

Updates in Cervical Cancer

Valerie Galvan Turner, MD

Assistant Professor Gynecologic Oncology

Gynecologic Oncology Director of Clinical Research

West Virginia University

Disclosures

- AstraZeneca-Merck Ovarian Cancer Advisory Board
- Tesaro Inc. Gemstone Expert Consultant
- Caris Precision Oncology Alliance (POA) WVU

Objectives

- Review pathophysiology of cervical cancer
- Review the history of and current treatments for cervical cancer
- Review FIGO 2018 Staging Updates
- Review new recommendations for the role of minimally invasive surgery in the treatment of cervical cancer

Myth

- Women in the United States no longer die from cervical cancer



Fact



United States:

- About **4,250** women will die from cervical cancer (2019)
- About **13,170** new cases of invasive cervical cancer will be diagnosed (2019)

Worldwide:

- **528K** new cases per year (2018)
- **Fourth** most common cancer

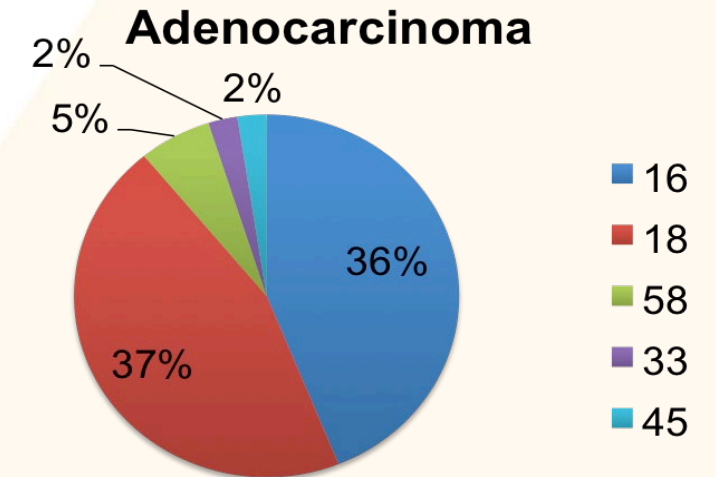
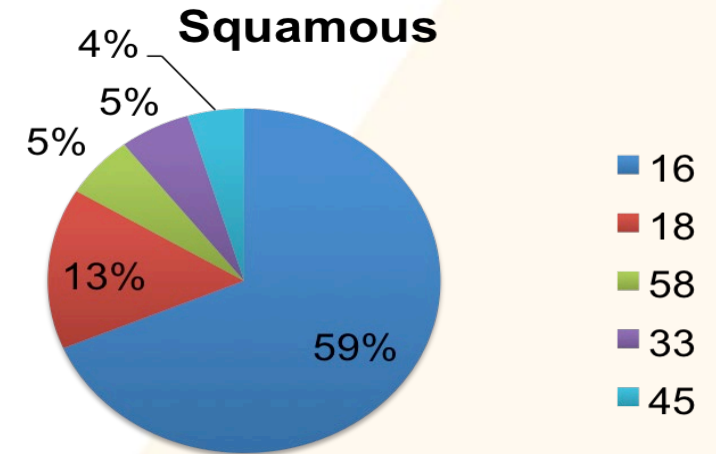


Risk Factors for Cervical Cancer

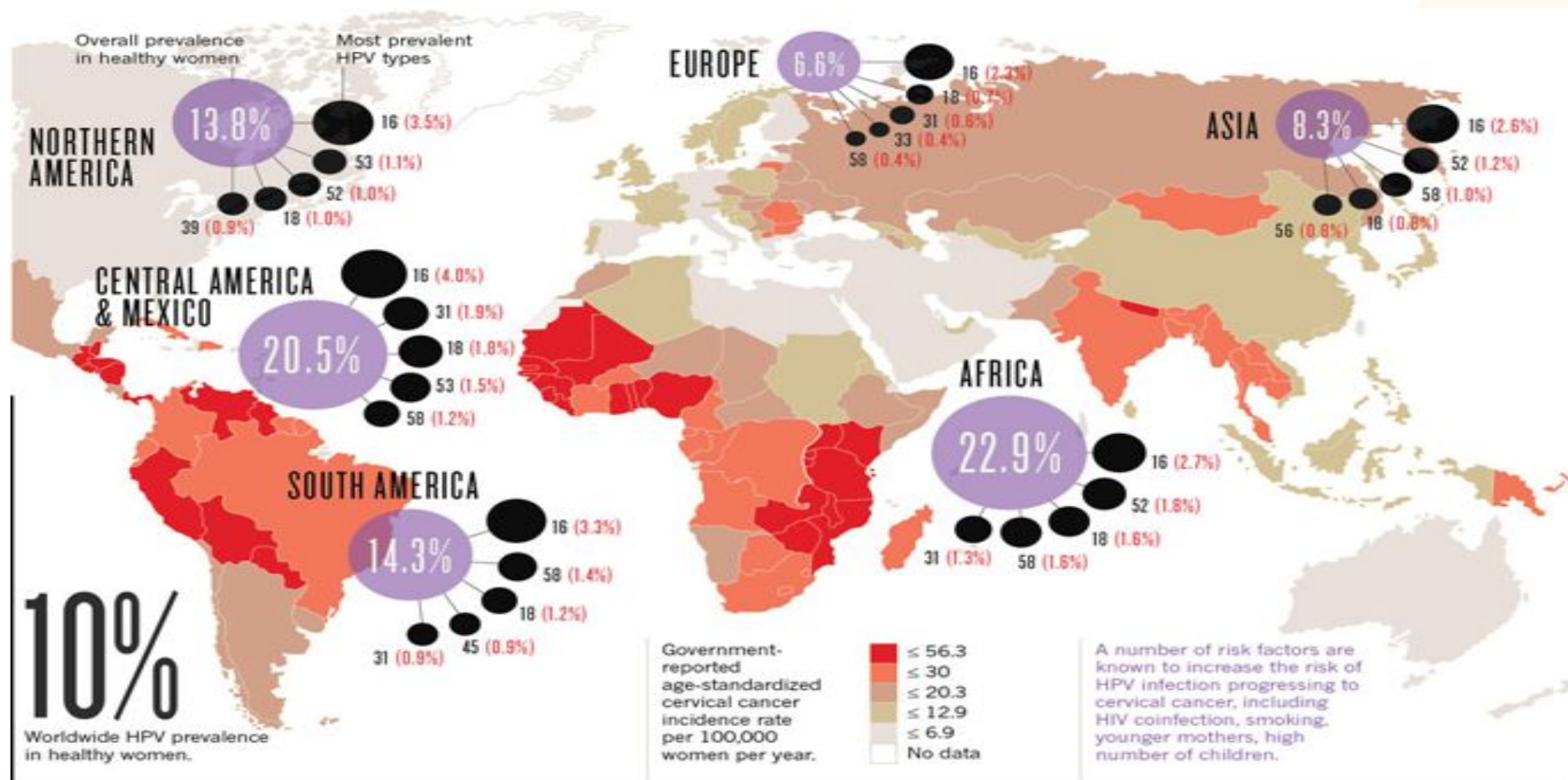
- Increasing Age
- HPV infection
- Immunosuppression
- Lower SES
- Multiple Partners
- Early Age Sexual Activity
- Tobacco Use
- History of VIN or VAIN
- Exposure to DES
- Infrequent or No Prior Screening*

HPV Subtypes

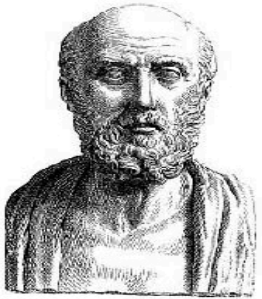
- High risk:
 - 16 and 18 most commonly associated with cancer
 - 18 more common in adenocarcinoma
 - HPV is detected in 99.7% of all cervical cancers
- Low Risk:
 - 6 and 11 associated with genital warts
 - 42, 43, 44



HPV Incidence



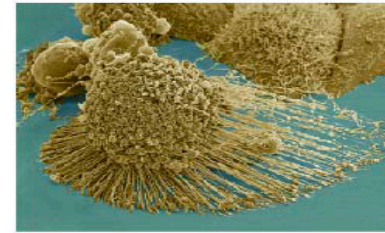
History



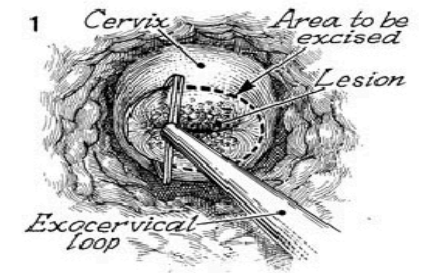
First description of cervical cancer by Hippocrates



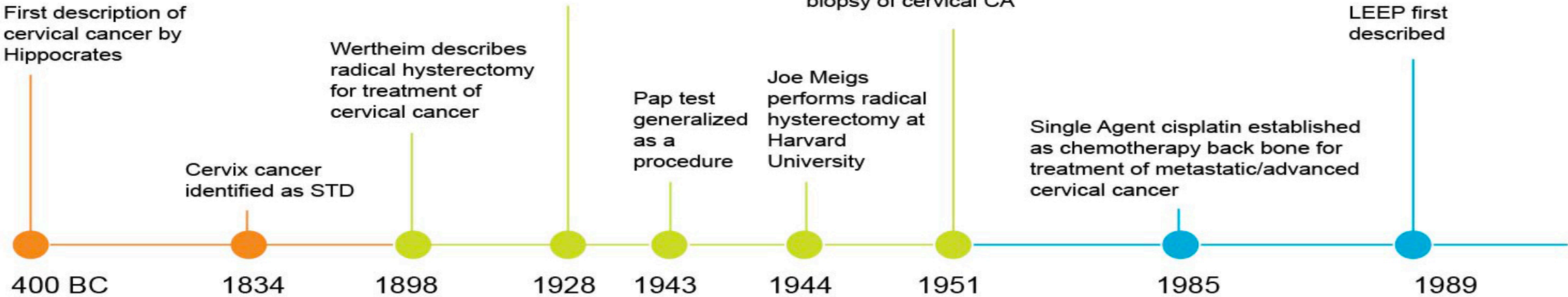
Papanikolaou develops cervical cytology smear



Hela cell line derived from biopsy of cervical CA



LEEP first described



DISCOVERY

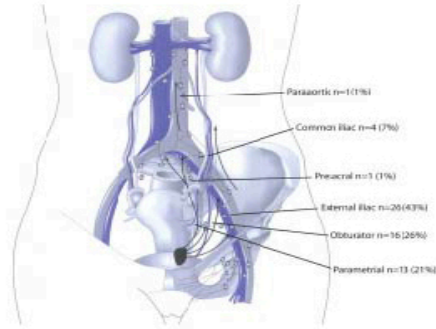
CYTOTOXIC THERAPY

FURTHER STUDY

History



Three large randomized prospective trials established chemoradiation as the treatment of choice for patients with advanced stage cervix cancer

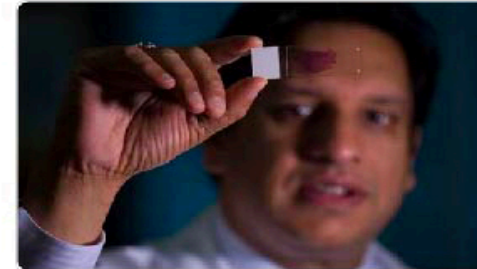


(Pargent et.al describes) Sentinel Lymph node mapping for cervix cancer



FDA approves first HPV vaccine

Medicare approves use of PET/CT for cervix cancer



Bevacizumab
(Tewari et.al showed addition of Bevacizumab for treatment of cervical cancer improved PFS)

Pembrolizumab
(Frenal et.al showed use of Pembrolizumab in patients with PD6-1 positive advanced cervical cancer had bad ORR 17%) Approved for use in patients with MSI-H/dMMR biomarkers

liquid pap developed

1996

1999

2000

2005

2006

2013

2017

SCREENING, IMAGING & VACCINES

TARGETED THERAPIES

FIGO Staging and Prognosis

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm*
IA1	Measured stromal invasion <3 mm in depth
IA2	Measured stromal invasion ≥3 mm and <5 mm in depth
IB	Invasive carcinoma with measured deepest invasion ≥5 mm (greater than Stage IA), lesion limited to the cervix uteri [¶]
IB1	Invasive carcinoma ≥5 mm depth of stromal invasion, and <2 cm in greatest dimension
IB2	Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
IB3	Invasive carcinoma ≥4 cm in greatest dimension
II	The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Involvement limited to the upper two-thirds of the vagina without parametrial involvement
IIA1	Invasive carcinoma <4 cm in greatest dimension
IIA2	Invasive carcinoma ≥4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes ^Δ
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent (with r and p notations) ^Δ
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. (A bullous edema, as such, does not permit a case to be allotted to Stage IV.)
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

FIGO	5 year OS
IA	93%
IB	80%
IIA	63%
IIB	58%
IIIA	35%
IIIB	32%
IVA	16%
IVB	15%

Factors Associated with Poor Prognosis

- Factors associated with poor prognosis (stage IB)
 - LVSI, Tumor Size, Depth of Stromal Invasion
- Factors associated with poor prognosis in more advanced (stage II,III,IV)
 - Para-aortic and pelvic lymph node status
 - Tumor size, age, PFS, Bilateral disease, clinical stage

Adenocarcinoma

- SEER based analysis of adenocarcinoma
 - Younger age, higher stage
 - Increased risk of death compared to SCC
 - Stage IB1-IIA (HR=1.39; 95% CI, 1.23-1.56)
 - Stage IIB-IVA (HR=1.21; 95% CI, 1.10-1.32)
- Adenosquamous may also be more aggressive

Overview

- Microinvasive
- Early Stage
 - Surgery vs Radiation
- Adjuvant Therapy
 - Intermediate Risk
 - High Risk
- Locally Advanced
 - Chemoradiation +/- Surgery
 - Neoadjuvant Approach
- Advanced and Recurrent Disease
- Targeted Therapeutics



Early Stage Disease: Surgery or RT

Surgery vs. Radiation

- Surgery:
 - Ovarian preservation
 - Smaller tumor
 - Select those likely to avoid postop RT
- Radiation
 - Consider oophorectomy
 - Non operative candidate
 - Consider compliance



Stage	Treatment Recommendation
Microinvasive Disease (IA1, IA2)	CKC +/- lymph node assessment, radical trachelectomy, simple hysterectomy (1A1), modified radical hysterectomy
Invasive Disease (IB1, IB2, IIA1)	modified radical hysterectomy + lymph nodes, radical hysterectomy + lymph nodes, radical trachelectomy +lymph nodes (IA2-IB1)
Invasive Disease (IB3, IIA2 and above)	Concurrent platinum-based chemoradiation (CCRT)
Advanced Disease (IVB)	Platinum doublet chemotherapy, CCRT*
Recurrent Disease	Platinum doublet chemotherapy with bevacizumab*, immunotherapy

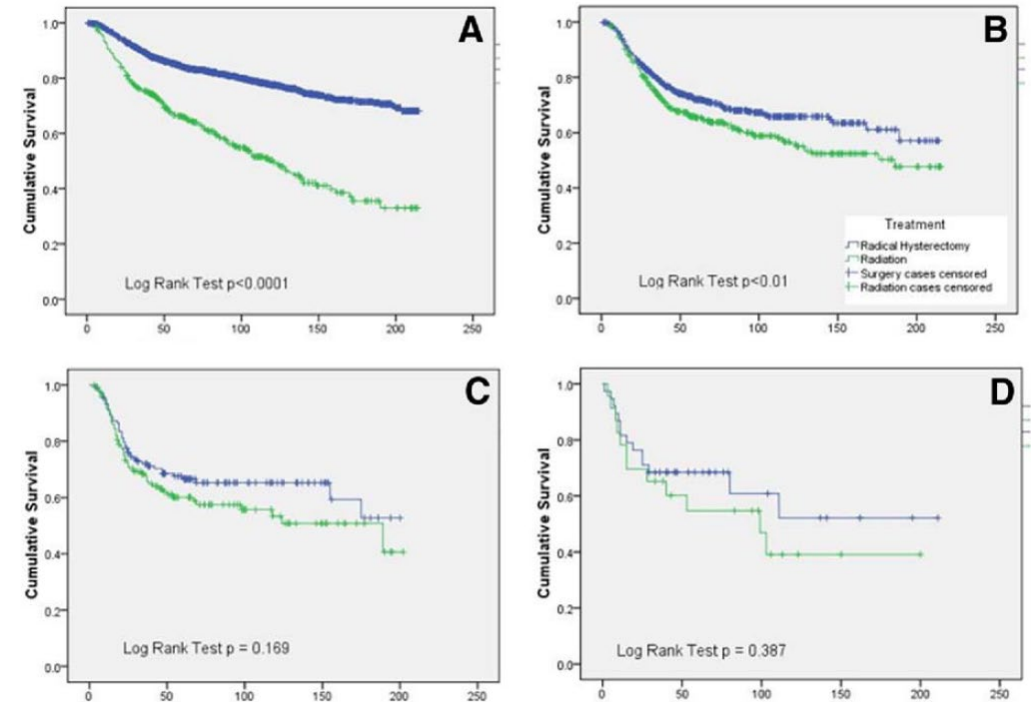
Bulky Stage IB and IIA: Treatment

- 3 different modalities, how do we sequence them?
 - Surgery Alone
 - (Chemo-)Radiation Alone
 - Surgery + (Chemo-)Radiation
 - *Chemoradiation + Surgery*
 - *Chemotherapy + Surgery*
 - *Chemotherapy + Surgery + Radiation*
- Consider:
 - Can you avoid RT?
 - Primary RT/chemo vs surgery +adjuvant RT-chemo and lower total dose, impact on sexual function and other toxicity?
 - Compliance for RT?
 - Residual tumor?
 - Higher risk path factors?

SEER analysis of Rad Hyst v RT

- Stage IB1-IIA (4,012 surgery, 873 XRT)
- Rad Hyst improved OS (HR 0.41, CI 0.35-0.50)
- Tumors <4 cm (HR 0.38 (CI: 0.30-0.48))
- Tumors 4-6 cm (HR 0.51 (CI: 0.36-0.72))
- Tumors >6 cm survival was equivalent
- Nonrandomized, complications not available
- 49% of Rad Hyst patients received XRT, unknown if chemo also
- Path review not available, so unable to stratify by DOI, LVSI, etc.

FIGURE 2
Tumor size



Kaplan-Meier analysis of patients who were treated by radical hysterectomy (*blue*) vs radiation (*green*) stratified by tumor size: A, <4 cm, B, 4-6 cm, C, 6.1-8 cm, and D, >8 cm.

Early stage: Intermediate Disease

“Sedlis” GOG 92: Early Stage Intermediate Risk

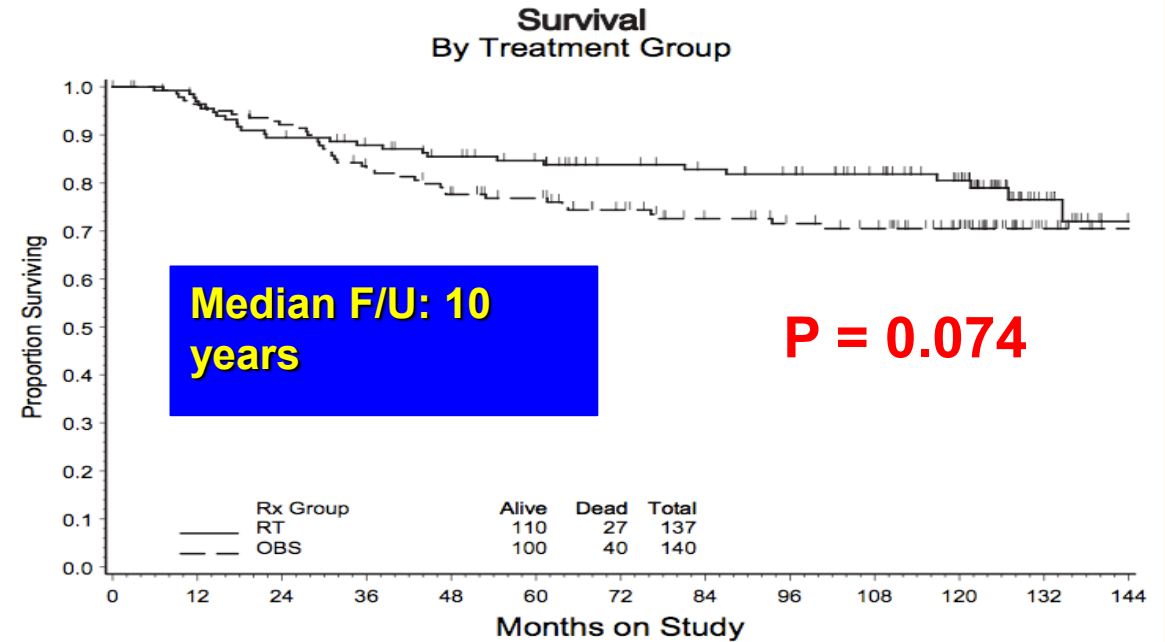
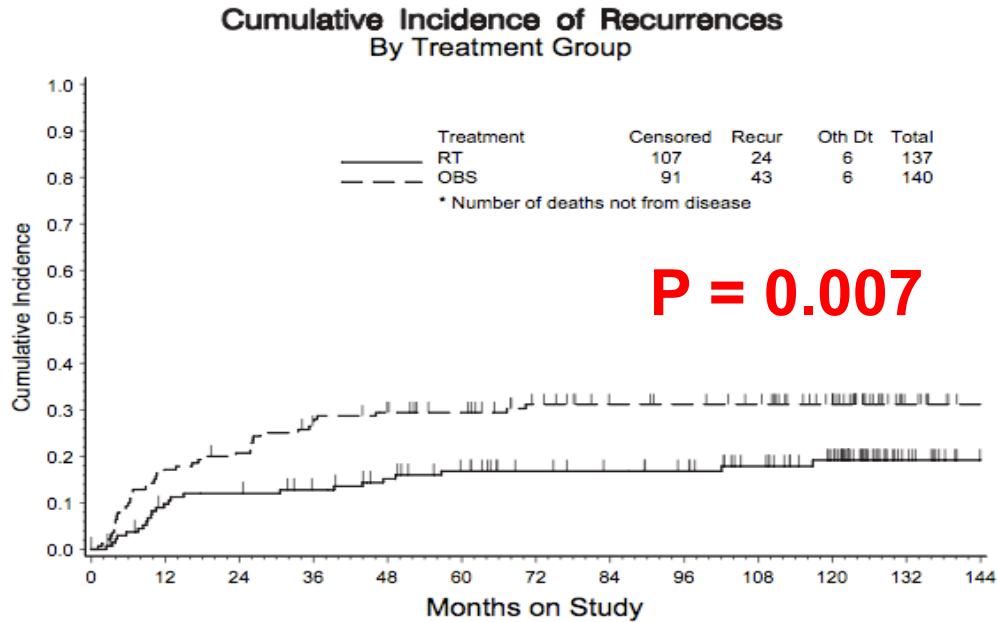
Stage IB Rad hyst PLND (node neg) randomized to EBRT vs. Observation with:

LVSI	Stromal Invasion	Tumor Size	Patients
+	Deep 1/3	Any	128 (46%)
+	Middle 1/3	≥ 2 cm	65 (23%)
+	Superficial 1/3	≥ 5 cm	2 (0.7%)
-	Deep or Mid 1/3	≥ 4cm	82 (30%)

2 yr RFI: 88% vs 79%. RR = 0.53 , p = 0.008

**OS close to significance
Study powered to detect 46%
difference in OS (26-30%
reduction in study)**

“Sedlis” GOG 92: Early Stage Intermediate Risk



GOG 263 High Risk Early Stage

- Phase III Adjuvant EBRT vs RT-Chemo
- IA2-IIA s/p rad hyst PLND with intermediate risk factors
- Randomized to RT vs RT-Chemo
 - RT: EBRT or IMRT (28 fractions)
 - Chemo: Cisplatin 40mg/m² weekly, up to 6 weeks

High Risk Early Stage

GOG 109 High Risk Early Stage

- (1991-96) Randomized, 268 patients. Post-operative clinical stage IA2, IB, and IIA, s/p radical hysterectomy and pelvic lymphadenectomy, with *high risk features*.
- Randomized to RT vs RT+CT.
- Conclusion: Addition of cisplatin based chemotherapy to RT significantly improves progression free survival and overall survival following surgery for high-risk, early stage patients

RTOG 0724 High Risk Early Stage

- GOG 109-R also known as RTOG 724
- Randomized to RT-Chemo vs RT-Chemo followed by adjuvant chemo
 - RT: EBRT or IMRT (28 fractions)
 - Chemo: weekly cisplatin up to 6 weeks +/- Carbo/Taxol x 4 cycles

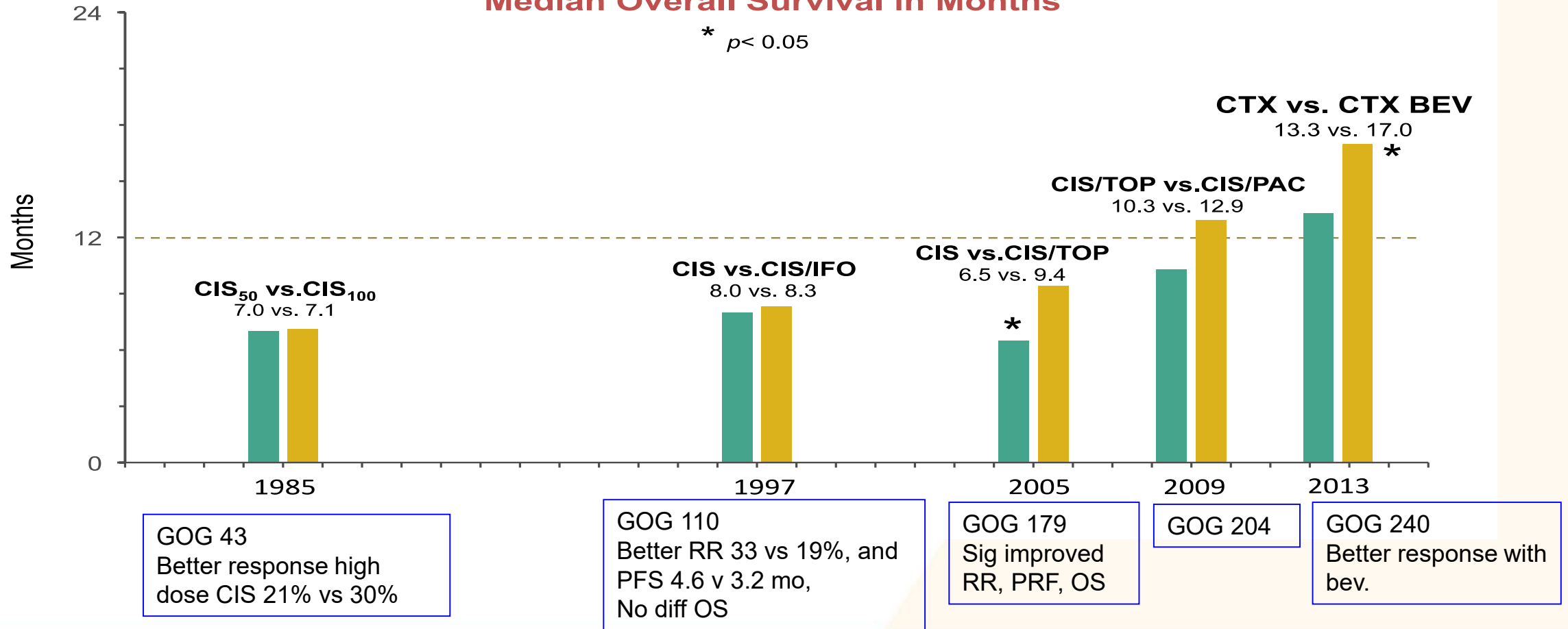
Advanced/Recurrent Disease

Chemotherapy in Advanced Cervical Cancer

Phase III Studies

Median Overall Survival in Months

* $p < 0.05$



Advanced Disease: IIB-IV

- General principles
 - Radiation is the mainstay treatment
 - Adding platinum can eradicate micrometastasis and acts as a radiation sensitizer
 - Chemo-radiation is superior to radiation alone

Immunotherapy and Cervical Cancer

Pembrolizumab for MSI-H/dMMR

- May 2017
- First drug approved by the FDA for having a biomarker (MSI-H or dMMR) for solid tumor
- Indications: adult or pediatric patient with solid tumor that have progressed following prior treatment and who have no satisfactory alternative treatment options
- Based on n=149 (multiple tumor types) across 5 trials*, 39.6% had complete or partial response. Of these, 78% had durable response ≥ 6 mo.
- Beware of immune-mediated side effects

* Trials included
Keynote-016
Keynote-164
Keynote-012
Keynote-028
Keynote-158

Summary Advanced/Recurrent Cervix

- Taxane/Platin combination is preferred
- Bevacizumab provides additional survival advantage
- Limited efficacy of other single agent drugs
- Consider pembrolizumab if tumor MSI-H or dMMR. Future trials for checkpoint inhibitors in progress without requirement of MSI-H/dMMR.



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.

THE UNIVERSITY OF TEXAS
MDAnderson
Cancer Center
Making Cancer History®

LACC Trial

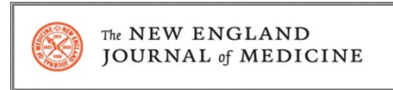
Primary Objective LACC Trial



Compare **disease-free survival at 4.5 years** amongst patients who underwent a total **laparoscopic or robotic radical hysterectomy (MIS)** vs. a **total abdominal radical hysterectomy (open)** for early stage cervical cancer.

LACC Trial

Study Schema



Open: June 2008
Accrual: 631
Closed: June 2017*

Stage IA1 LVSI,
IA2, IB1
Squamous,
Adenocarcinoma, or
Adenosquamous
Cervical Cancer

R
A
N
D
O
M
I
Z
E

Total Abdominal
Radical Hysterectomy

N= 312

Total Laparoscopic/Robotic
Radical Hysterectomy

N= 319

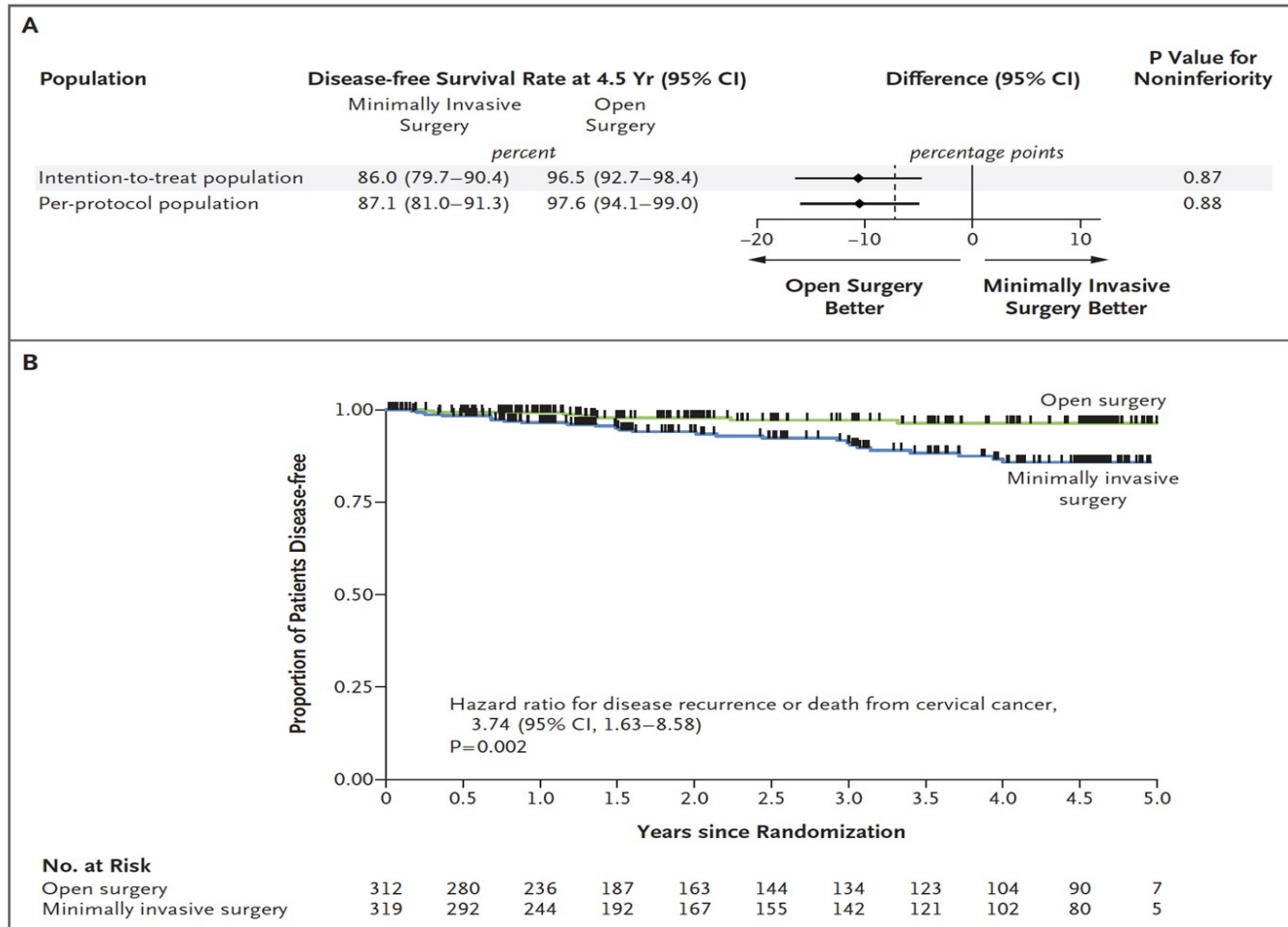
*Recommendation of study termination by DSMC

LACC Trial

Surgery by Randomized Treatment

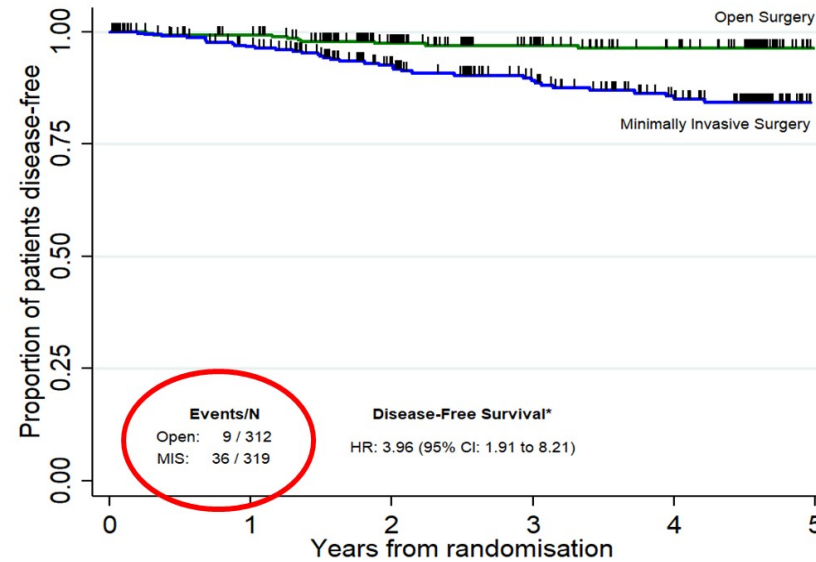
	Open	MIS
Randomized patients	312	319
• Open	274 (88%)	2 (1%)
• MIS	8 (3%)	289 (91%)
• Withdrawn prior to surgery	19 (6%)	12 (4%)
• Surgery abandoned	11 (4%)	16 (5%)
• Lost to follow-up	18 (6%)	14 (4%)
Surgery performed as randomized	274 (88%)	289 (91%)
Method of MIS	N=8	N=289
• Laparoscopic	7 (88%)	244 (84%)
• Robotic	1 (13%)	45 (16%)
MIS converted to Laparotomy	1 (0.3%)	10 (3%)

LACC Trial



LACC Trial

LACC Trial Update 2019

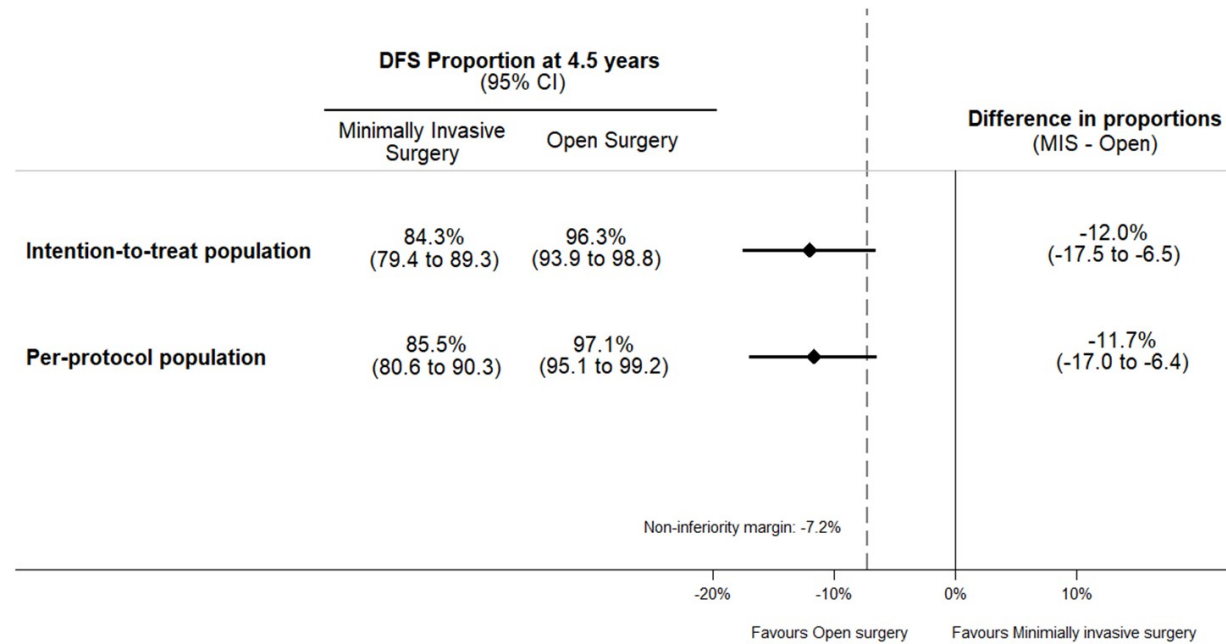


Number at risk		0	1	2	3	4	5				
Open surgery	312	(2)	280	(5)	219	(1)	162	(1)	132	(0)	11
Minimally invasive surgery	319	(10)	283	(11)	217	(7)	163	(6)	130	(2)	12

*DFS defined as disease recurrence or death due to cervical cancer

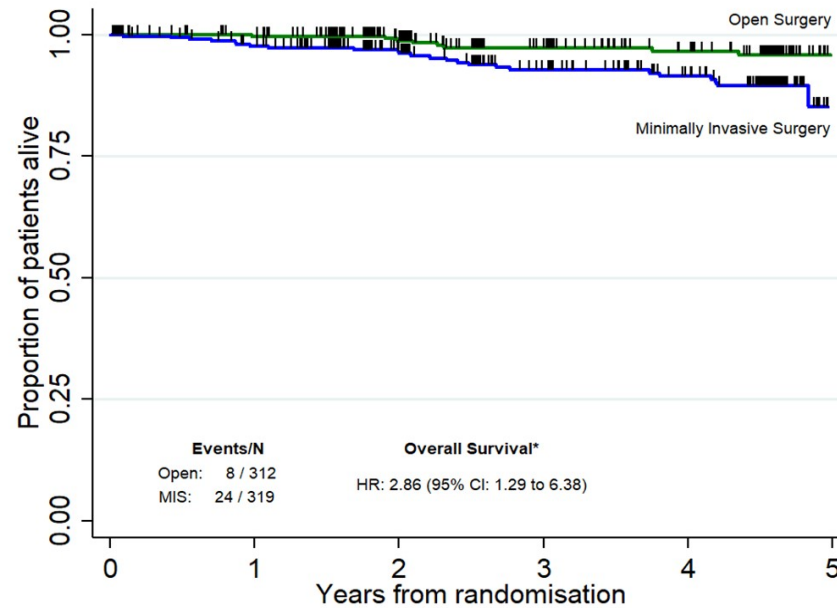
LACC Trial

LACC Trial Update 2019



LACC Trial

LACC Trial Update 2019



Number at risk		0	1	2	3	4	5				
Open surgery	312	(1)	281	(2)	223	(3)	164	(1)	134	(1)	11
Minimally invasive surgery	319	(7)	289	(4)	227	(7)	171	(2)	142	(4)	12

*OS defined as death due to any cause

The NEW ENGLAND JOURNAL of MEDICINE

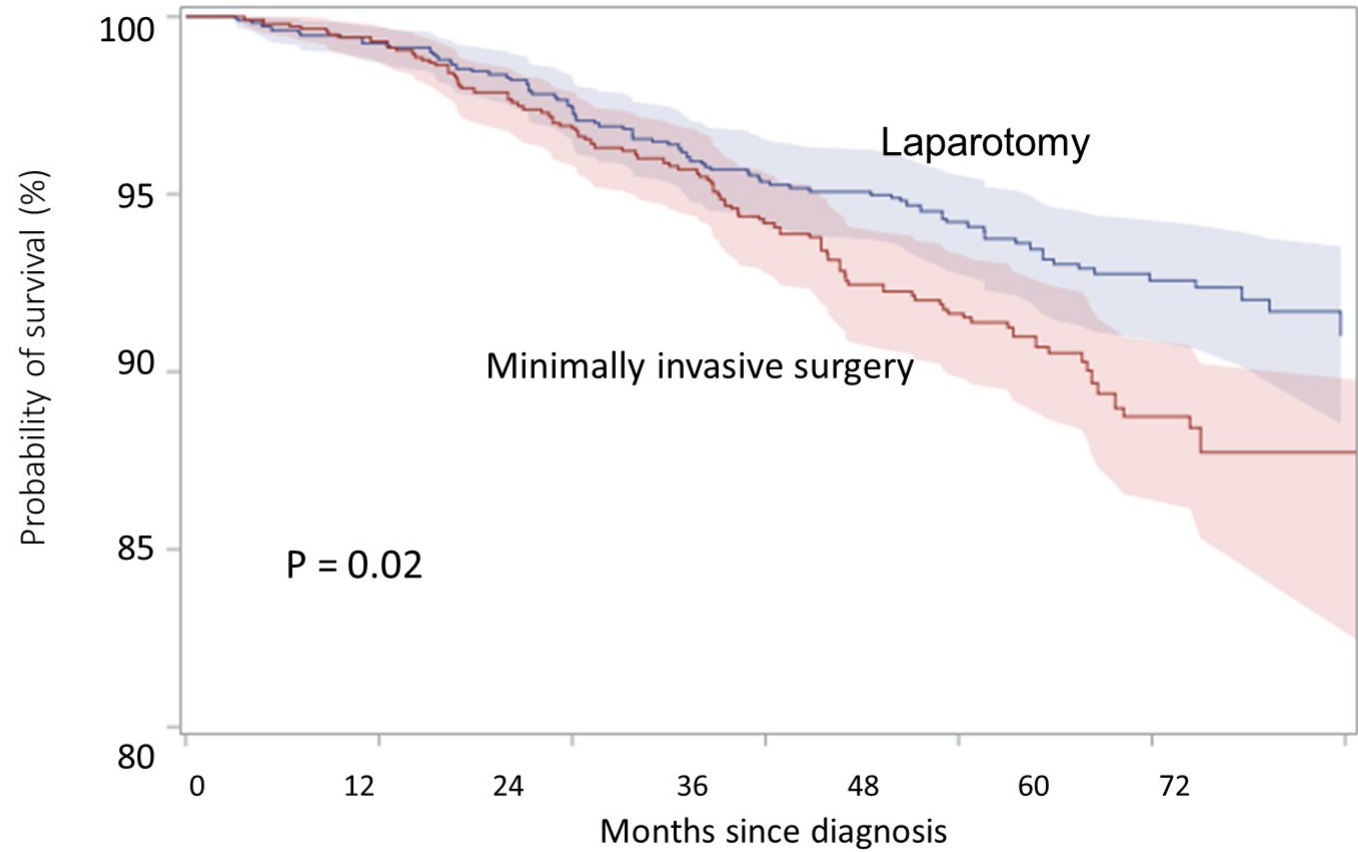
ORIGINAL ARTICLE

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.

MIS **48% higher hazard of death** from any cause compared with laparotomy (HR 1.48; 95% CI 1.10-1.98)

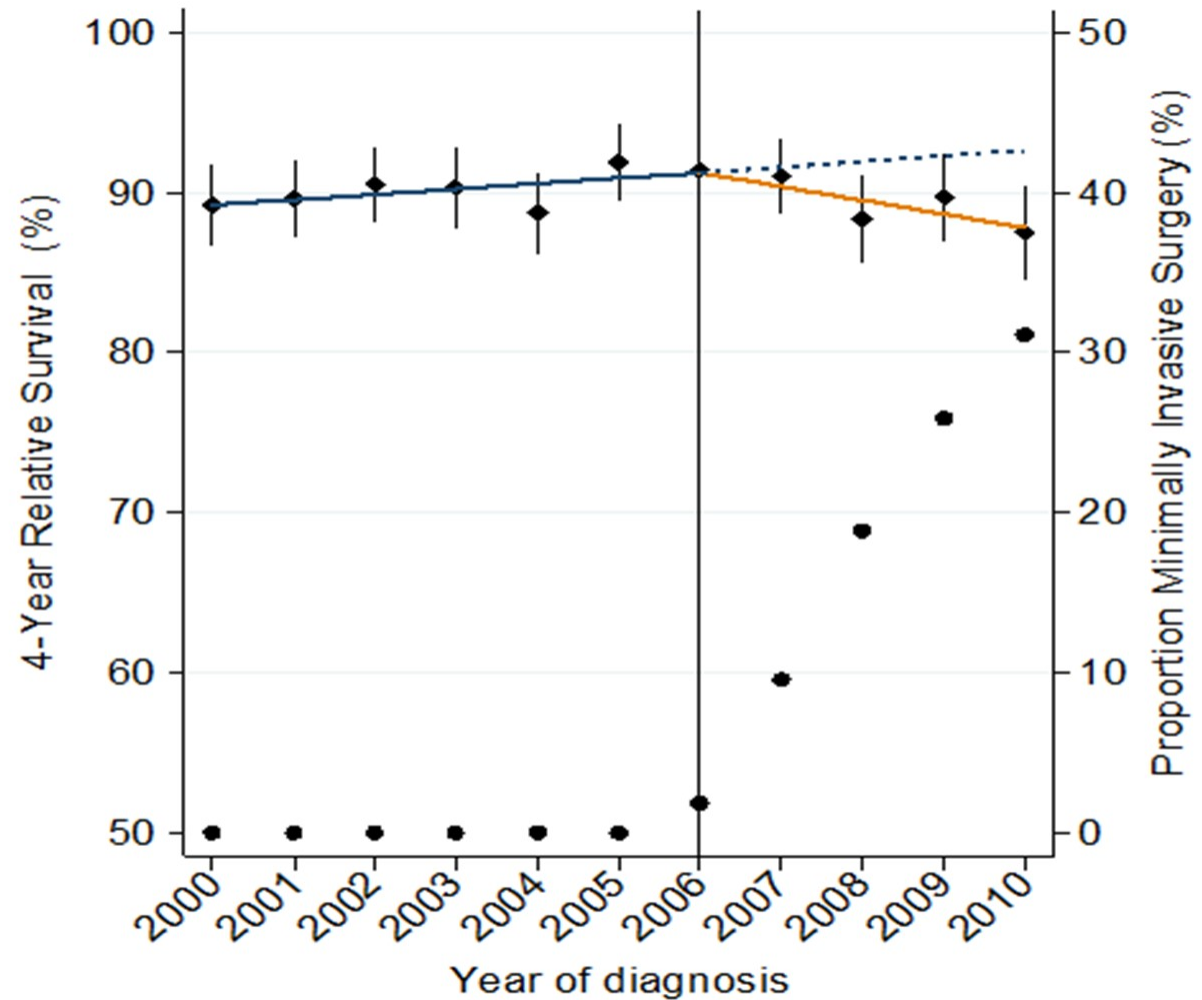
Adjusted probability of death within 4-years:
MIS (8.4%) vs. Open (5.8%)



Open	1,166	1,116	1,051	953	728	410	118
MIS	1,055	1,005	940	834	586	257	76

Time Interrupted Series (SEER Data)

Adoption of MIS was associated with a significant change of temporal trend, with **4-year survival declining by 1.0%** (95%CI 0.3-1.6 per year annually after 2006)



J Gynecol Oncol. 2018 Jul;29(4):e73
<https://doi.org/10.3802/jgo.2018.29.e73>
 pISSN 2005-0380 eISSN 2005-0399

JGO JOURNAL OF GYNECOLOGIC ONCOLOGY

Expert Opinion **Unexpected result of minimally invasive surgery for cervical cancer**

[Check for updates](#)

Hiroyuki Kanao, **Yoichi Aoki**, **Nobuhiro Takeshima**

Department of Gynecologic Oncology, Cancer Institute Hospital, Tokyo, Japan

OPEN ACCESS

LETTER TO THE EDITOR

**The LACC Trial
 Has Minimally Invasive Surgery
 for Early-Stage Cervical Cancer
 Been Dealt a Knockout Punch?**

International Journal of Gynecological Cancer • Volume 28, Number 7, September 2018

J Gynecol Oncol. 2018 Jul;29(4):e74
<https://doi.org/10.3802/jgo.2018.29.e74>
 pISSN 2005-0380 eISSN 2005-0399

JGO JOURNAL OF GYNECOLOGIC ONCOLOGY

Expert Opinion **How should gynecologic oncologists react to the unexpected results of LACC trial?**

[Check for updates](#)

Jeong-Yeol Park, **Joo-Hyun Nam**

Department of Obstetrics and Gynecology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea

OPEN ACCESS

Gabfra Science | Statement Thieme

Comment on the LACC Trial Investigating Early-stage Cervical Cancer by the Uterus Commission of the Study Group for Gynecologic Oncology (AGO) and the Study Group for Gynecologic Endoscopy (AGE) of the German Society for Gynecology and Obstetrics (DGGG)

Stellungnahme zur LACC-Studie bei frühem Zervixkarzinom der Kommission Uterus der Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) und der Arbeitsgemeinschaft Gynäkologische Endoskopie (AGE) der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe (DGGG)

J Gynecol Oncol. 2018 Jul;29(4):e75
<https://doi.org/10.3802/jgo.2018.29.e75>
 pISSN 2005-0380 eISSN 2005-0399

JGO JOURNAL OF GYNECOLOGIC ONCOLOGY

Expert Opinion **Minimally invasive surgery for cervical cancer: consequences for treatment after LACC Study**

[Check for updates](#)

Rainer Kimmig, **Thomas Lind**

¹Department of Obstetrics and Gynaecology, West German Cancer Center, University Hospital of Essen, Essen, Germany
²Department of Gynaecological Oncology, Royal Marsden Hospital, London, UK
³St. George's University of London, London, UK

OPEN ACCESS

J Gynecol Oncol. 2019 Mar;30(3):e43
<https://doi.org/10.3802/jgo.2019.30.e43>
 pISSN 2005-0380 eISSN 2005-0399

JGO JOURNAL OF GYNECOLOGIC ONCOLOGY

Correspondence **Rethinking the next step after unexpected results associated with minimally invasive radical hysterectomy for early cervical cancer**

[Check for updates](#)

Seung Yeon Pyeon, **Yun Jung Hur**, **Jong-Min Lee**



Editorial

Minimally Invasive Radical Hysterectomy Has Many Benefits Compared with Open Radical Hysterectomy: Will the LACC Trial Cause the Premature Demise of This Procedure?



Studies Warn Against Minimally Invasive Surgery for Cervical Cancer

The New York Times
"At M.D. Anderson, we have completely stopped performing minimally invasive surgery for cervical cancer," said Dr. Pedro T. Ramirez, a leading expert in minimally invasive surgery for gynecologic cancers, and the lead author of one study. "Throughout the gynecologic oncology community, we're seeing a transition back to the predominance of open surgery."
[link](#)



Minimally Invasive Surgery Is Standard for Cervical Cancer. But A New Study Shows It's Not Effective

TIME
"We learned that people in the minimally invasive surgery arm had a four times higher likelihood of having a recurrence and of potentially dying than with the approach [after four to five years] Pedro Ramirez, director of minimally invasive surgery at MD Anderson and one of the studies."
[link](#)



More deaths seen for less invasive cervical cancer surgery

Associated Press (appeared in over 250 additional outlets)
"We immediately as a department changed our practice and changed completely to the open approach," said Dr. Pedro Ramirez of the University of Texas MD Anderson Cancer Center in Houston.
[link](#)



Keyhole surgery may be riskier for cervical cancer, studies find

NBC News
The results were so startling that the University of Texas MD Anderson Cancer Center has stopped offering minimally invasive surgery for most women with early stage cervical cancer, and several of the researchers at other institutions said they were advising their patients to opt for more invasive surgery.
[link](#)



In cervical cancer surgery, minimally invasive is worse than open, study says

CNN
Small studies of minimally invasive radical hysterectomy had "shown that it was safe," though most "just focused on what happened in the short term," explained Dr. Jose Alejandro Rauh-Hain, senior author of one of the new studies and an assistant professor of gynecologic oncology and reproductive medicine at the University of Texas MD Anderson Cancer Center in Houston.
[link](#)



For Cervical Cancer Patients, Less Invasive Surgery Is Worse For Survival

NPR
"Patients who underwent the minimally invasive surgery had four times greater likelihood of [cancer] recurrence than when they had the surgery through the open approach," says Dr. Pedro Ramirez at the MD Anderson Cancer Center in Houston.
[link](#)



Minimally invasive surgery for cervical cancer may cause it to return

NBC Nightly News
Two major studies in the New England Journal of Medicine find a minimally invasive surgery for early-stage cervical cancer nearly doubles the risk of death compared to traditional surgery.
[link](#)



Less-radical surgery may pose higher death risk in early cervical cancer

Reuters
"You have a four-times greater likelihood of recurrence" with the less-invasive technique, whether or not a robot is used in the operation, said Dr. Pedro Ramirez of the University of Texas MD Anderson Cancer Center in Houston, who led a randomized comparison of the procedures published in the New England Journal of Medicine.
[link](#)



Minimally invasive surgery may not be best treatment for cervical cancer, studies show

ABC News Radio
It's believed that minimally invasive surgery using laparoscopy or robotic assisted surgery can decrease recovery time in the hospital and post-operative complications. However, at the University of Texas MD Anderson Cancer Center, two studies found that women with early stage cervical cancer actually had worse outcomes after a minimally invasive radical hysterectomy than those who underwent a traditional open abdominal hysterectomy.
[link](#)



Less-Invasive Surgery for Cervical Cancer May Bring More Risks, Studies Find

HealthDay
"Minimally invasive surgery was adopted as an alternative to open radical hysterectomy before high-quality evidence regarding its impact on survival was available," said Dr. Jose Alejandro Rauh-Hain of the University of Texas MD Anderson Cancer Center in Houston, who helped lead the study.
[link](#)



Minimally invasive surgery for cervical cancer carries higher risk of recurrence and death, MD Anderson studies find

Houston Chronicle (page one)
"The takeaway is simple: stop doing minimally invasive surgery for radical hysterectomy," said Dr. Pedro Ramirez, an MD Anderson professor of gynecologic oncology and reproductive medicine and the primary investigator of one of the studies. "It results in more cancer than open surgery."
[link](#)

Laparoscopic radical hysterectomy: An ESGO statement

LAPAROSCOPIC RADICAL HYSTERECTOMY: AN ESGO STATEMENT

Updated recommendation: Open approach is the gold standard

A randomised study by Ramirez et al. and an epidemiological study by Melamed et al. (1-2), found that the minimal invasive surgery approach for radical hysterectomy for cervical cancer is associated with shorter disease-free and overall survival than open surgery. These findings were confirmed in a recent population-based survey in England (3). In light of the results obtained by these studies, the ESGO Scientific Committee and Council herewith issue a statement that the current ESGO recommendation regarding the approach for radical surgery for cervical cancer ("Minimal invasive approach is favoured" (4)) is **no longer valid** and should be removed and replaced by "Open approach is the gold standard".

Summary of Updates

- 2017 Pembrolizumab first drug approved by the FDA for having a biomarker (MSI-H or dMMR) for solid tumor
- FIGO 2018 Staging includes advanced imaging and new stage IB3, IIIC1, IIIC2
- Surgical management no longer recommended for IB3 and IIA2
- Pelvic exenteration can still be offered but outcomes are poor
- Laparotomy should be standard of care for patients with greater than stage IA1 disease

THANK YOU.

Questions?