Radical Hysterectomy: Open *vs* Minimal Access

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Disclosures

- Have entered patients in to all major gynaecological trials in the UK
- UK CI for SHAPE trial
- I do not undertake minimal access surgery

Do gynaecological oncologists suffer from a lack of surgical equipoise?

Why is this a problem?

- Surgeons love new toys
- Some surgeons know they are right and can't wait for the results of a clinical trial
- Do gynaecological oncologists suffer from a lack of surgical equipoise?

So why is this such a hot topic?

- MAS has short term surgical benefits
  - Intra-operative
  - Post-operative
- Most MAS data comes from trials of endometrial cancer
  - LAP2
- MAS has been accepted as the same as open surgery from an oncological outcome point of view

November 2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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., Reitan Ribeiro, M.D., Alessandro Buda, M.D., Xiaojian Yan, M.D., Yao Shuzhong, M.D., Naven Chetty, M.D., David Isla, M.D., Mariano Tamura, M.D., Tao Zhu, M.D., Kristy P. Robledo, Ph.D., Val Gebski, M.Stat., Rebecca Asher, M.Sc., Vanessa Behan, B.S.N., James L. Nicklin, M.D., Robert L. Coleman, M.D., and Andreas Obermair, M.D.

LACC trial - Ramirez

- Open *vs* Laparoscopic or Robotic
- All centres had to provide data from at least 10 MAS procedures
- Two un-edited videos of MAS
- At all sites surgeons had to do both Open or MAS
- Planned to recruit 740 women, 370 in each arm

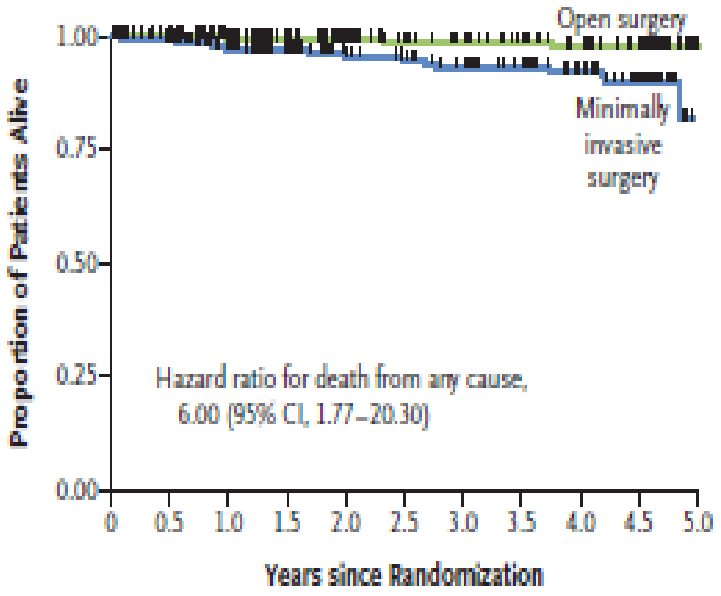
LACC trial - Ramirez

- Trial was closed prematurely by data and safety committee
- 319 women underwent MAS and 312 Open
- Women in MAS arm had an increased incidence of recurrence and death
  - 91.2% *vs* 97.1% HR 3.74 for recurrence
  - 93.8% *vs* 99.0% HR 6.00 for all cause mortality

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Open Surgery (N=312)	Minimally Invasive Surgery (N=319)
Age — yr	46.0±10.6	46.1±11.0
Body-mass index†	26.2±5.3	27.2±5.6
Histologic subtype — no. (%)		
Squamous-cell carcinoma	210 (67.3)	214 (67.1)
Adenocarcinoma	80 (25.6)	87 (27.3)
Adenosquamous carcinoma	6 (1.9)	9 (2.8)
Not reported	16 (5.1)	9 (2.8)
Stage of disease — no. (%)		
IA1: lymphovascular invasion	5 (1.6)	5 (1.6)
IA2	20 (6.4)	21 (6.6)
IB1	287 (92.0)	293 (91.8)
ECOG performance-status score — no. (%)‡		
0	289 (92.6)	292 (91.5)
1	23 (7.4)	27 (8.5)
Median length of hospital stay (range) — days	5 (0–69)§	3 (0–72)
Treatment received — no. (%)		
Open surgery	274 (87.8)	2 (0.6)
Minimally invasive surgery	8 (2.6)	289 (90.6)
Patient withdrew before surgery	19 (6.1)	12 (3.8)
Surgery was aborted	11 (3.5)	16 (5.0)

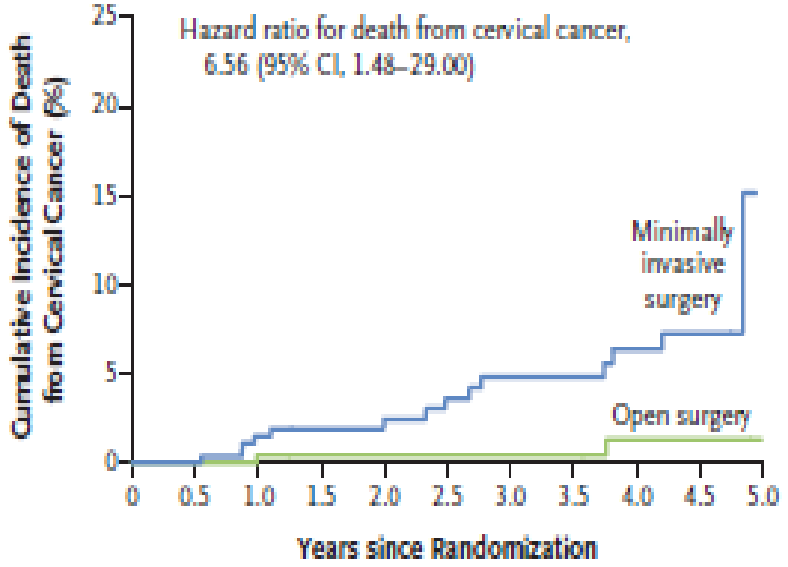
A Overall Survival



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

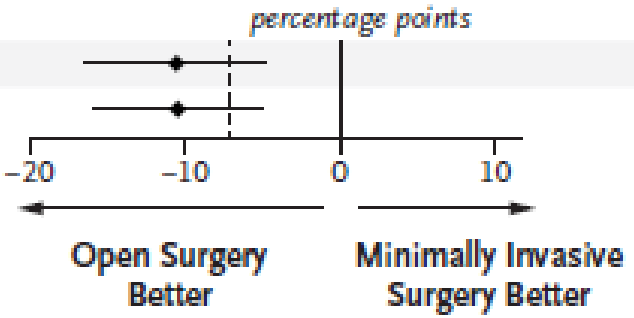
B Disease-Specific Survival



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

Population	Disease-free Survival Rate at 4.5 Yr (95% CI)		Difference (95% CI)	P Value for Noninferiority
	Minimally Invasive Surgery	Open Surgery		
	percent		*percentage points*	
Intention-to-treat population	86.0 (79.7–90.4)	96.5 (92.7–98.4)		0.87
Per-protocol population	87.1 (81.0–91.3)	97.6 (94.1–99.0)		0.88



November 2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Survival after Minimally Invasive Radical Hysterectomy for Early-Stage Cervical Cancer

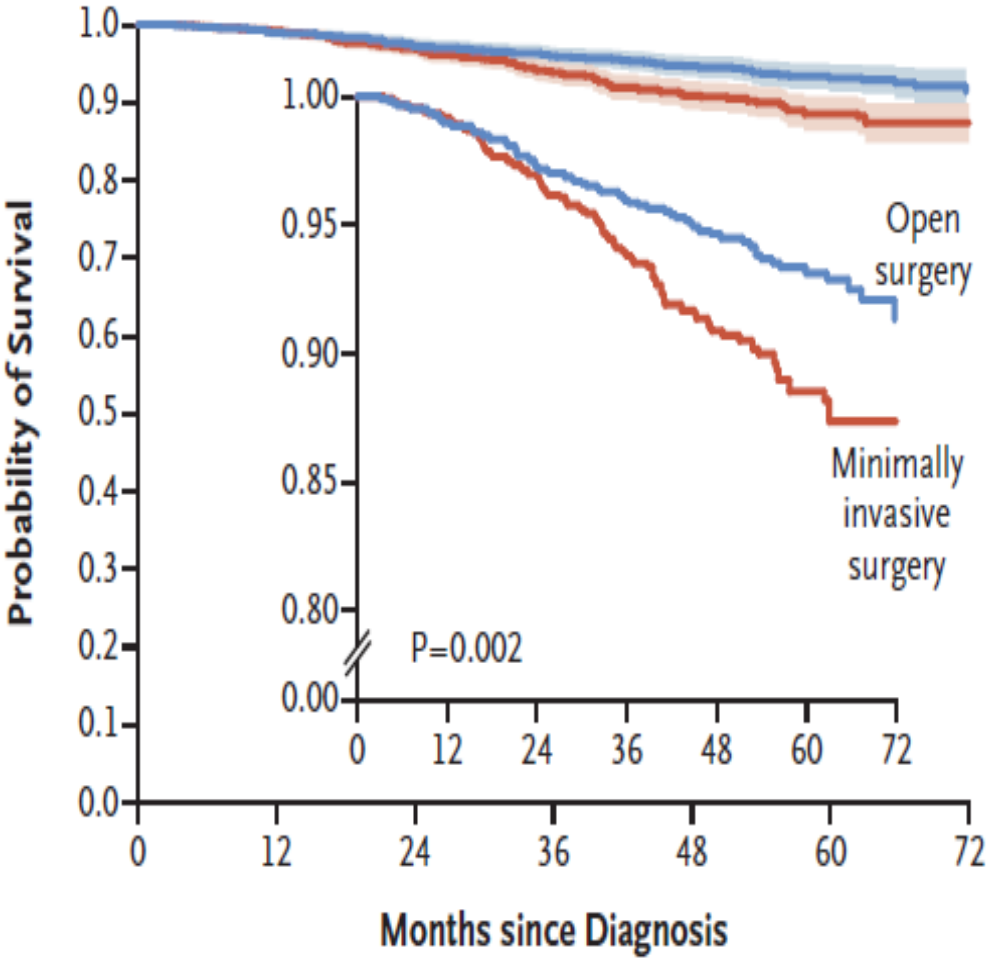
Alexander Melamed, M.D., M.P.H., Daniel J. Margul, M.D., Ph.D.,
Ling Chen, M.D, M.P.H., Nancy L. Keating, M.D., M.P.H.,
Marcela G. del Carmen, M.D., M.P.H., Junhua Yang, M.S.,
Brandon-Luke L. Seagle, M.D., Amy Alexander, M.D., Emma L. Barber, M.D.,
Laurel W. Rice, M.D., Jason D. Wright, M.D., Masha Kocherginsky, Ph.D.,
Shohreh Shahabi, M.D., E.M.H.A., and J. Alejandro Rauh-Hain, M.D., M.P.H.

US population study - Melamed

- Open *vs* Laparoscopic or Robotic
- National Cancer database
- 70% of all new cancers from 1500 hospitals
- Data from SEER
- 2010 to 2013
- 1236 Open, 1334 MAS

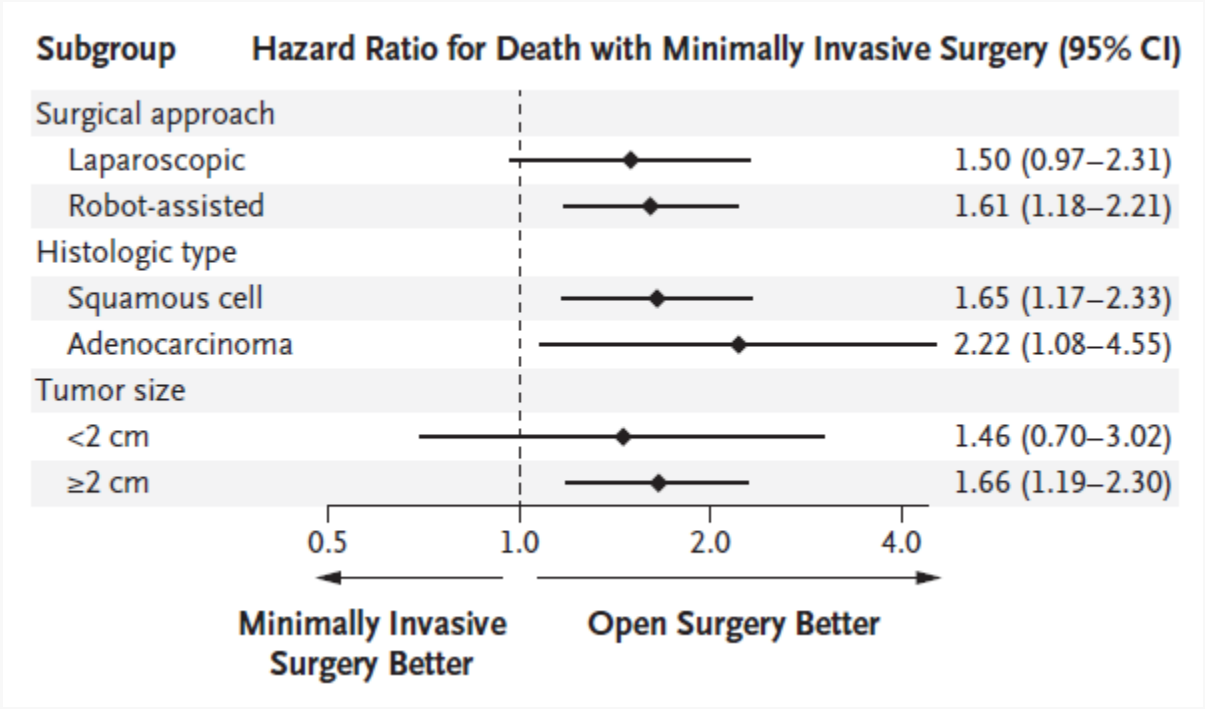
Table 1. Selected Characteristics of Patients Who Underwent Radical Hysterectomy for Stage IA2 or IB1 Cervical Carcinoma, According to Surgical Approach, before and after Inverse Probability of Treatment Weighting.*

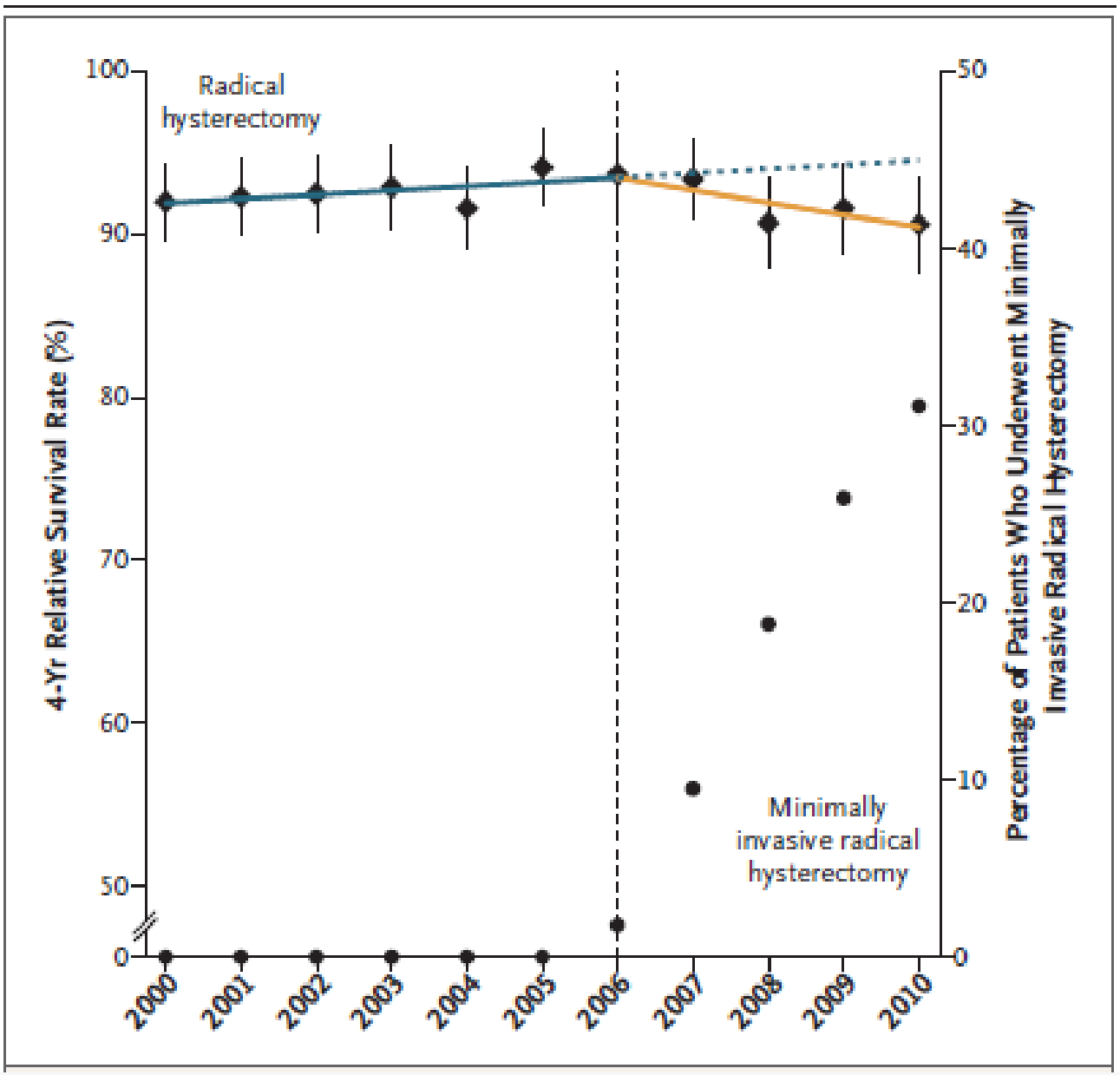
Characteristic	Cohort before Inverse Probability of Treatment Weighting			Cohort after Inverse Probability of Treatment Weighting		
	Open Surgery (N=1236)	Minimally Invasive Surgery (N=1225)	P Value†	Open Surgery (N=1340)	Minimally Invasive Surgery (N=1334)	P Value‡
	number (percent)			*number (percent)*		
Year of diagnosis			<0.001			1.00
2010	408 (33.0)	211 (17.2)		338 (25.2)	336 (25.2)	
2011	310 (25.1)	317 (25.9)		336 (25.1)	334 (25.1)	
2012	268 (21.7)	356 (29.1)		344 (25.7)	342 (25.6)	
2013	250 (20.2)	341 (27.8)		323 (24.1)	322 (24.1)	
Race or ethnic group§			<0.001			1.00
White	789 (63.8)	853 (69.6)		899 (67.1)	896 (67.2)	
Black	160 (12.9)	95 (7.8)		140 (10.4)	140 (10.5)	
Hispanic	196 (15.9)	169 (13.8)		196 (14.6)	191 (14.3)	
Asian	71 (5.7)	82 (6.7)		83 (6.2)	84 (6.3)	
Other or unknown	20 (1.6)	26 (2.1)		23 (1.7)	23 (1.7)	
Facility type			<0.001			0.94
Nonacademic	544 (44.0)	654 (53.4)		657 (49.0)	656 (49.2)	
Academic	692 (56.0)	571 (46.6)		683 (51.0)	678 (50.8)	
Stage of disease			0.04			0.94
IA2	127 (10.3)	159 (13.0)		157 (11.7)	155 (11.6)	
IB1	1109 (89.7)	1066 (87.0)		1183 (88.3)	1179 (88.4)	
Histologic type			0.01			1.00
Squamous cell	789 (63.8)	709 (57.9)		820 (61.2)	815 (61.1)	
Adenocarcinoma	381 (30.8)	452 (36.9)		450 (33.6)	450 (33.7)	
Adenosquamous	66 (5.3)	64 (5.2)		70 (5.2)	69 (5.2)	
Tumor size			0.005			0.99
<2 cm	459 (37.1)	534 (43.6)		543 (40.5)	541 (40.6)	
≥2 cm	615 (49.8)	543 (44.3)		626 (46.7)	624 (46.8)	
Unknown	162 (13.1)	148 (12.1)		171 (12.8)	169 (12.6)	



No. at Risk

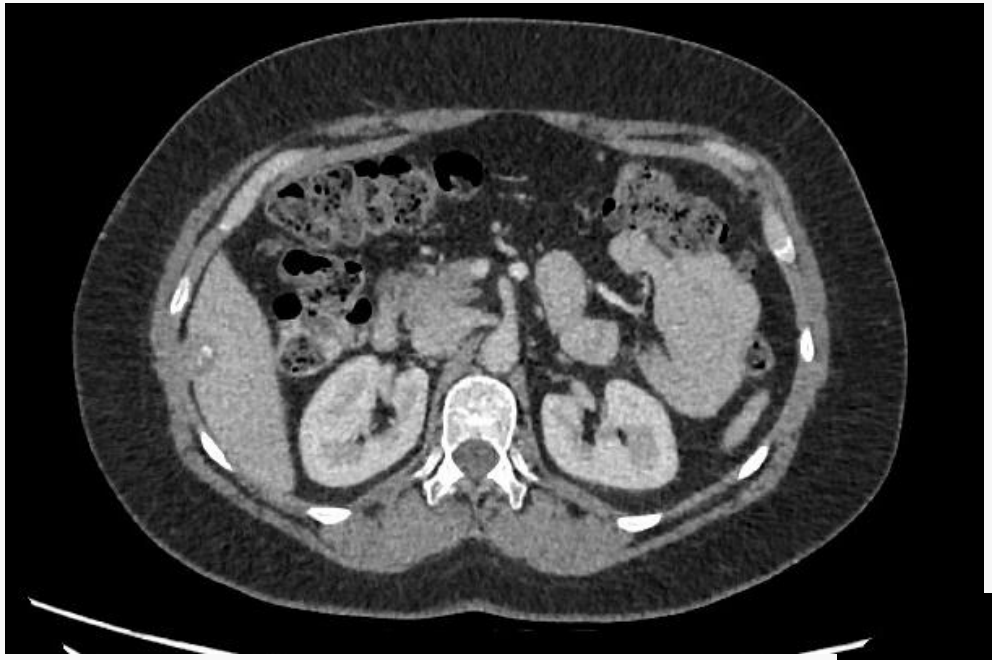
Open surgery	1236	1174	1092	909	625	356	104
Minimally invasive surgery	1225	1161	1061	818	490	217	60

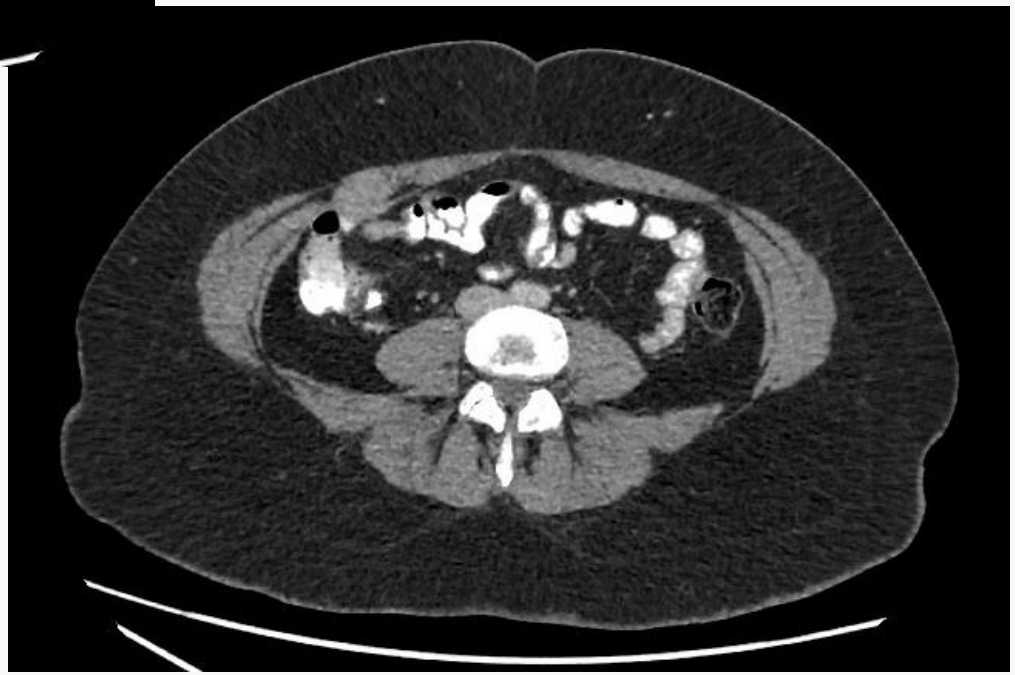

Subgroup
Hazard Ratio for Death with Minimally Invasive Surgery (95% CI)
Surgical approach
Laparoscopic
1.50 (0.97–2.31)
Robot-assisted
1.61 (1.18–2.21)
Histologic type
Squamous cell
1.65 (1.17–2.33)
Adenocarcinoma
2.22 (1.08–4.55)
Tumor size
<2 cm
1.46 (0.70–3.02)
≥2 cm
1.66 (1.19–2.30)
0.5
1.0
2.0
4.0
Minimally Invasive Surgery Better
Open Surgery Better


Radical hysterectomy
Minimally invasive radical hysterectomy
4-Yr Relative Survival Rate (%)
Percentage of Patients Who Underwent Minimally Invasive Radical Hysterectomy
100
90
80
70
60
50
0
50
40
30
20
10
0
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010

US population study - Melamed

- Four year mortality worse for MAS
  - 9.1% *vs* 5.3% HR 1.65 for death
- Prior to adoption of MAS
  - Four year mortality remained stable
    - Increased by 0.3% per year
- After adoption of MAS
  - Four year mortality remained stable
    - Decreased by 0.8% per year





Sheffield Gynaecological Cancer Centre

Sheffield Teaching Hospitals

BJOG July 2019 – Martin Hirsch

Survival of women with early-stage cervical cancer in the UK treated with minimal access and open surgery

P Martin-Hirsch,[a] N Wood,[a] NL Whitham,[a] R Macdonald,[b] J Kirwan,[b] A Anagnostopoulos,[b] R Hutson,[c] G Theophilou,[c] M Otify,[c] M Smith,[d] E Myriokefalitaki,[d] W Quinland,[d] F Mahon-Daly,[e] RD Clayton,[f] H Nagar,[g] I Harley,[g] S Dobbs,[g] N Ratnavelu,[h] A Kucukmetin,[h] AD Fisher,[h] A Tailor,[i] S Butler-Manuel,[i] K Madhuri,[i] RJ Edmondson[e,f]

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- Case series from 8 self selected centres
- Only looked at MAS surgery
- 779 cases but only 597 underwent radical surgery and 463 had MAS
- Median follow up 23 months
- Different population when compared with LACC control arm

Table 1. Clinical characteristics of UK cohort and comparison against control arm of LACC

	UK series		LACC study*		*P*
	n	%	*n*	%	
Age (years)					
Median	40		46		
Range	23–88				
Histological type					
Squamous	416	56	210	67	<0.01
Adeno	252	35	80	27	
Mixed	28	4	6	2	
Other	27	4			
Not recorded	56		16		
Grade					
1	129	22	29	10	<0.05
2	278	47	111	39	
3	185	31	61	22	
Not recorded	187		81	29	
Lymphovascular space invasion					
Present	289	37	81	29	<0.01
Absent	406	52	185	66	
Not recorded	84	11	16	6	
Size of tumour					
< 2 cm	452	58	147	52	<0.01
≥ 2 cm	256	33	121	43	
Not recorded	71	9	14	5	

*Data from control arm (open surgery) within LACC study, taken from ref. 1.

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- No difference in survival between LACC open surgery control arm and this series
  - 1.4% *vs* 0.96%
- However the two study populations are different
  - Logistic regression model to account for this
  - Increased mortality risk in the UK series
    - 1.27 fold increase from 1.4% to 1.78%

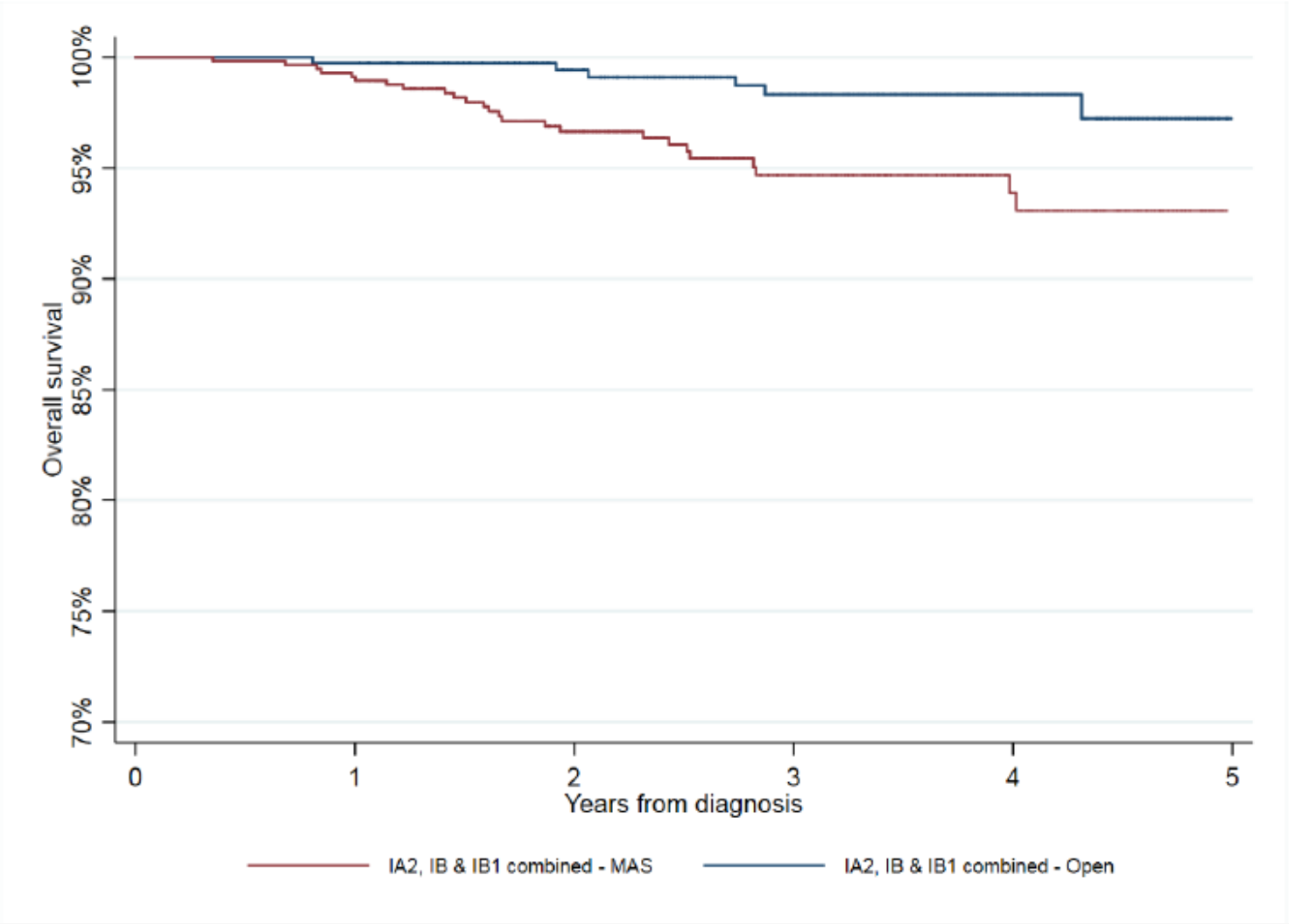
NRCAS data - England

- Population data
  - HES
  - SACT – chemotherapy dataset
  - RTDS – radiotherapy dataset
  - ONS mortality data
- 2013 to 2016
- 365 Open, 564 MAS
- MAS increased from 48% to 76%

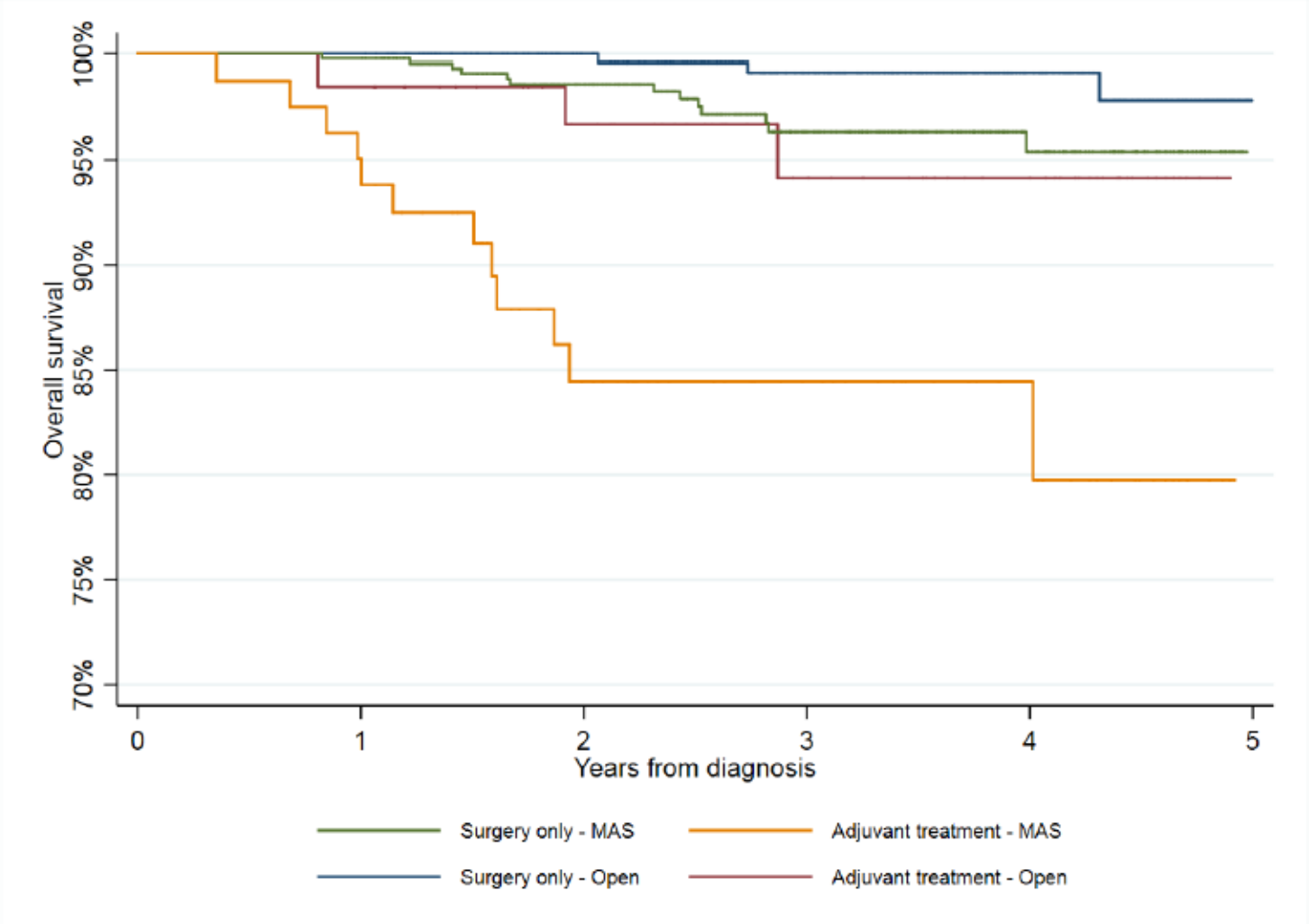
NRCAS data - England

- Four and half year mortality worse for MAS
  - 6.9% *vs* 2.8% HR 4.0

- MAS/open – all patients in either group



- MAS/open groups by adjuvant treatment status



Why the difference in BJOG data

- A self selected series – BJOG
- Different population from LAAC trial
- Short follow up in BJOG series – median 23 months
- NRCAS data only becomes statistically significant after 4 years
- Melamed paper – median follow up 45 months
- Ramriez paper median follow up 30 months

Possible explanations

- Use of a uterine manipulator which is placed into the cancer
- Raised intra-abdominal pressure with CO_2

- Some centres in the LACC trial only contributed a few patients
- The surgeons were not as good as me at the technique

What does this data mean for future practice?

- If you practice evidence based medicine
  - There is no role for minimal access surgery for early stage cervical cancer outside of on going or future clinical trials.

What does this data mean for future practice?

- If you practice evidence based medicine
  - There is no role for minimal access surgery for early stage cervical cancer outside of on going or future clinical trials.
- If you are a gynaecological oncologist
  - I don’t believe the data as the trials are flawed so I will continue to offer minimal access surgery because I know I am right, I like doing the operation and patients do go home earlier.

Why is it a problem if gynaecological oncologists prefer to ignore trial data?

- Surgical trials are complex and difficult to organise
- Funders remain concerned about low recruitment rates to surgical trials
- Surgical bias and preferences seems to over ride clinical based practice
- Patients will continue to be offered surgical procedures with no proven clinical effectiveness

Why is this a problem for gynaecological oncology surgical trials

- Surgical trials tend to be in to be in early stage cancers with good prognosis and so long median follow up is required
- The period at the end of a trial leaves a surgical void
  - What should I do until the data becomes available
- SHAPE trial
  - Now closed
  - May need a further 3 years for data to mature
  - What should I do now

Conclusions

- Data from a variety of sources report higher mortality rates for early stage cervical cancer and MAS
- Only further randomised clinical trials can address the outstanding issues given the epidemiological data would suggest data from case series could be unreliable
- MAS for endometrial cancer has not been proven to be oncologically the same as open surgery in any randomised trial

Original research

INTERNATIONAL JOURNAL OF GYNECOLOGICAL CANCER

A comparison of disease recurrence between robotic versus laparotomy approach in patients with intermediate-risk endometrial cancer

Jiheon Song ,[1] Tien Le,[2] Laura Hopkins,[3] Michael Fung-Kee-Fung,[2] Krystine Lupe,[1] Marc Gaudet,[1] Choan E,[1] Rajiv Samant[1]

Table 2 Data showing a higher recurrence rate was observed in the robotic surgery group than the laparotomy group

	Total (n=135)	Robotic surgery (n=77)	Laparotomy (n=58)
Recurrence, n (%)	8 (5.9)	8 (10.4)	0 (0.0)
Loco-regional	3 (2.2)	3 (3.9)	0 (0.0)
Distant	5 (3.7)	5 (6.5)	0 (0.0)
5 year DFS, %	95.3	91.8	100.0
5 year OS, %	95.2	95.5	94.2

DFS, disease-free survival; OS, overall survival.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