Early Cervical Cancer: Surgical Conditions Following the LACC Trial

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Minimally Invasive Surgery DFS and Mortality Rates

SEER Data

- 4-year mortality
  - 9.1-5.3= **-3.8%**

LACC

- For DFS
  - MIS* **-10.6%** (>-7.2%)

* MIS: Minimally Invasive Surgery

Melamed A, N Engl J Med 2018; Ramirez PT, N Engl J Med 2018

MIS vs Open Surgery (SEER Data)

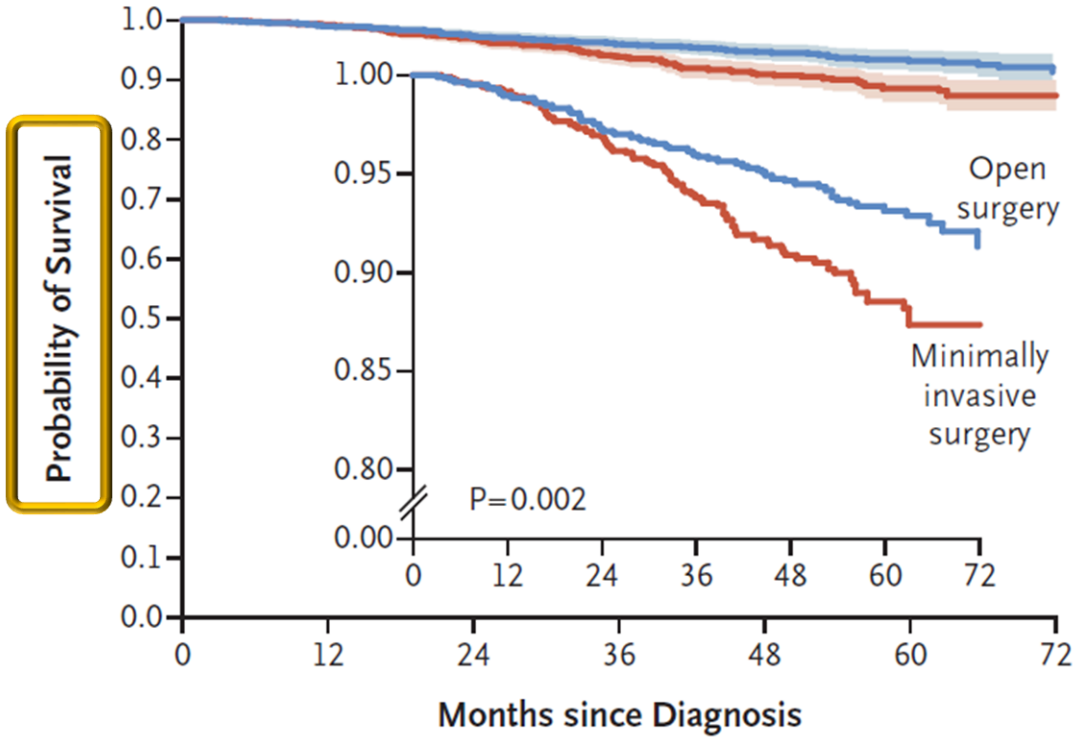
Case# 1225 MIS vs 1236 open surgery

Median FU 45 months

- Lymph Node counts: 20.2/19.2
- Pozitive LN status; 10.7/8.9%
- Parametrial involution; 11.0/9.5%
- Pozitive surgical margine; 5/4.4%
- **Death in 90 days; 9.1/5.3% (94/70)**
- **4-years OS; in MIS "shorter"**

Melamed A, N Engl J Med 2018

SEER Data OS

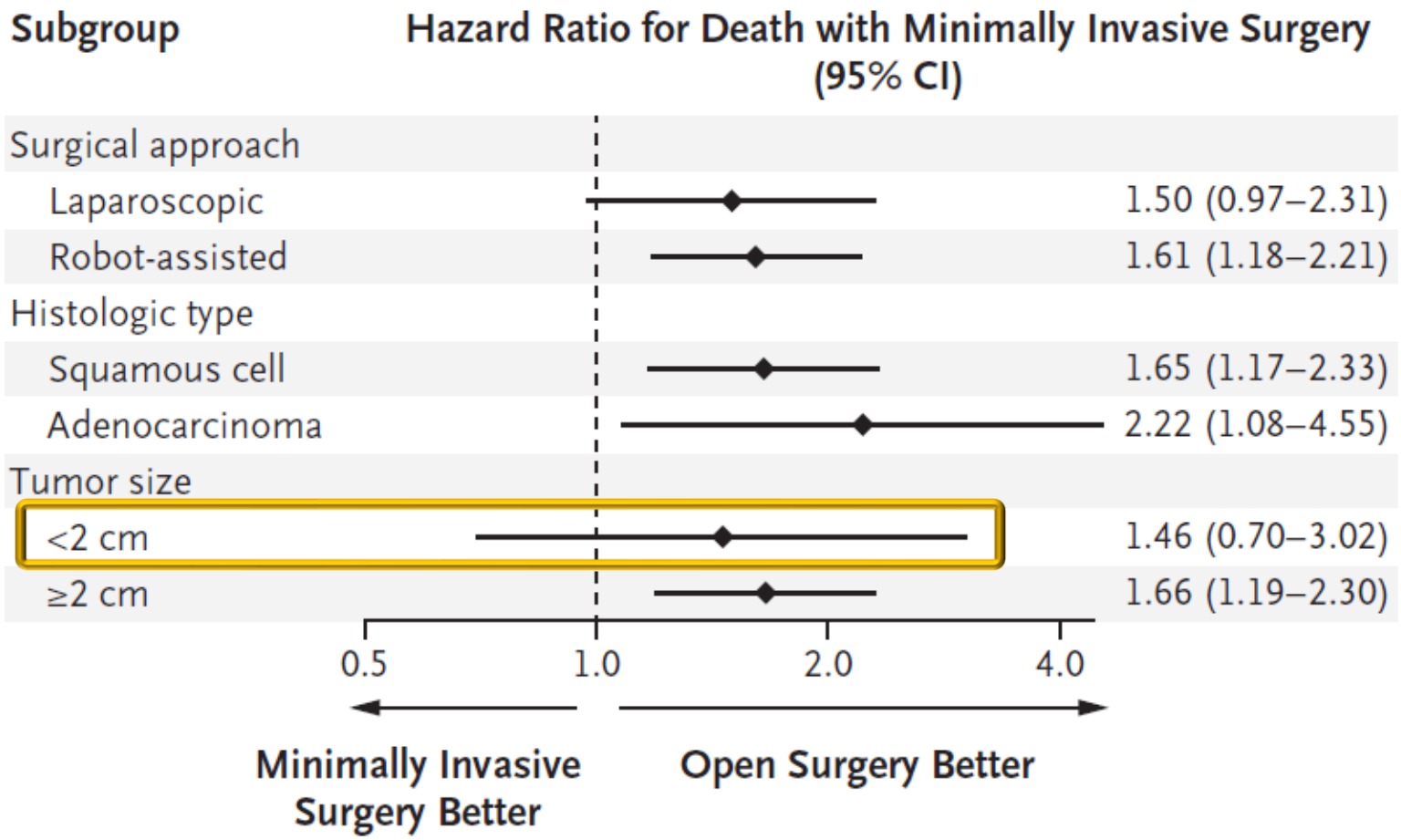


No. at Risk

Open surgery	1236	1174	1092	909	625	356	104
Minimally invasive surgery	1225	1161	1061	818	490	217	60

Melamed A, N Engl J Med 2018

MIS vs Open Surgery



Melamed A, N Engl J Med 2018

Survival Factors After MIS (SEER)

Resection width unknown in MIS

Sacrouterine ligament, parametrium (especially anterior parametrium) resection width is insufficient

Surgical margin distance is closer in MIS

Melamed A, N Engl J Med 2018

Conclusions for SEER Data

- Maniplators can cause tumor spread
- MIS may be non-inferior in highly experienced surgeons
- The results of operations performed during the learning curve may be poor
- In this study, the causes of recurrence or death are not clear

Melamed A, N Engl J Med 2018

Robotic Radical Hysterectomy Metaanalysis

- 26 Non-randomized trials
- According to current knowledge; robotic radical hysterectomy (RRH) is **superior** to abdominal radical hysterectomy (ARH)
  - *Less blood lost*
  - *Shorter hospital stay*
  - *Fewer febrile morbiditiy*
  - *Fewer wound-related complications*
  - ***RH with Robotic and LS are equal in terms of intraoperative and short-term postoperative outcomes***

Shazly SAM, Gynecol Oncol 2015

LACC TRIAL

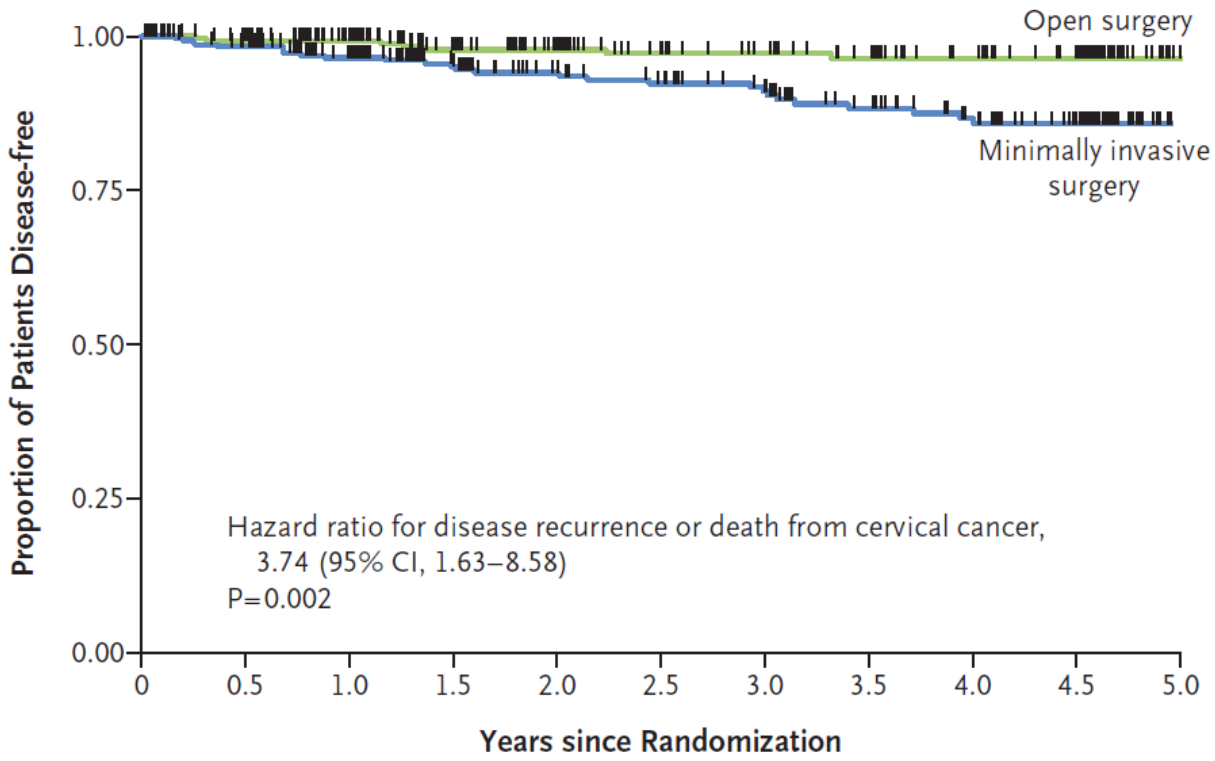
MIS vs Abdominal RH: LACC Trial

- Case #631; Stage IA1 (LVSI pozitive), IA2 or IB1
  - *MIS #319*
  - *Open Surgery #312*
- **Median FU 2.5 Yıl**
- 4.5 Years DFS
  - *MIS 86.0%*
  - *Open Surgery 96.5%*

  } P=0.87 (NS)
- 3 Years OS
  - *MIS 93.8%*
  - *Open Surgery 99.0%*
- Recurrence
  - *MIS #27*
  - *Open Surgery #7*

Ramirez PT, N Engl J Med 2018

LACC Trial DFS

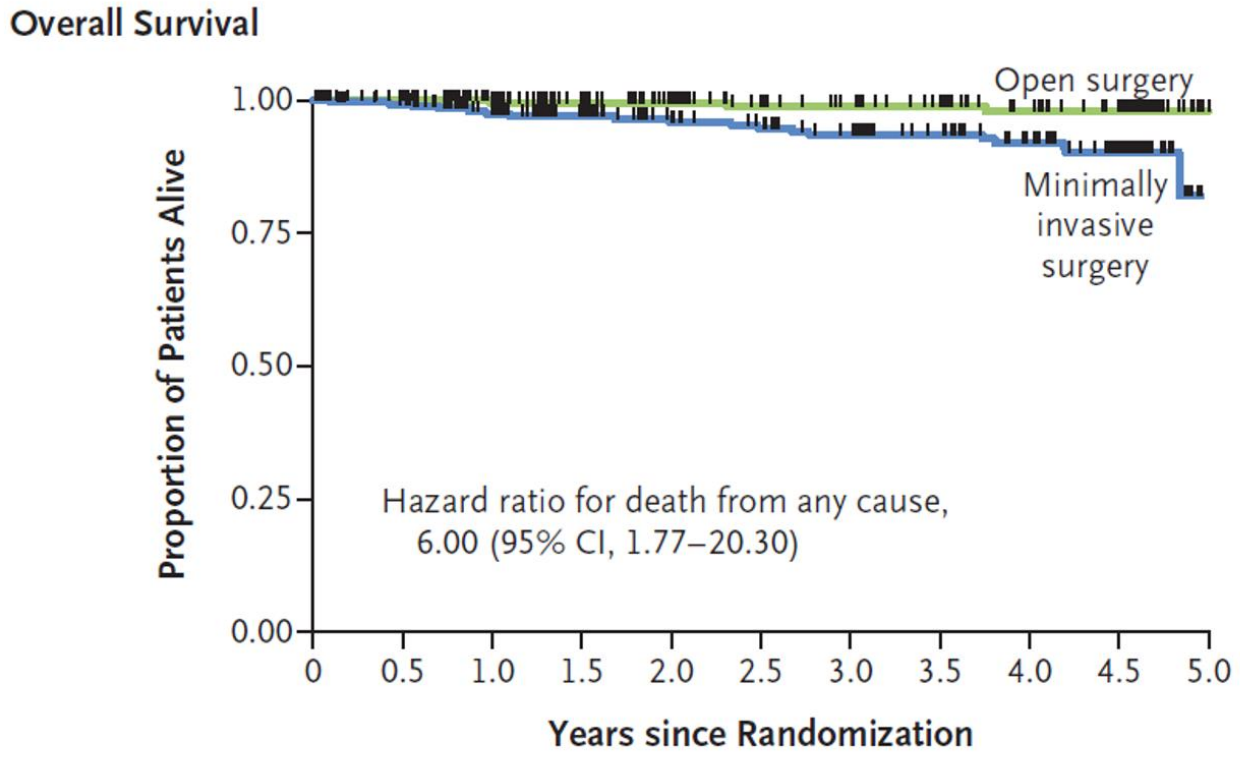


No. at Risk

Open surgery	312	280	236	187	163	144	134	123	104	90	7
Minimally invasive surgery	319	292	244	192	167	155	142	121	102	80	5

Ramirez PT, N Engl J Med 2018

LACC Trial OS



No. at Risk

Open surgery	312	282	237	190	164	146	136	125	104	90	7
Minimally invasive surgery	319	297	249	198	174	163	150	133	113	87	5

Ramirez PT, N Engl J Med 2018

LACC Trial: Letter to the Editor

- 4.5 years DFS
  - *MIS 86.0%*
  - *Open Surgery 96.5%*

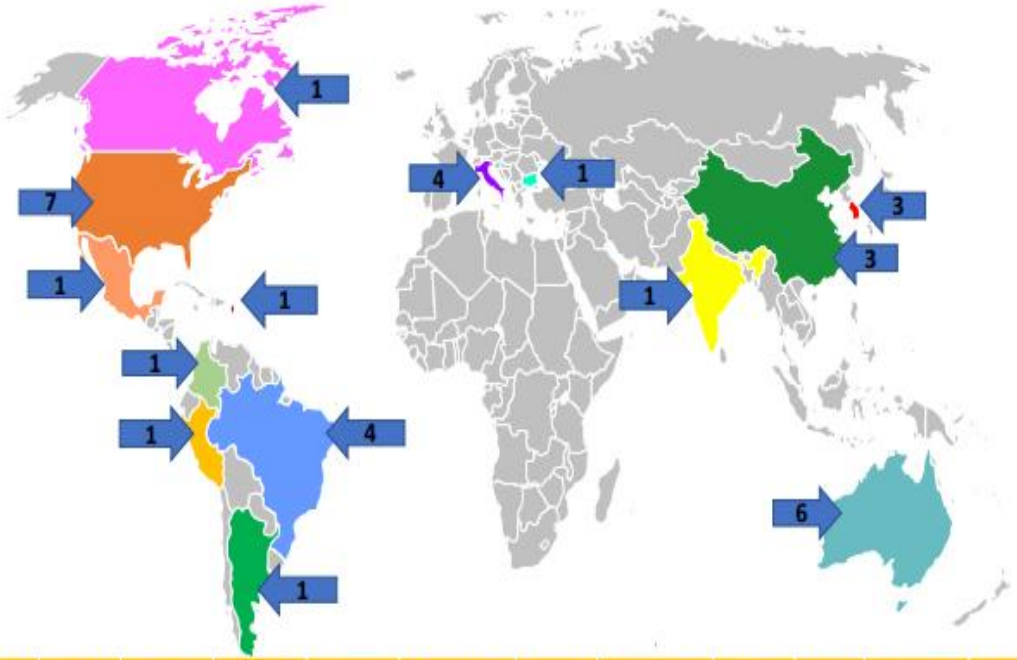
} P=0.87 (NS)

- 'Null Hypothesis' should be accepted
- In the null hypothesis the power should be 90% and can not be 80-85%

Leitao MM Jr, Int J Gynecol Cancer 2018

LACC: Distribution of Cases by Country

LACC TRIAL (NCT00614211)
Open January 2008 – Closed to Recruitment June 2017 (631 pts)



Country/ Territories	Australia	USA	Puerto Rico	Canada	Mexico	Argentina	Brazil	Colombia	Peru	Italy	Bulgaria	China	South Korea	India
Recruited	94	58	5	14	22	3	128	47	75	47	12	89	36	1

Distribution of Surgeons

There were participating surgeons who had not completed a fellowship in gynecologic oncology, others were general surgeons with a surgical oncology fellowship, and most had not published their results with laparoscopic radical hysterectomy

Vergote I, J Minim Invasive Gynecol 2019

Bias in Histopathology

Histopathologies		TARH 282 (%)	MIS 291 (%)
Histology	Scuamose	145 (51)	150 (52)
	Adenoca	58 (21)	59 (20)
	Adenoscuamose	12 (4)	11 (4)
	Other	**66 (23)**	**66 (23)**
	Loss	1 (0)	5 (2)
Grade	1	29 (10)	34 (11)
	2	113 (40)	115 (40)
	3	61 (22)	61 (21)
	Unknown	**79 (28)**	**81 (28)**
Invasion	Superficial	61 (22)	85 (29)
	2/3	73 (26)	50 (17)
	Profundal	56 (20)	64 (22)
	Unknown	**92 (33)**	**92 (32)**

Ramirez PT, N Engl J Med 2018

Bias in Histopathology

Histopathologies		TARH 282 (%)	MIS 291 (%)
Tumor diameter	<2 cm	89 (32)	95 (33)
	≥2 cm	101(36)	97 (20)
	Unknown	**92 (33)**	**99 (34)**
LVSI	Negative	186 (66)	196 (67)
	Positive	81 (29)	70 (24)
	Unknown	**15 (5)**	**25 (9)**
Parametriums	Negative	251 (89)	254 (87)
	Positive	**11 (4)**	**19 (7)**
	Unknown	**20 (7)**	**18 (6)**
Vaginal surgical margin	Negative	248 (88)	258 (89)
	Positive	6 (2)	5 (%)
	Unknown	**28 (10)**	**28 (10)**

Ramirez PT, N Engl J Med 2018

Unknown Data

- Unknown data in open surgery
  - *Tumor diameter; 33%*
  - *Parametrial involvement; 7%*
  - *Vaginal surgical margin positivity; 10%*
  - *LVSI; 5%*
- Unknown data in LS surgery
  - *The length of the removed parametrial tissue*
- Unknown adjuvant treatment indications

Ramirez PT, N Engl J Med 2018; Vergote I, J Minim Invasive Gynecol 2019

Completed Data Rates

Primary target (DFS)	
Median FU time (min-max)	2.5 years (0.0-6.3)
4.5 Year completion (%)	**219/558 (39.2%)**
Sufficient information in 4.5 years (%)	59.7%
OS	
Median FU time (min-max)	2.5 years (0.0-6.3)
4.5 Year completion (%)	**208/558 (37.3%)**
Sufficient information in 4.5 years (%)	54.3%

Ramirez PT, N Engl J Med 2018

DFS

GOG 109

- DFS; 80% in high-risk group

GOG 92

- DFS **88%** in moderate risk group
- Recurrence 18%

LACC

- **DFS 96.5% of patients with stage IB1 in 92% of open surgery arm**
- MIS **86.0%**

Peters WA, J Clin Oncol 2000; Sedlis A, Gynecol Oncol 1999; Ramirez PT, N Engl J Med 2018; Leitao MM Jr, Int J Gynecol Cancer 2018

Follow-up Times

- 39.2% of the data is completed in 4.5 years
- Median FU only 2.5 years
- Results 2 years later significant
- The most important example in our field is that the results of the first two years of “GOG 99” do not match the results of the 4th year

Ramirez PT, N Engl J Med 2018; Roberts JA, Gynecol Oncol 1998; Keys HM, Gynecol Oncol 2004

Recurrence Zones

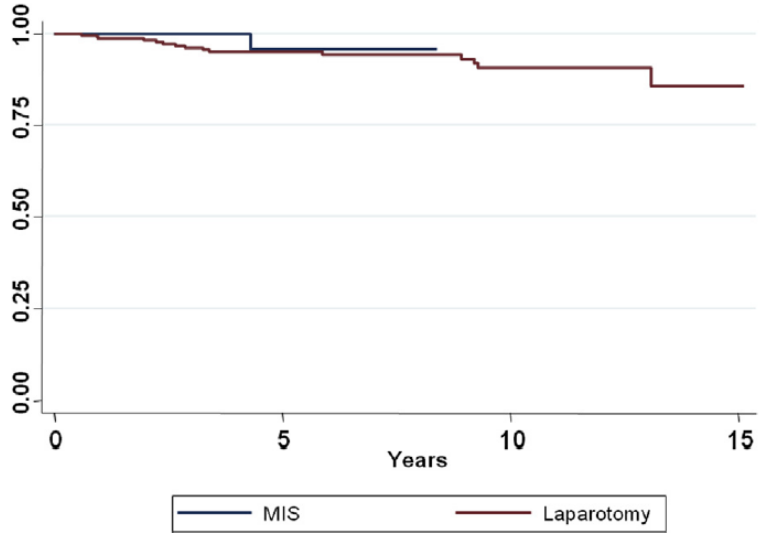
Operation	TARH	TLRH/TRRH
Total recurrences	7	24
Recurrence Zones		
Vaginal cuff	**3 (43%)**	**4 (17%)**
Pelvis	0 0(%)	**7 (29%)**
Abdomen	0 0(%)	**1 (4%)**
Distant	1 (14%)	2 (8%)
Multiple recurrences	2 (29%)	7 (29%)
Other	1 (14%)	3 (13%)

MIS vs Open Surgery

Result	MIS (101)	Open (282)	p
KT (%)	17 (16.7)	60 (21.3)	0.32
XRT (%)	20 (10.8)	69 (24.5)	0.28
Recurrence (%)	5 (5.0)	18 (6.4)	0.86

Fig. 2

Overall survival for 383 patient cohort that underwent RH for early-stage cervical carcinoma. This Kaplan-Meier graph depicts the overall survival for women in our cohort stratified by mode of surgical procedure. Because MIS techniques were introduced in later eras, the duration of follow-up was shorter for the MIS group. There was no statistical difference between the 2 groups (log-rank p = .29).



Diver E, J Minim Invasive Gynecol 2017

MIS vs Open Surgery

Characteristic	MIS (n = 101)	Open (n = 282)	p
Pelvic lymph nodes harvested, n, mean ± SD	19.4 ± 8.9	16.0 ± 8.3	.001
Pelvic lymph nodes positive, n, mean ± SD	11 (10.9)	24 (8.5)	.55
Margins positive, n (%)	5 (5.0)	13 (4.6)	.54
Perioperative complications, n (%)	15 (17.2)	46 (18.7)	.87
Conversion to laparotomy, n (%)	3 (3.0)	N/A	N/A
EBL, cc3, median	50 (5–500)	500 (37.5–2000)	.001
Perioperative RBC transfusion, n (%)	3 (3.0)	74 (26.2)	.001
Hospital stay, d, mean ± SD	1.9 ± 2.6	4.9 ± 5.3	.001

Diver E, J Minim Invasive Gynecol 2017

Less Radical Surgery

Cases in fifteen years #36; Conization +BPLND				
Stage IB1	TD 11.7 mm	Adenoca 33%	Grade 3 14%	LVSI 14%

"Cervical conization represents a feasible conservative management of stage IB1 cervical cancer and shows a low risk of relapse, provided that patients are selected carefully.

Conization would be suitable to treat stage IB lesions smaller than 15–20 mm. with pathologic negative lymph nodes."

Maneo A, Gynecol Oncol 2011

Can LACC Trial Explain This Success of Less Radical Surgery?

OF COURSE NOT

WHAT DO WE HAVE TO LEARN FROM LACC TRIAL?

Result

- The LACC trial did not respond to the comparison of minimally invasive surgery with open surgery
- Surgeon factor appears to be an important factor
- No problem for tumors <2 cm
- Colpotomy should not be performed in a CO_2 circulating environment to prevent tm spread

Vaginal Closure with EndoGIA

To demonstrate a method of vaginal closure with EndoGIA surgical stapler

Vaginal closure with EndoGIA before the colpotomy provides a safe and easy method to prevent tumor spillage and could improve the unfavorable results related with MIS in patients with cervical cancer

Boyraz G, JMIG 2018

Combined Laparoscopic-vaginal Technique

- Case# 1952
- Median FU 99 (range 1-288) months
- The 3-, 4.5-, and 10-year DFS
  - *96.8%, 95.8%, and 93.1% respectively*
- The 3-, 4.5-, and 10-year OS
  - *98.5%, 97.8%, and 95.8%, respectively*

Kohler C, Int J Gynecol Cancer 2019

Combined Laparoscopic-vaginal Technique

- Recurrence location
  - ***Loco-regional in 50% of cases with recurrence (n=10)***
  - *Interestingly, 9/20 recurrences occurred more than 39 months after surgery*
- This technique with avoidance of spillage and manipulation of tumor cells provides excellent oncologic outcome for patients with early cervical cancer
- Their retrospective data suggest that laparoscopic-vaginal surgery may be oncologically safe and should be validated in further randomized trials

Kohler C, Int J Gynecol Cancer 2019

We Learned

Preventing from the tumor spillage during the laparoscopic radical hysterectomy for cervical cancer is very important

For this reason;	***We have to seal the fallopian tubes like in the endometrial cancer surgery***
	We have to avoid from the colpotomy as usual
	If you perforate with the manipulator DO NOT continue MIS, convert to open surgery

The War Continues!

Thank You for Your Attention!

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