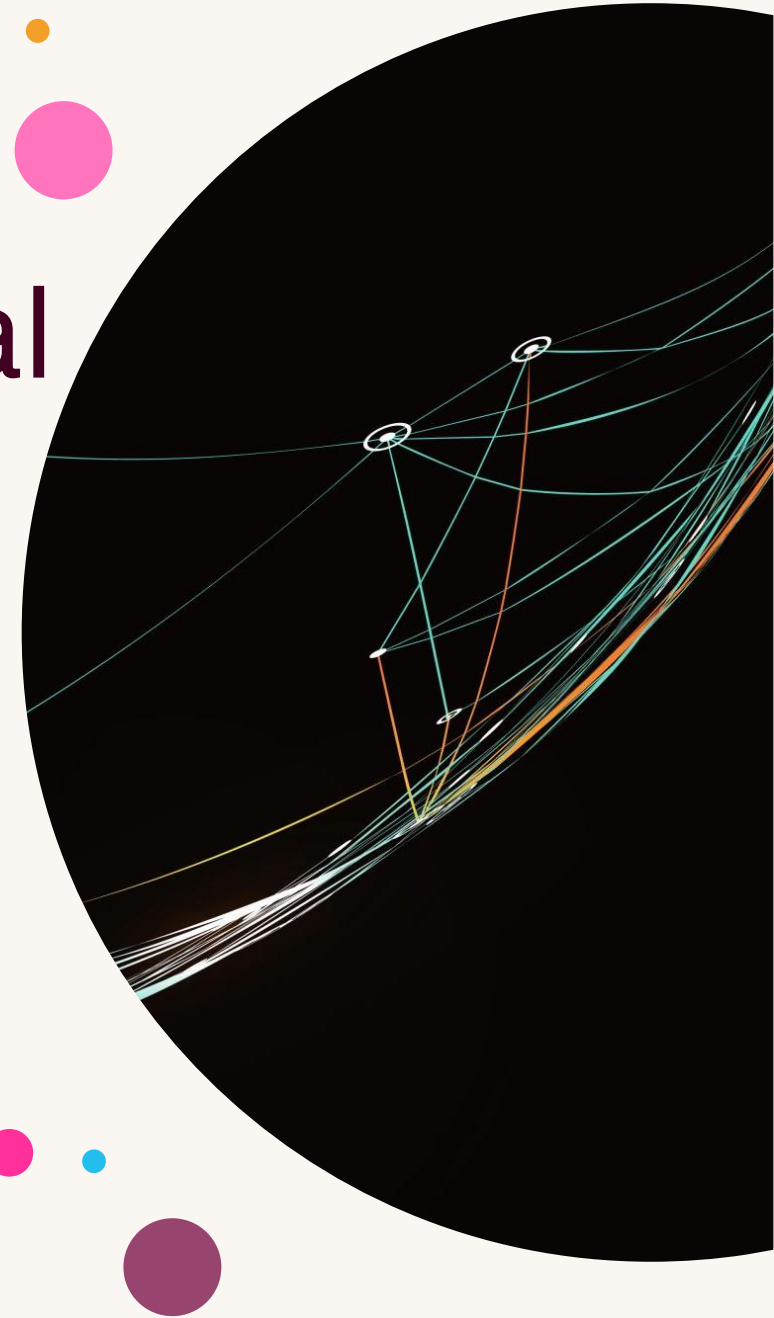
What is the best surgical management for early cervical cancer less than 2 cm?

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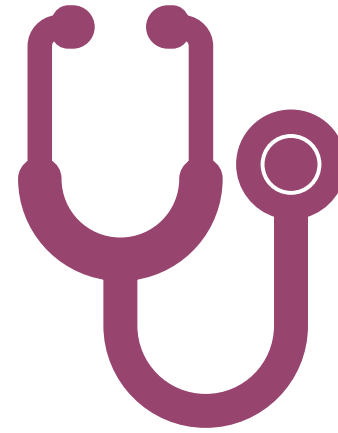
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Disclosure

I have NO financial disclosure or conflicts of interest with the presented material in this presentation.

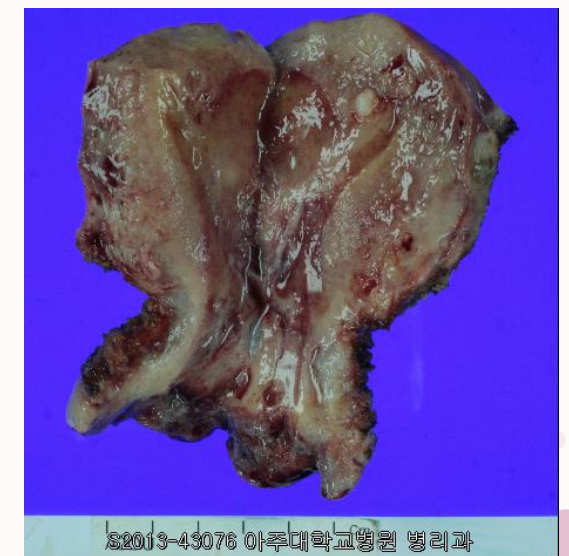
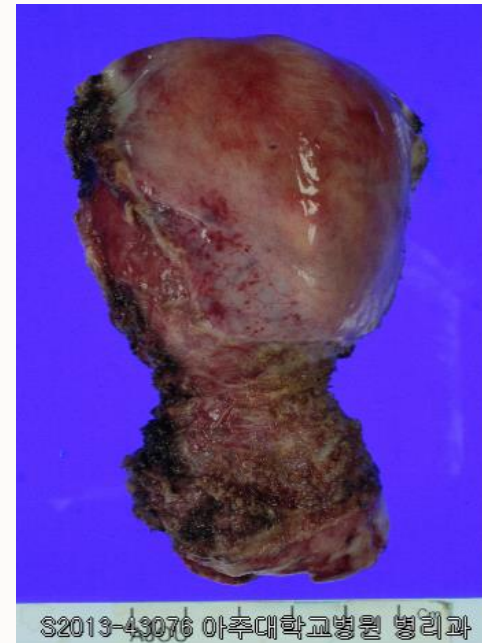
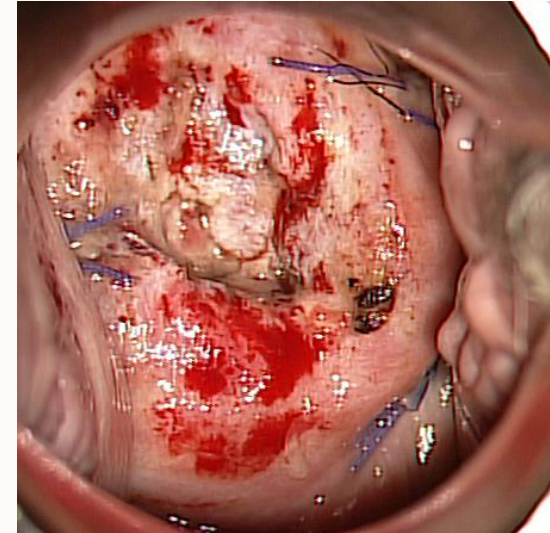




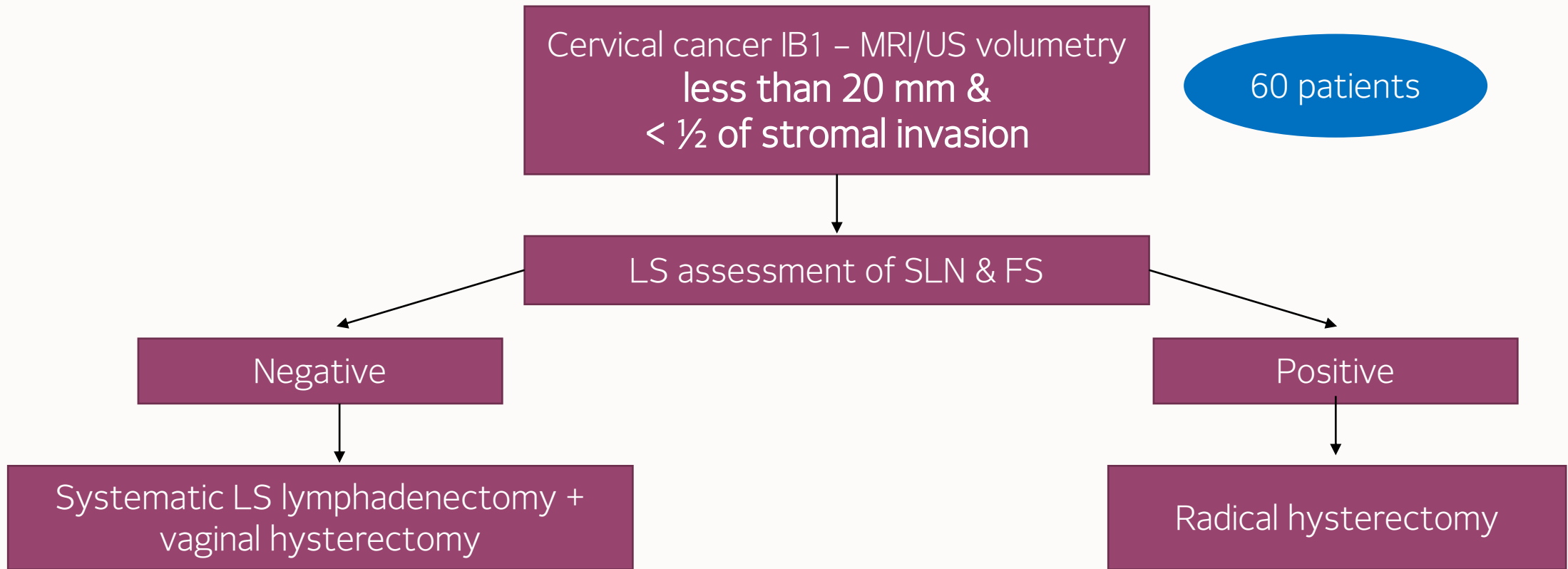
**Occult invasive SCC
following MIS simple
hysterectomy**

49 years old

- Outside cervical cytology: HSIL
- Outside cone: microinvasive SCC
- MIS simple hysterectomy (vaginal colpotomy, 2013-12)
 - Invasive SCC, tumor size 15 mm
 - 7/12 mm cervical stroma invasion
 - Margin (-)
- Adjuvant radiotherapy
- NED until now



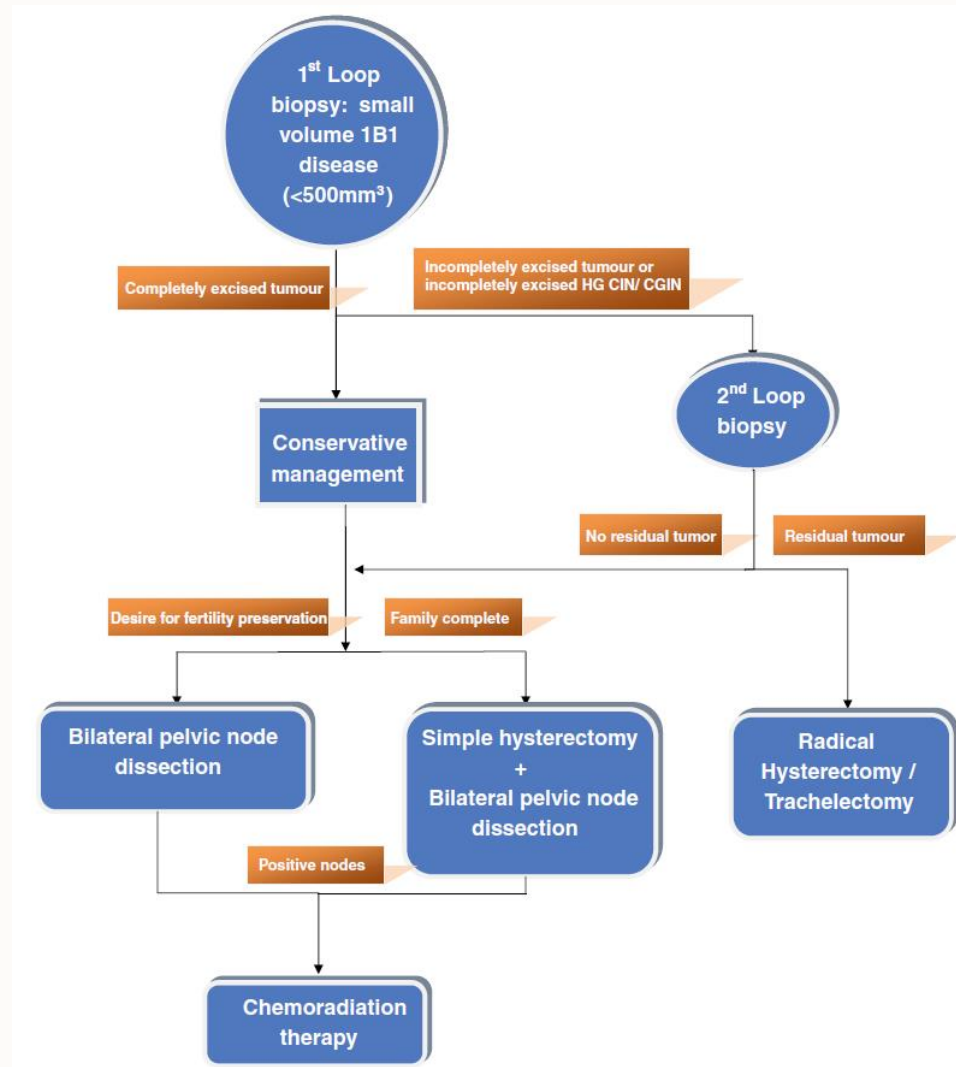
SLNM and less radical surgery (1)



SLNM and less radical surgery (2)

Variables	Number (%) / total 60 patients
Median age (years)	44.6 (33.0 – 64.0)
Prior LEEP or Cone	45 (75.0)
Radical hysterectomy	3 (5.0)
Less radical surgery (LAVH)	57 (95.0)
Histology	50 SCC & 10 AC
FIGO stage	
IA1 with LVSI	3 (5.0)
IA2	11 (18.3)
IB1	46 (76.7)
Positive SLNs	5 (8.3)
Adjuvant RT	5 (8.3)
Recurrence	0
Median follow-up (months)	47 (12 – 92)

Cone or simple hysterectomy – UK (1)



Cone or simple hysterectomy – UK (2)

Variables	Number (%) / total 62 patients
Median age (years)	35.0 (27.0 – 67.0)
Prior LEEP or Cone	45 (75.0)
Less radical surgery Cone LAVH/TLH	35 (56.5) 27 (43.5)
Histology	49 SCC, 11 AC, & 2 ASC
FIGO stage IB1	62
Positive LNs	1 (1.6)
Adjuvant treatment	0
Recurrence	0
Median follow-up (months)	56 (13 – 132)

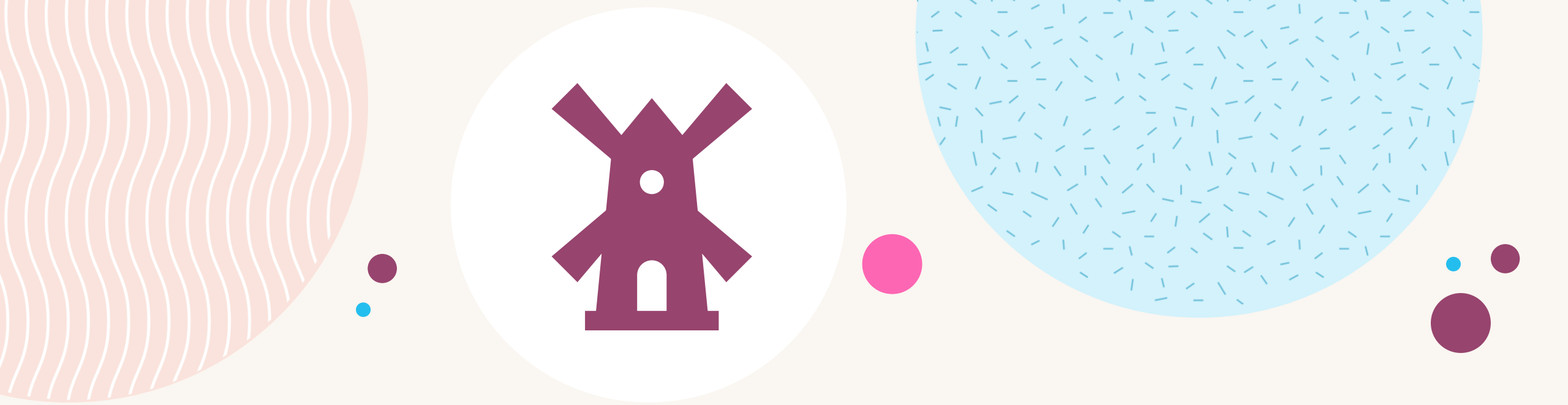
Rationale for less radical surgery

Author	Year	Low-risk criteria	N	Parametrial involvement in low-risk group (%)
Kinney [13]	1995	Squamous histology only, tumor <2 cm, no LVSI*	83	0.0%
Covens [14]	2002	All histologies, tumor <2 cm, DOI** <10 mm, negative pelvic lymph nodes	536	0.6%
Stegeman [15]	2007	Squamous, adenocarcinoma, adenosquamous or clear cell histology, tumor <2 cm, DOI** <10 mm, no LVSI*, negative pelvic lymph nodes	103	0.0%
Wright [16]	2008	All histologies, tumor <2 cm, no LVSI*, negative pelvic lymph nodes	270	0.4%
Frumovitz [19]	2009	Squamous, adenocarcinoma or adenosquamous histology, tumor <2 cm, no LVSI*	125	0.0%

*LVSI: lymphovascular space involvement
 **DOI: depth of invasion

All retrospective data

N=1117 < 1%



SHAPE trial (2023 ASCO Annual Meeting)



Background & rationale

- Higher proportion of women presenting at a younger age and with low-risk, early-stage disease
- Radical surgery
 - Long-term surgical side effects including compromised bladder, bowel, and sexual function
- Parametrial involvement in low-risk group <1%

Definition of low-risk cervical cancer

SC, AC, ASC histology

FIGO stage IA2 and IB1

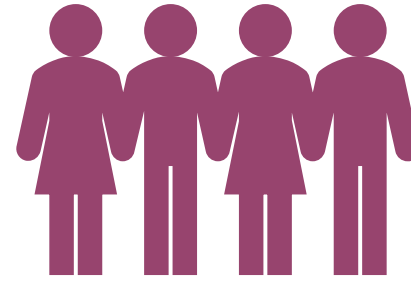
<10 mm stromal invasion on LEEP/Cone

<50% stromal invasion on MRI

Maximal dimension of ≤ 20 mm

Key baseline characteristics (1)

Variables	SH N = 350 (%)	RH N = 350 (%)
Median age	42 (26 – 77)	45 (24 – 80)
<50 years old	271 (77.4)	246 (70.3)
Diagnostic procedure		
Prior LEEP/cone	254 (72.6)	226 (64.6)
Cervical biopsy	84.0% 52 (14.9)	75.3% 77 (22.0)
Both	40 (11.4)	41 (11.7)
Missing	4 (1.1)	6 (1.7)



Why did patients in the SH group receive more conization than patients in the RH group?

84.0%

Vs.

75.3%

Key baseline characteristics (2)

Variables	SH N = 350 (%)	RH N = 350 (%)
FIGO stage		
IA2	30 (8.6)	28 (8.0)
IB1	320 (91.4)	322 (92.0)
Histology		
SCC	218 (62.3)	214 (61.1)
AC	114 (32.6)	131 (37.4)
ASC	18 (5.1)	5 (1.4)

Key surgical characteristics

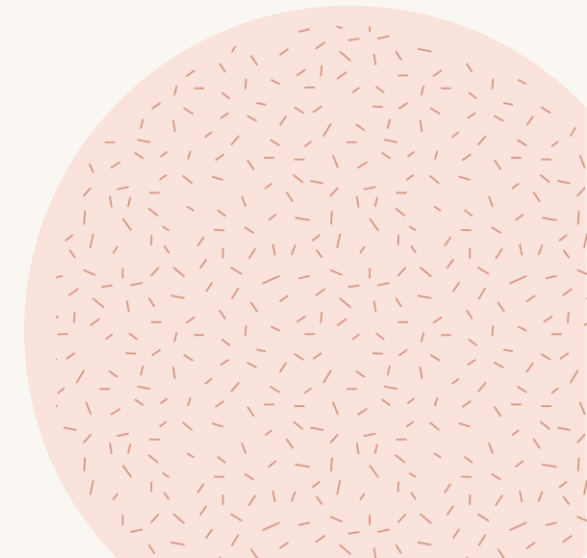
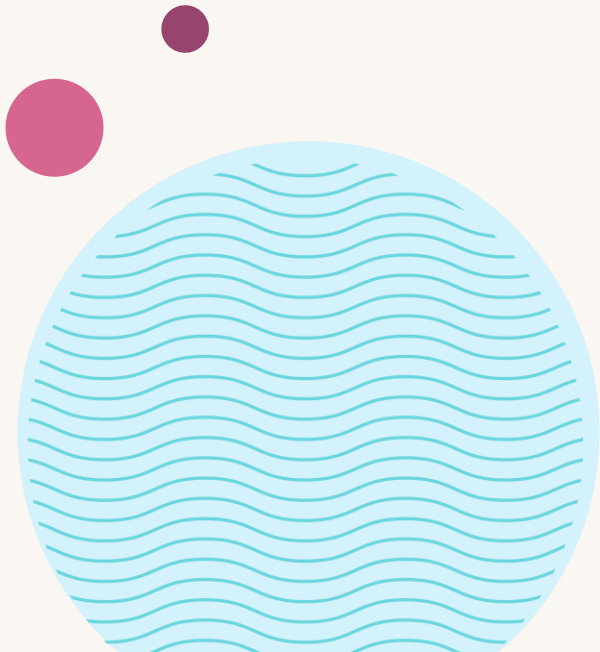
Variables	SH N = 338 (%)	RH N = 344 (%)	P-value
Types of surgical approach			
Open	57 (16.9)	99 (28.8)	0.0003
Laparoscopic	188 (55.6)	152 (44.2)	0.0036
Robotic	82 (24.3)	87 (25.3)	0.79
Vaginal	11 (3.3)	4 (1.2)	0.07
SN mapping	218 (62.3)	214 (61.1)	
Planned	114 (32.6)	131 (37.4)	0.87
Successful	18 (5.1)	5 (1.4)	0.90

Why did more patients in the SH group undergo laparoscopic surgery than in the RH group?

55.6%

Vs.

44.2%



Key pathological characteristics

Variables	SH N = 338 (%)	RH N = 344 (%)	P-value
Residual disease at the remaining cervix	154 (45.6)	163 (47.4)	0.65
LVSI	45 (13.3)	45 (13.1)	1.00
Positive nodes	11 (3.3)	15 (4.4)	0.55
Positive vaginal margins	7 (2.1)	10 (2.9)	0.62
Positive parametrium	0	6 (1.7)	0.03
Lesions >2 cm	15 (4.4)	14 (4.1)	0.85

Postoperative characteristics

Variables	SH N = 338 (%)	RH N = 344 (%)	P-value
Adjuvant treatment	31 (9.2)	29 (8.4)	0.79

Variables	SH N = 350 (%)	RH N = 350 (%)
Pelvic recurrences	11 (3.1)	10 (2.9)
Extra-pelvic recurrences	7 (2.0)	2 (0.6)
Death (cervical cancer)	4 (1.1)	1 (0.3)

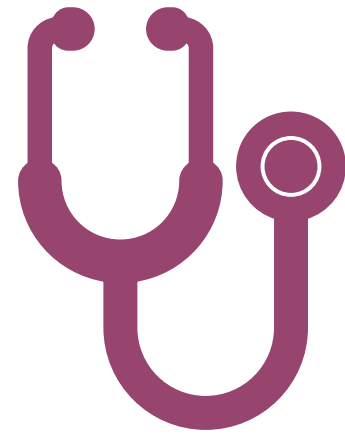
Pelvic recurrence at 3 years

	SH N = 350 (%)	RH N = 350 (%)
Pelvic recurrence at 3 years	2.52%	2.17%

Difference: 0.35% with upper 95% confidence limit 2.32% < 4%
→ Non-inferiority of SH to RH could be concluded

Conclusions (SHAPE trial)

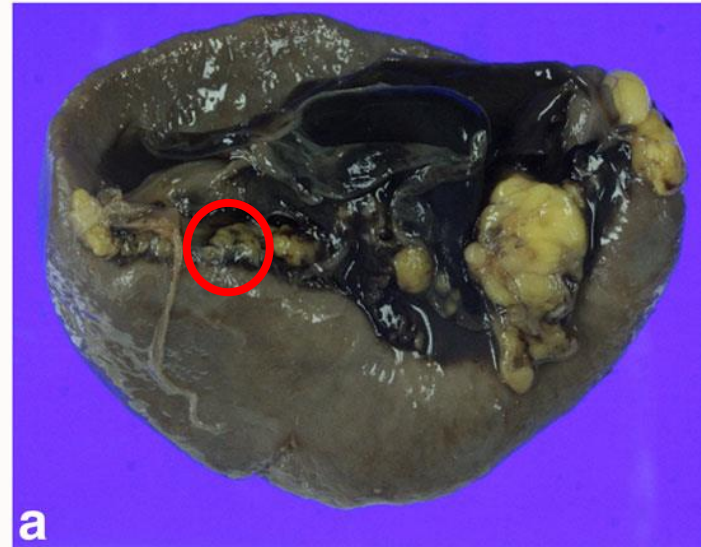
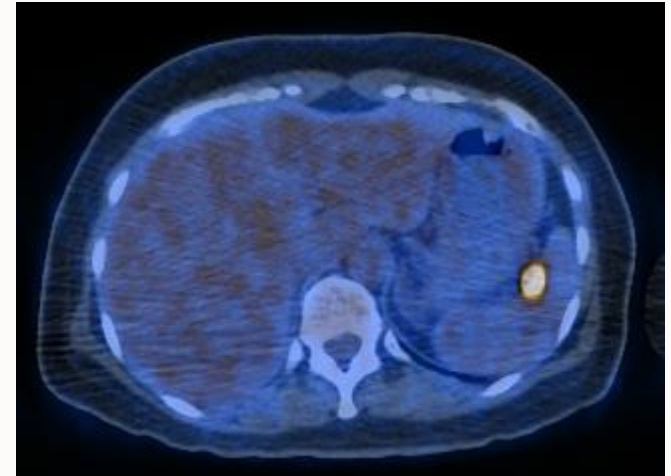
- Following adequate/rigorous preoperative assessment, SH can now be considered the **new standard of care** for patients with low-risk early-stage cervical cancer, supporting the concept of surgical de-escalation in those patients
 - Stage IA2-IB1 ≤ 2 cm
 - < 10 mm depth of stromal invasion (LEEP/cone)
 - $< 50\%$ depth of stromal invasion (preop MRI)
- RH can be converted to SH, including **minimally invasively**.



Catastrophic outcomes following MIS-RH

39 years old

- CDB: invasive SCC
- MRI: 2x1.8cm cervical mass, PMI (-), metastasis (-)
- LRH (intracorporeal colpotomy, 2012-11)
 - Invasive SCC 3cm
 - 11/15 mm cervical stroma invasion
 - Margin (-), LN (-)
- FU imaging: metastasis in **splenic hilum**
- Splenectomy (2013-12)
- **Death** (peritoneal seeding, 2015-12)



Patterns of recurrence and survival after abdominal versus laparoscopic/robotic radical hysterectomy in patients with early cervical cancer

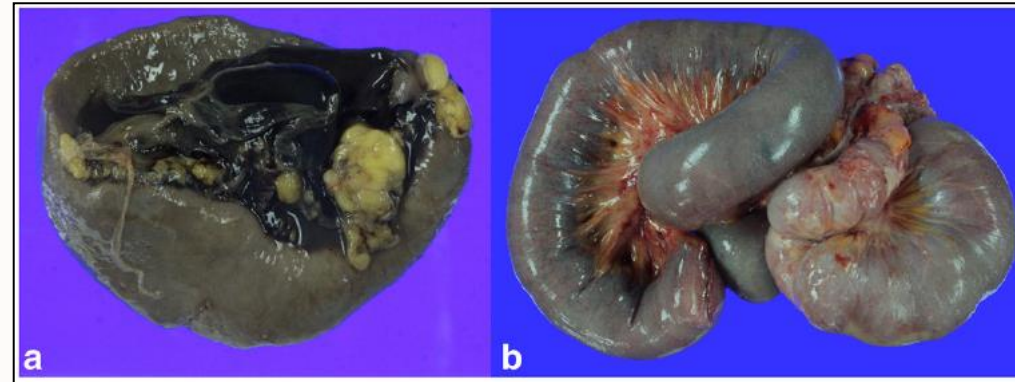
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Table 2 Univariate and multivariate analysis of clinicopathologic factors associated with disease recurrence in patients with cervical cancer treated with minimally invasive surgery

	Number of patients	Number of recurrences (%)	DFS	Univariate analysis	Multivariate analysis	
			Mean (months)	P value	HR (95% CI)	P value
Colpotomic approaches				0.022	4.009 (1.059–15.183)	0.041
LRH-VC	79	4 (5.1)	85.2			
LRH/RRH-IC	49	8 (16.3)	32.4			

Intracorporeal colpotomy

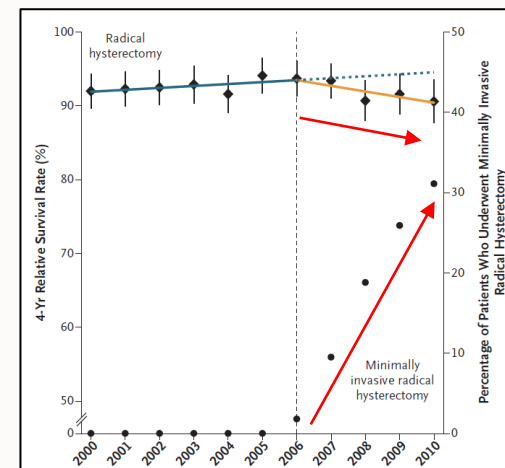
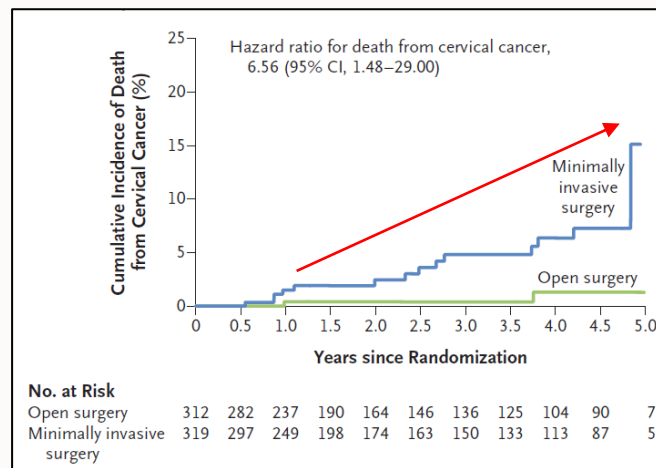
Figure 2 Gross specimens of spleen and colon after metastatectomy showing metastatic cervical carcinoma on (a) the splenic hilar surface and (b) bowel serosa.



- MIS-RH may have higher rates of disease recurrence
- Total laparoscopic IC under CO₂ PNP may carry a risk of **positive vaginal cuff margin**, as well as **intraperitoneal tumor spreads**

Laparoscopic Approach to Cervical Cancer (LACC) trial

- Women undergoing minimally invasive RH for early cervical cancer had **worse survival** than those who received abdominal RH.
- In the epidemiologic study of US, the adoption of MIS coincided with a **decline in the survival rate after 2006**.



LACC trial – MIS-RH

- Uterine manipulator
- An effect of the insufflation gas and circulating CO₂ on tumor-cell growth or spread
- Intracorporeal colpotomy

standard practice. There are several potential reasons for the inferior oncologic outcomes in the minimally invasive surgery group, among these that the routine use of a uterine manipulator might increase the propensity for tumor spillage. In addition, an effect of the insufflation gas (CO₂) on tumor-cell growth or spread has been suggested in previous studies.^{27,28} Kong et al.²⁹ evaluated 128 patients with cervical cancer who underwent minimally invasive radical hysterectomy and compared recurrence between patients who underwent vaginal colpotomy (79 patients) and those who underwent intracorporeal colpotomy (49 patients). The rate of disease recurrence was higher in the intracorporeal colpotomy group than in the vaginal colpotomy group (16% vs. 5%), and among patients with recurrence in the intracorporeal group, 62% had intraperitoneal spread or carcinomatosis. The authors concluded that exposure of cervical cancer to circulating CO₂ may result in tumor spillage into the peritoneal cavity. Our trial was not designed to answer questions about the cause of the inferior outcomes with minimally invasive surgery; thus, further investigation is warranted.

MIS-RH studies after LACC trial

- Cons – MIS-RH
 - US, Canada, England, Italy, Spain
- Pros – MIS-RH
 - Korea (2cm), China (2-4cm)
 - Japan (no-look no-touch technique), Germany (transvaginal closure)
 - Sweden (no uterine manipulator)
- MIS-RH following conization
 - Favorable to survival outcomes

Melamed A et al., NEJM 2018; Uppal S et al., JCO 2019; Cusimano MC et al., J Obstet Gynecol 2019; <https://www.bgcs.org.uk/wp-content/uploads/2019/07/NCRAS-cervical-cancer-surgery-analysis-May-2019-final.pdf>; Corrado G et al., 2018; Chiva L et al., Int J Gynecol Cancer 2020; Paik ES et al., Gynecol Oncol 2019; Kim SI et al., Gynecol Oncol 2019; Kim JH et al., Cancer Res Treat 2019; Hu TWY et al., Cancer Manag Res. 2019; Hu TWY et al., Int J Gynecol Cancer 2020; Köhler C et al. Int J Gynecol Cancer 2019; Kanao H et al. J Gynecol Oncol 2019; Alfonzo E et al., Eur J Cancer 2019.



**Tumor size ≤ 2 cm -
optimal surgical candidates**

MIS RH, tumor size ≤ 2 cm – not inferior

Author (year)	Inclusion criteria (2018 FIGO stage)	Number of patients	Follow-up (median, months)	Results
Kim et al. (2019)	IB1 (≤ 2 cm) MRI tumor size	MIS RH = 122 ARH = 122	66.2	Similar OS PFS 5-yr OS 98.6% vs. 96.4% 3-yr PFS 90.0% vs. 93.1%
Wenzel et al. (2020)	IA2 LVSI+, IB1 Clinical tumor size	MIS RH = 166 ARH = 218	DFS = 35 (0-100) OS = 56 (1-109)	Similar OS DFS 5-yr OS 96.4 vs. 98.5% 5-yr PFS 96.0% vs. 91.4%
Chen C et al. (2020)	IB1 (≤ 2 cm) Pathologic tumor size	MIS RH = 926 ARH = 926	36	Similar OS DFS 5-yr OS 96.4 vs. 98.5% 3-yr PFS 96.0% vs. 91.4%

MIS RH, tumor size ≤ 2 cm – worse outcome

Author (year)	Inclusion criteria (2018 FIGO stage)	Number of patients	Follow-up (median, months)	Results
Paik et al. (2019) KGOG 1028 study	IB1, IIA1 (≤ 2 cm) Clinical tumor size	MIS RH = 62 ARH = 186	69.1 (3.0-173.3)	Similar OS MIS RH: Inferior DFS (HR 12.987, [95% CI 1.451-116.244, $p = 0.003$])
Odetto et al. (2019)	IA1 LVSI+, IA2, IB1 MRI tumor size	MIS RH = 58	39 (11-83)	Recurrence rate: 12%
Chen X et al. (2020)	IB1, IIA1 (≤ 2 cm) Clinical or MRI tumor size	MIS RH = 129 ARH = 196	MIS = 51.8 (2-115) ARH = 49.5 (3-108)	Similar OS Inferior DFS (90.4% vs. 97.7%; $p = 0.02$)
Uppal et al. (2020)	IA1, IB1 Pathologic tumor size	MIS RH = 182 ARH = 82	MIS = 30.7 (13.75-51.44) ARH = 44.6 (20.98-67.39)	Similar OS DFS But, patients with residual tumor: higher recurrence (aHR, 6.31; 95% CI, 1.24 to 31.9)

Reasons for contradictory results

Retrospective nature

A small number of study populations

Inaccurate determination of tumor size

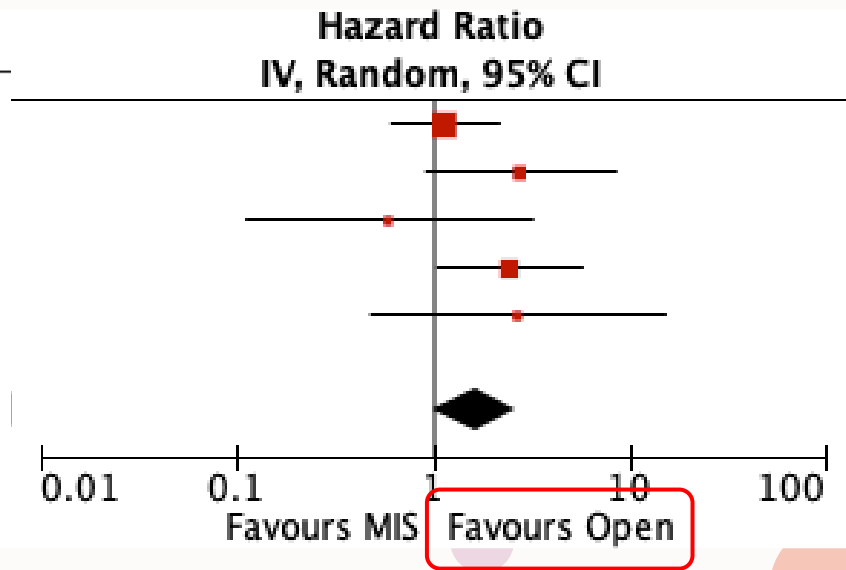
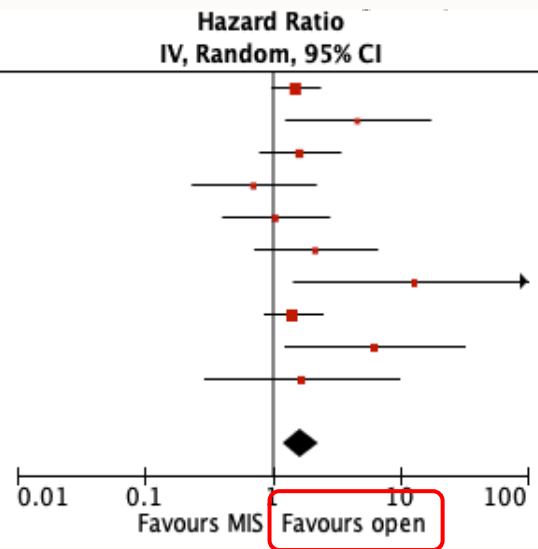
Uncontrolled several confounders

Tumor size <2 cm: a systematic review and meta-analysis

- Patients who underwent MIS RH had worse PFS than those who had ARH (HR 1.68, 95% CI 1.20 to 2.36, I² 26%).
- Patients who had MIS RH had a trend towards worse OS compared with those who had ARH (HR 1.64, 95% CI 1.00 to 2.68).

Study or Subgroup	log[Hazard Ratio]	SE	MIS Open		Weight	Hazard Ratio	
			Total	Total		IV, Random, 95% CI	IV, Random, 95% CI
Chen C et al, 2020	0.4121	0.2206	926	926	25.1%	1.51	[0.98, 2.33]
Chen X et al, 2020	1.5347	0.6643	129	196	5.8%	4.64	[1.26, 17.06]
Chiva et al, 2020	0.4886	0.3695	128	160	14.3%	1.63	[0.79, 3.36]
Hu et al, 2020	-0.3425	0.5677	147	147	7.5%	0.71	[0.23, 2.16]
Kim et al, 2019	0.0526	0.4893	122	122	9.5%	1.05	[0.40, 2.75]
Nam et al, 2012	0.7747	0.5629	162	173	7.6%	2.17	[0.72, 6.54]
Paik et al, 2019	2.5639	1.1182	62	186	2.2%	12.99	[1.45, 116.23]
Rodriguez et al 2021	0.3646	0.2712	486	492	20.7%	1.44	[0.85, 2.45]
Uppal et al, 2020	1.8421	0.8301	182	82	3.9%	6.31	[1.24, 32.11]
Yang et al 2020	0.5277	0.8938	50	57	3.4%	1.70	[0.29, 9.77]
Total (95% CI)			2394	2541	100.0%	1.68	[1.20, 2.36]

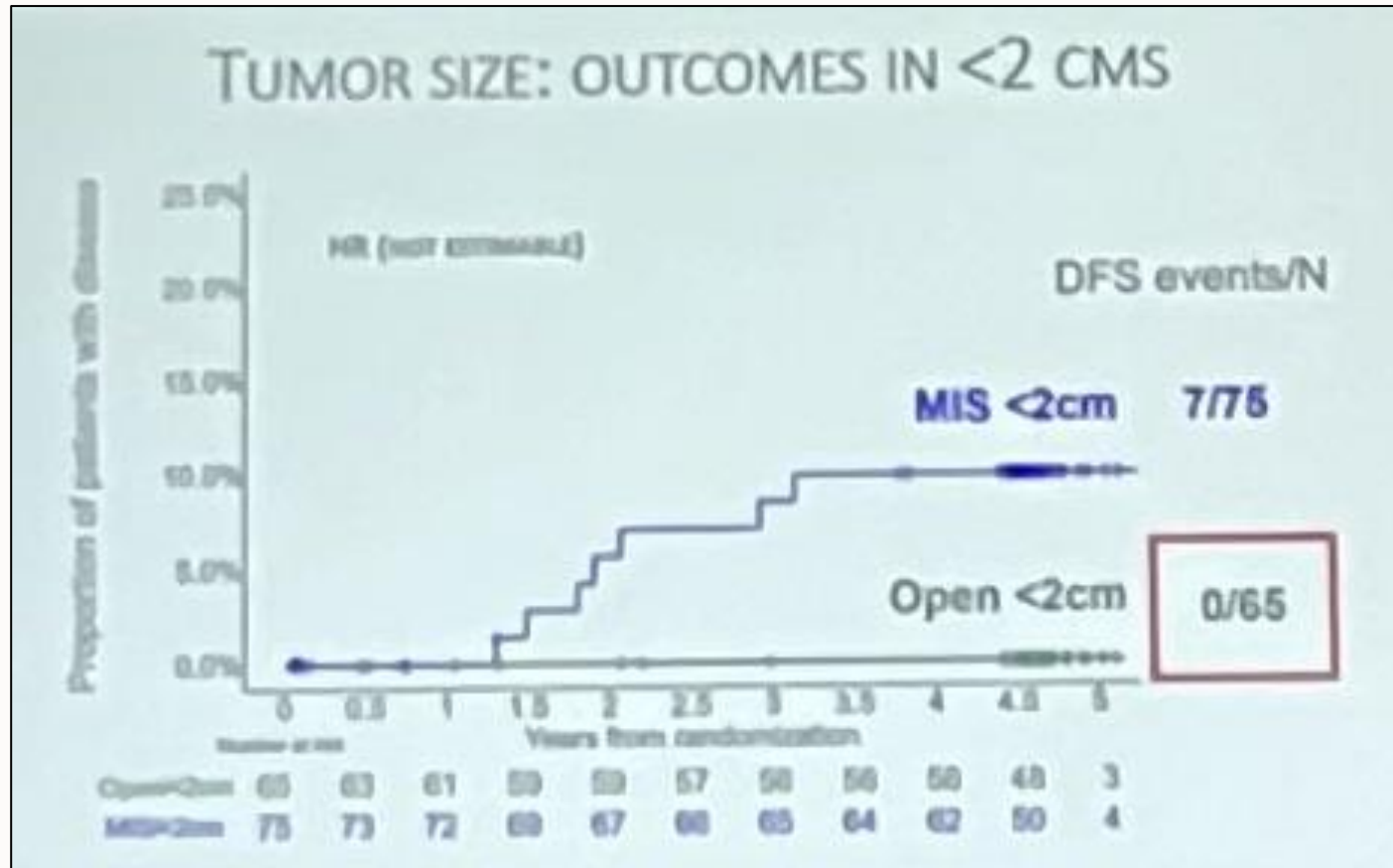
Heterogeneity: Tau² = 0.07; Chi² = 12.10, df = 9 (P = 0.21); I² = 26%
 Test for overall effect: Z = 3.05 (P = 0.002)



Tumor size & treatment (LACC trial)

	Recurrence		Death	
	Open	MIS	Open	MIS
No residual disease	0/60	2/60	0/60	0/60
Tumor < 2cm	0/65	7/75 (9.3%)	0/65	2/75 (2.7%)
Tumor size ≥ 2cm	6/110 (5.5%)	23/110 (20.9%)	7/110 (6.4%)	19/110 (17.3%)

Tumor size < 2cm - DFS



Recurrence - carcinosarcoma

	Open	MIS
Total recurrences	11	37
Carcinosarcoma (randomized)	1 (9%)	8 (22%)
Carcinosarcoma (received)	0	9 (24%)
Site of recurrence		
Vault	3 (27%)	6 (16%)
Pelvis	0 (0%)	10 (27%)
Abdomen	0 (0%)	2 (5%)
Distant	3 (27%)	2 (5%)
Multiple	3 (27%)	14 (38%)
Other	2 (18%)	3 (8%)

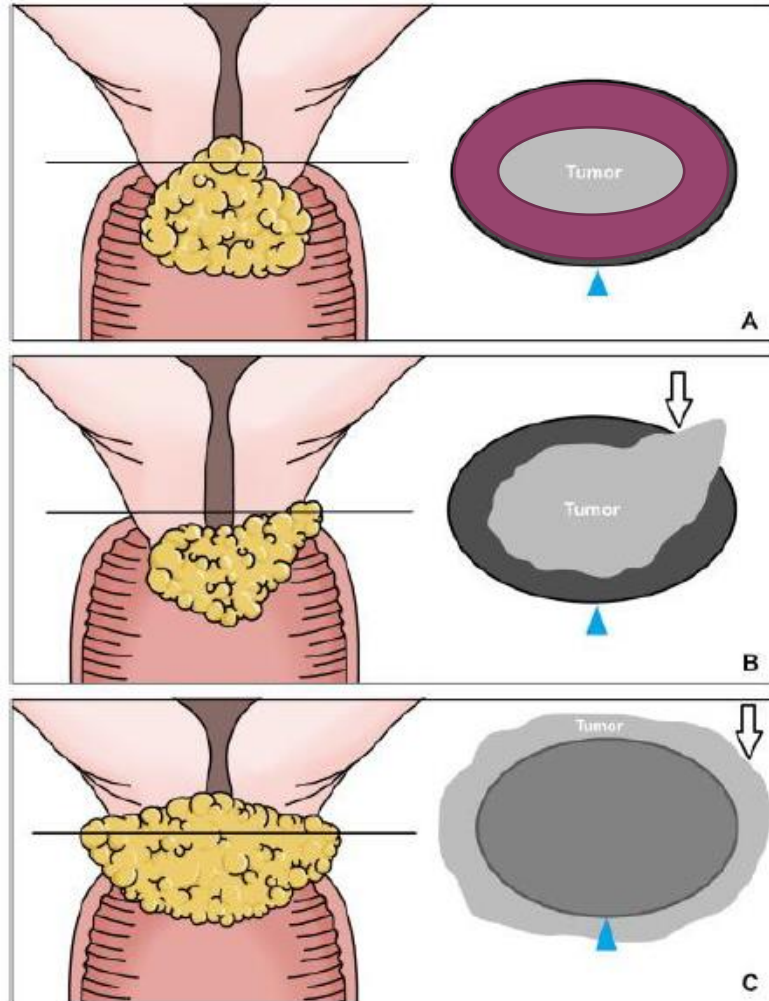
Endophytic vs. exophytic growth

- P2L2, 56 years old
- SCC, MR tumor size 2 cm
- PMI (+), LN (-), Margin (-)



- P2L2, 36 years old
- SCC, MR tumor size 4.1cm
- PMI (-), LN (-), Margin (-)



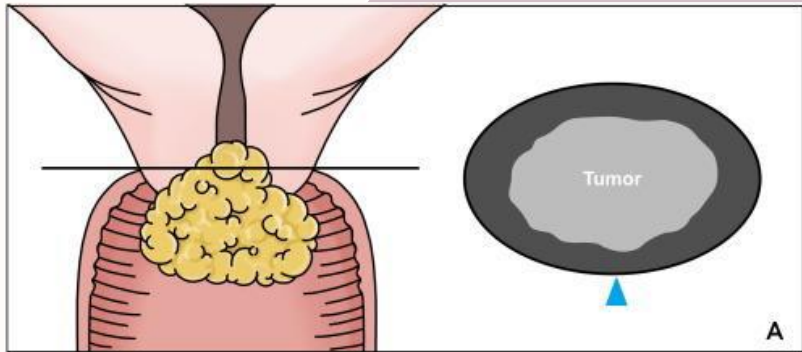


Intact T2-hypointense cervical stromal ring (arrowhead) in FIGO stage IB patients (A).

Focal disruption (arrow) of the cervical stromal ring (arrowhead) but no definite parametrial mass in FIGO stage IB patients (B).

Full-thickness loss of hypointense cervical stroma (arrowhead) with nodular or irregular mass (arrow) extending into the parametrium in FIGO stage IIB patients (C).

Intact cervical stromal ring on MRI



Surgery

<50% stromal invasion on MRI (SHAPE)

Surgical Technique

- Colpotomic Approach



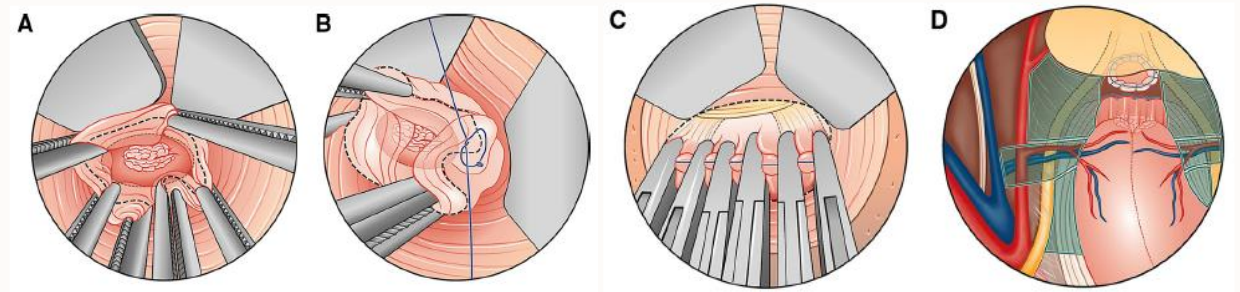
Intracorporeal colpotomy



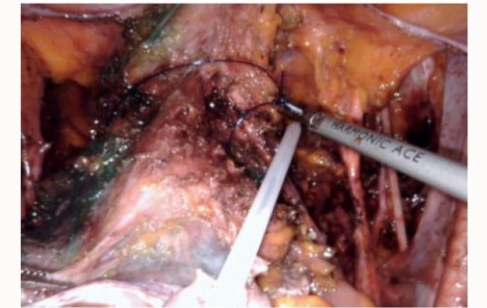
Vaginal colpotomy

Surgical techniques to prevent tumor spillage during colpotomy

- Transvaginal closure



- Intracorporeal suture ligation around the vagina



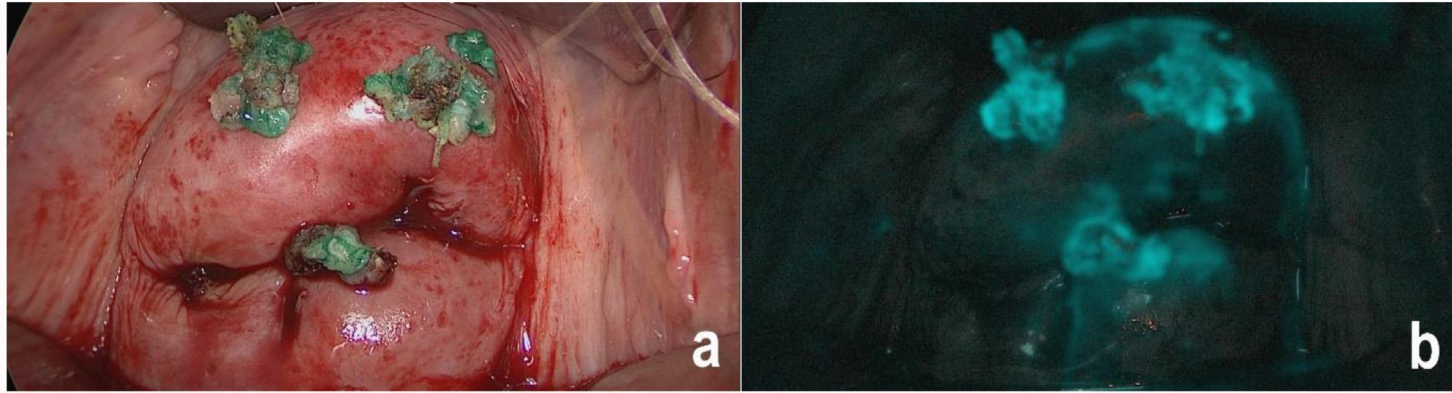
- Intracorporeal endoscopic stapling

Spillage and displacement of indocyanine green-stained tissues from uterine cervix to pelvic peritoneum: A proof of concept study for colpotomy approach in minimally invasive surgery

Tae-Wook Kong^a, Jimin Lee^b, Sun Hyung Yum^b, Jeeyeon Kim^a, Joo-Hyuk Son^a, Suk-Joon Chang^{a,*}, Hee-Sug Ryu^b

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Intracorporeal colpotomy (N = 10)

VS.



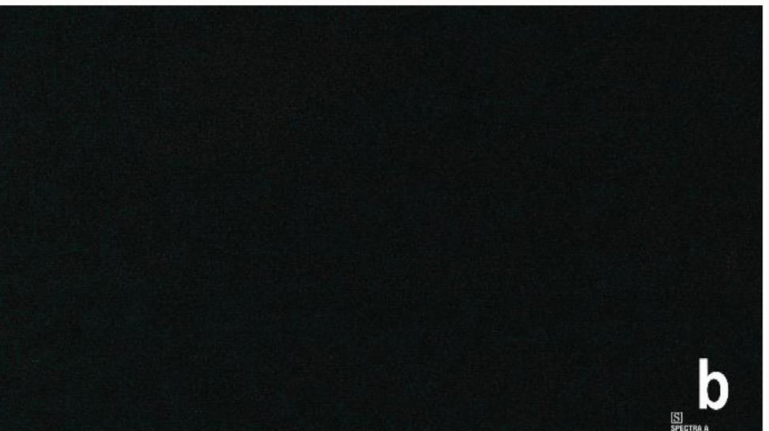
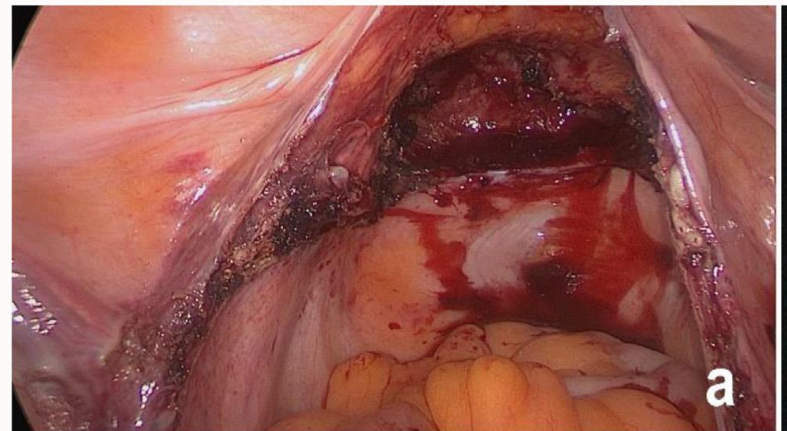
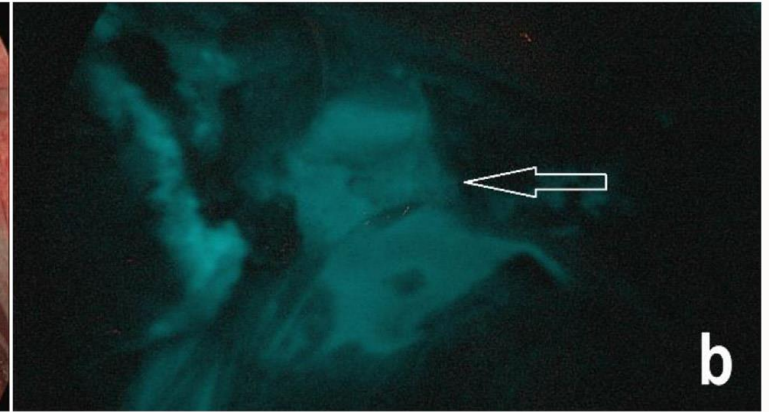
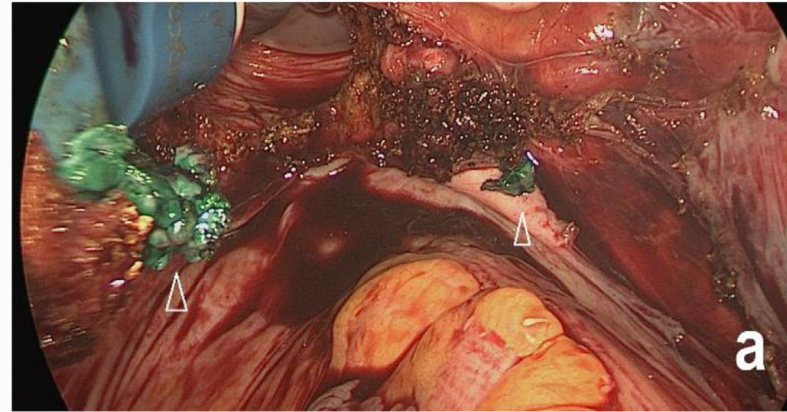
Vaginal colpotomy (N = 10)

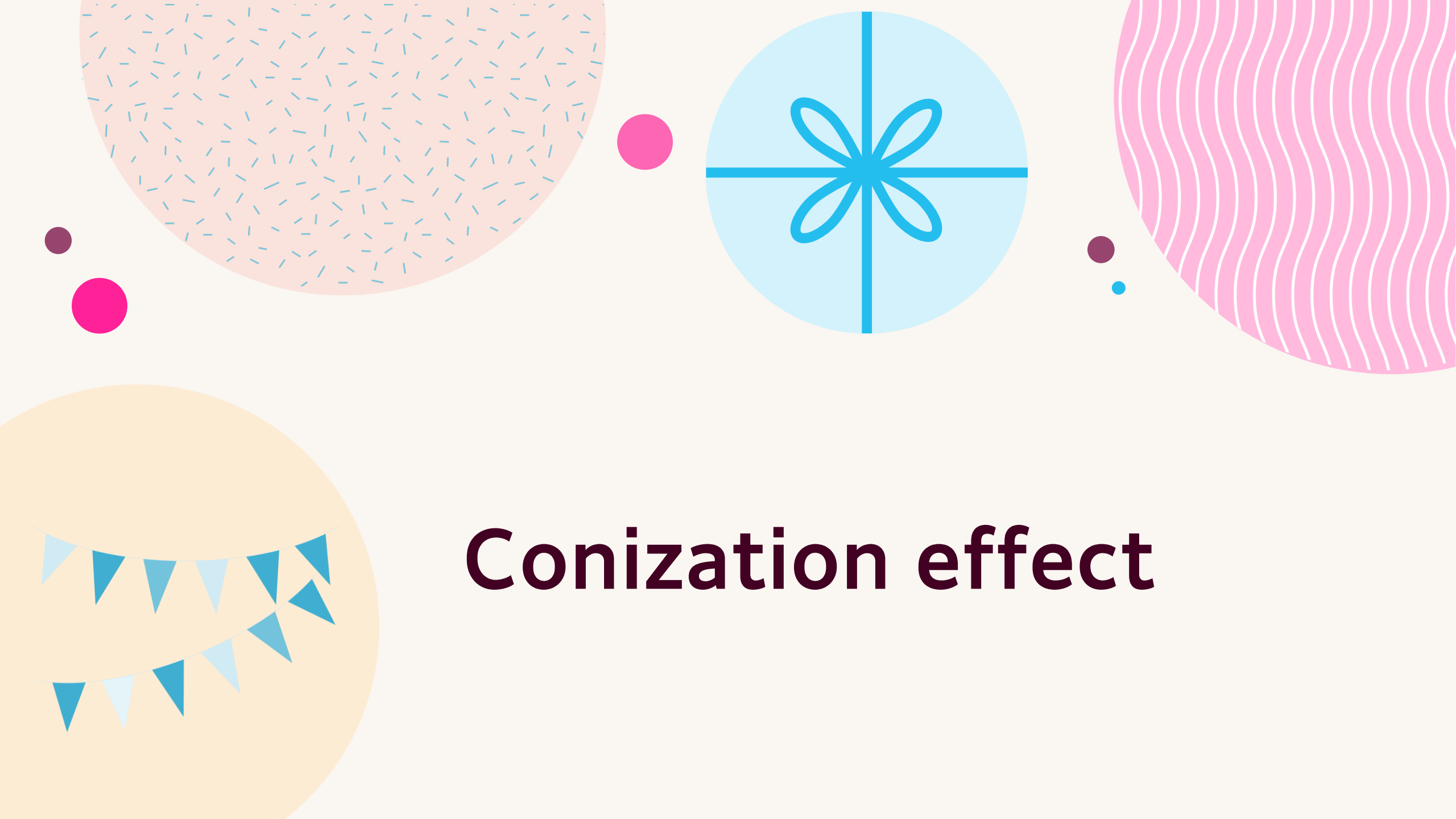
Spillage and displacement of indocyanine green-stained tissues from uterine cervix to pelvic peritoneum: A proof of concept study for colpotomy approach in minimally invasive surgery

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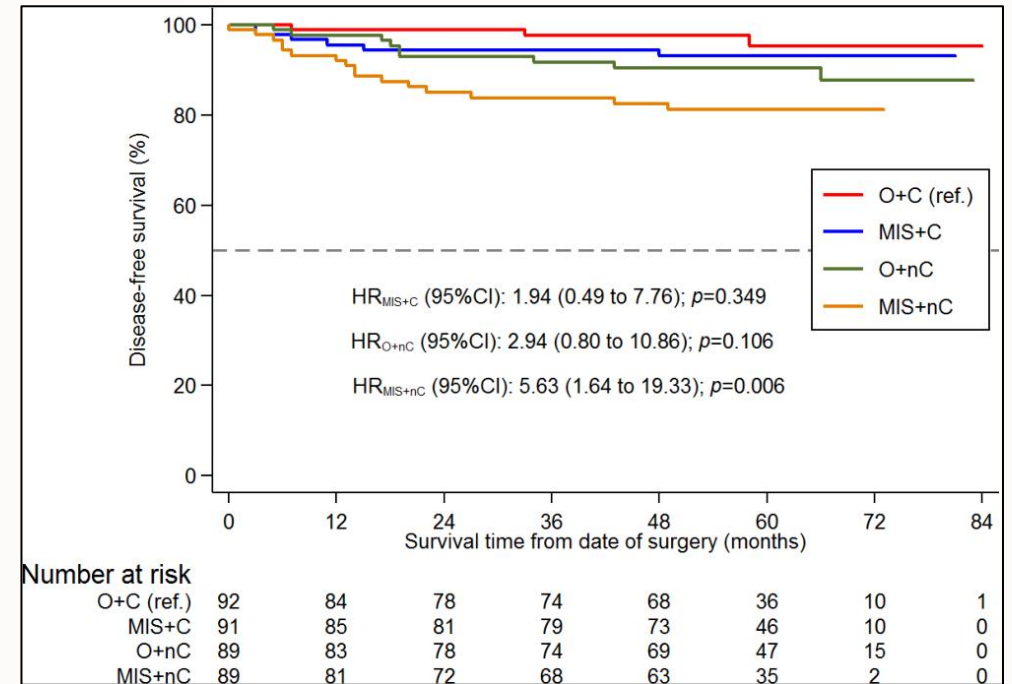
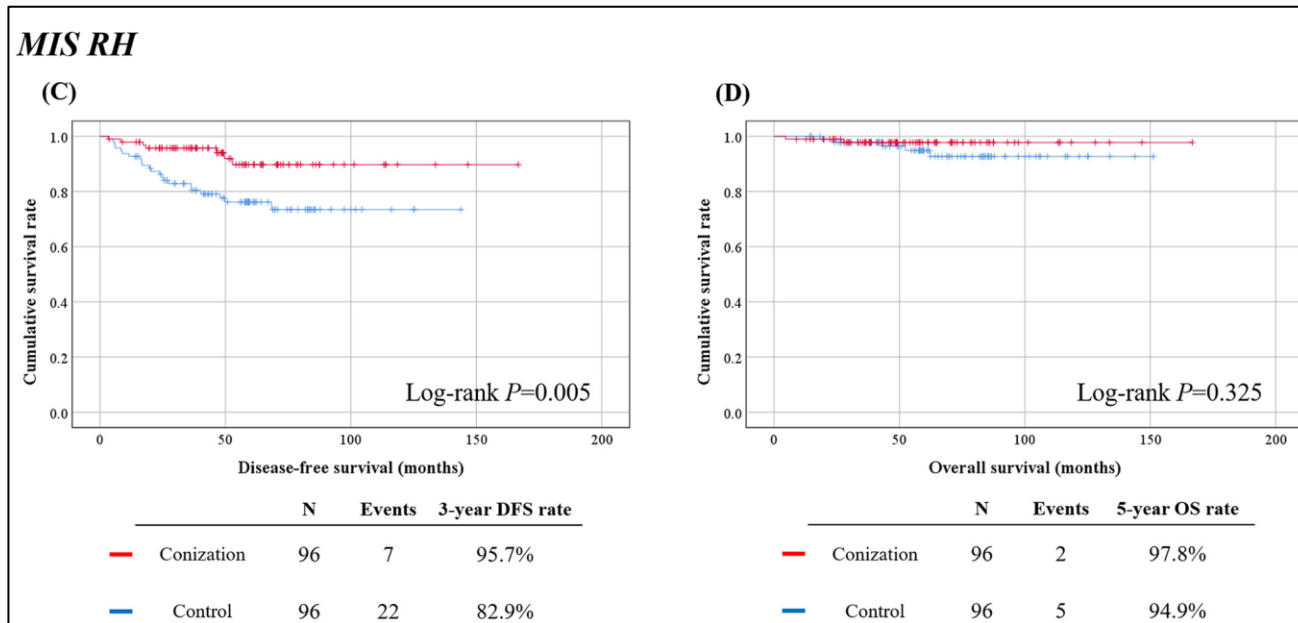




Conization effect

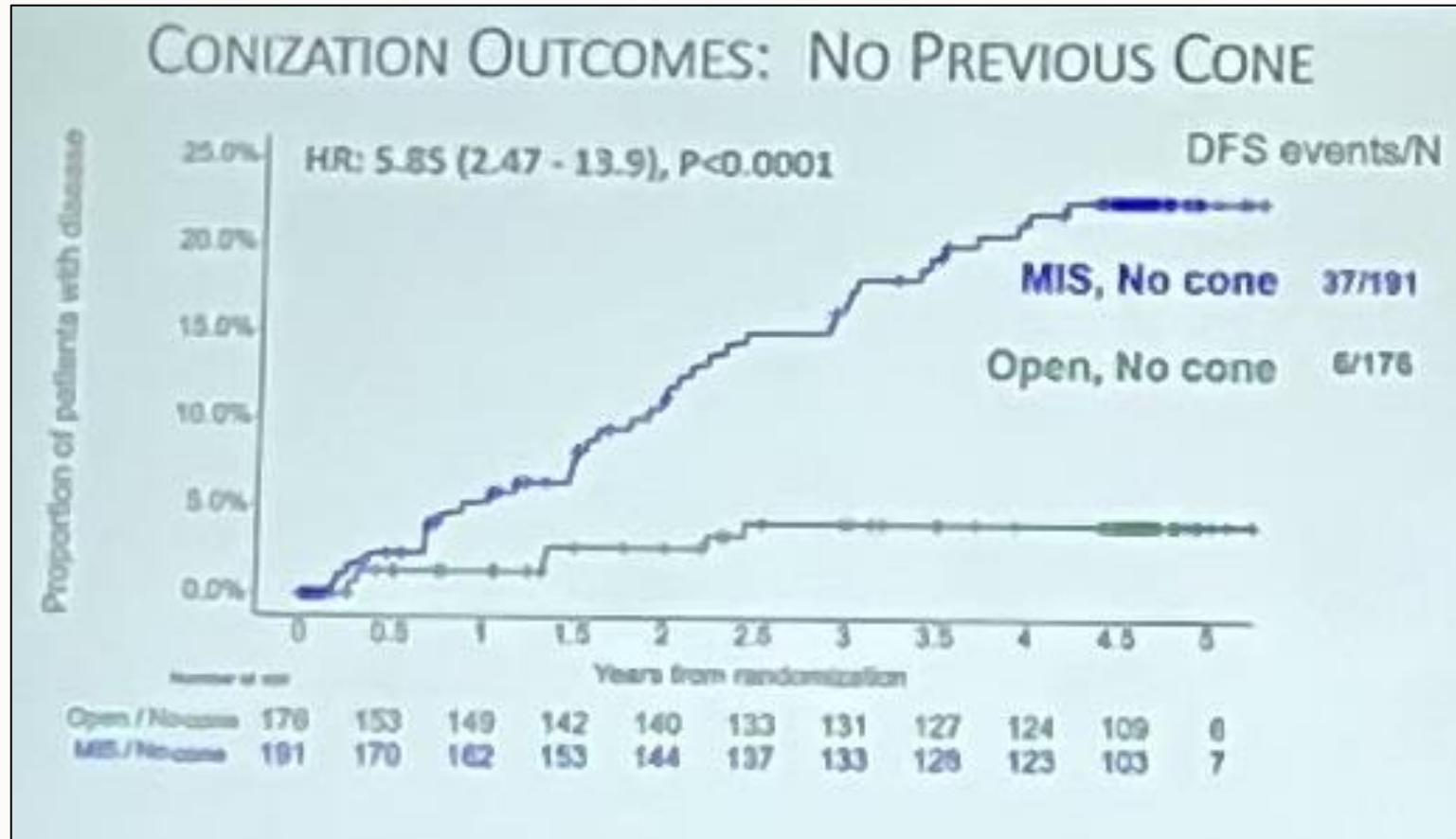
Prior conization

- 2009 FIGO stage IB1 patients
- Cervical conization before MIS RH had a significantly lower risk of relapse.



5.63 times higher relapse MIS RH nC vs ARH C

Conization effect – None-cone group (LACC trial)



MIS: 19.3%

Open: 3.4%

Conization effect – Cone group (LACC trial)



MIS: 4.7%

Open: 3.7%

Non-conization vs. conization groups

	Non-conization group	Conization group	<i>p</i> - value
Cervical stroma invasion	8 mm	6 mm	<i>p</i> < 0.001
Adjuvant therapy	41.0%	27.7%	<i>p</i> = 0.015
	25.0%	10.4%	<i>p</i> = 0.008
	48.0%	31.3%	<i>p</i> < 0.001

The none-cone group had more intermediate- or high-risk pathological features, which might have contributed to higher recurrence rates.

Summary – MIS RH or SH candidate

- No tumor exposure during MIS parametrectomy or SH
 - 2cm (2018 FIGO stage IB1r)
 - Intact cervical stromal ring on MRI
 - <50% depth of stromal invasion (SHAPE)
- <2cm tumors
 - MIS is worse than open surgery (LACC)
 - Superstrict criteria (SHAPE – Cone/MRI)

Summary – Colpotomy

- No tumor exposure during MIS colpotomy
 - Vaginal colpotomy
 - Vaginal protective maneuvers
- Vaginal protective maneuvers or vaginal colpotomy
 - Not prospectively evaluated
 - No data on learning curve

Summary - Conization

- No residual tumor in the remaining uterus (no tumor spillage during surgery)
 - Low recurrence rate
- Conization may be required in patients who have not been diagnosed with invasive cancer by colposcopy-directed biopsy alone.
- Favorable outcomes is not because of cone but rather patient profile (low risk pathologic features).

Conclusions

- To perform MIS RH or SH in early-stage cervical cancer patients, it is necessary to evaluate not only **the size of the tumor** but also the **degree of cervical stroma invasion** on preoperative MRI **very rigorously**.
- **MIS procedure** should only be used in the context of **research or clinical trial**.