GLOBAL CONGRESS ON MIGS

NOVEMBER 14-17 • Austin, Texas

SYLLABUS

Debate 3 -
Cervical Cancer After the LACC Trial. Is There Still Room for MIS?

Scientific Program Chair
Mauricio S. Abrão, MD

Honorary Chair
Thomas Lyons, MD, MS

President
Ted. T.M. Lee, MD
Professional Education Information

Target Audience
This educational activity is developed to meet the needs of surgical gynecologists in practice and in training, as well as other healthcare professionals in the field of gynecology.

Accreditation
AAGL is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The AAGL designates this live activity for a maximum of 1.0 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Disclosure of Relevant Financial Relationships
As a provider accredited by the Accreditation Council for Continuing Medical Education, AAGL must ensure balance, independence, and objectivity in all CME activities to promote improvements in health care and not proprietary interests of a commercial interest. The provider controls all decisions related to identification of CME needs, determination of educational objectives, selection and presentation of content, selection of all persons and organizations that will be in a position to control the content, selection of educational methods, and evaluation of the activity. Course chairs, planning committee members, presenters, authors, moderators, panel members, and others in a position to control the content of this activity are required to disclose relevant financial relationships with commercial interests related to the subject matter of this educational activity. Learners are able to assess the potential for commercial bias in information when complete disclosure, resolution of conflicts of interest, and acknowledgment of commercial support are provided prior to the activity. Informed learners are the final safeguards in assuring that a CME activity is independent from commercial support. We believe this mechanism contributes to the transparency and accountability of CME.
Table of Contents
Session Program (Description, Learning Objectives and Course Outline) .......................................................... 1
Disclosure.......................................................................................................................................................... 2

PRO
M.M. Leitao .................................................................................................................................................. 3

CON
A.Nickles Facer ........................................................................................................................................... 13

Cultural and Linguistic Competency ........................................................................................................ 20
Debate 3-Cervical Cancer After the LACC Trial. Is There Still Room for MIS?

Chair: Javier F. Magrina

Faculty: Mario M. Leitao, Amanda Nickles Fader

In the last three decades, a greater emphasis on reducing surgical morbidity and improving quality of life for women has led to the rapid advancement of minimally invasive gynecologic surgery. Despite the existence of few randomized controlled trials supporting the use of minimally invasive hysterectomy in benign disease and endometrial cancer, there is a lack of randomized data supporting the use of minimally invasive radical hysterectomy in cervical cancer.

Despite this, retrospective data suggesting superior surgical and comparable oncologic results led to widespread acceptance of this procedure across the Americas, Europe, Asia, and Australia. However, a recent international randomized controlled trial published in the New England Journal of Medicine comparing radical open versus minimally invasive hysterectomy has called into question the efficacy and safety of the latter procedure. Using this trial as a framework, this session and debate will focus on the importance of conducting randomized surgical trials in gynecology, the challenge with performing these trials, and how to interpret the data.

Learning Objectives: At the conclusion of this activity, the participant will be able to: 1) Examine the data supporting various surgical techniques for radical hysterectomy; 2) analyze the challenges of performing randomized surgical trials; and 3) Discuss the relevance of randomized gynecologic surgery trials and how to interpret the data.
PLANNER DISCLOSURE
The following members of AAGL have been involved in the educational planning of this workshop (listed in alphabetical order by last name).

Linda J. Bell, Admin Support, AAGL*
Linda D. Bradley, MD, Medical Director, AAGL*
Erin T. Carey, MD, MSCR
Honorarium: Teleflex Medical, MedIQ
Mark W. Dassel, MD
Contracted Research: Myovant Sciences
Linda Michels, Executive Director, AAGL*
Vadim Morozov, MD
Speaker: AbbVie
Consultant: Medtronic, Lumenis
Erinn M. Myers, MD
Speakers Bureau: Laborie Medical Technologies, Teleflex Medical
Other: Unrestricted educational grant to support NC FPMRS Fellow Cadaver Lab: Boston Scientific Corp. Inc.
Amy Park, MD
Speaker: Allergan
Nancy Williams, COO, CME Consultants*
Harold Y. Wu, MD*
Javier F. Magrina, MD*

FACULTY DISCLOSURE
The following have agreed to provide verbal disclosure of their relationships prior to their presentations. They have also agreed to support their presentations and clinical recommendations with the “best available evidence” from medical literature (in alphabetical order by last name).

Mario M. Leitao, Jr., MD
Consultant: Intuitive Surgical, Ethicon Endo-Surgery, Takeda, and Medtronic
Contracted Research: KCI/Acelity
Advisory Board: J&J/Ethicon
Lab Proctor: Intuitive Surgical
Amanda Nickles Fader, MD*

Content Reviewers have nothing to disclose.

Asterisk (*) denotes no financial relationships to disclose.

All relevant financial relationships noted have been mitigated.
Cervical cancer after the LACC trial: There is still room for MIS!

Mario M. Leitao, Jr., MD
Member & Attending Surgeon, Gynecology Service
Director, Gynecologic Oncology Fellowship Program
Director, Minimal Access and Robotic Surgery (MARS) Program
Department of Surgery
Professor, Weill Cornell Medical College

Cervical cancer after the LACC trial: There is still room for MIS!

Disclosure

Consultant: Intuitive Surgical, Ethicon Endo-Surgery, Takeda, and Medtronic
Contracted Research: KCI/Acelity
Advisory Board: J&J/Ethicon
Lab Proctor: Intuitive Surgical

LACC Trial

Primary outcome

Based on less than optimal outcomes in mostly 13 out of only 33 centers in the world....

NO MORE MIS for radical hysterectomy for all the patients being treated at the more than 16,500 hospitals in the world for the end of time!
LACC Trial

One of the conclusions

outcome. Finally, the results of this trial cannot be generalized to patients with “low-risk” cervical cancer (tumor size, <2 cm; no lymphovascular invasion; depth of invasion, <10 mm; and no lymph-node involvement), because the trial was not powered to evaluate the oncologic outcomes of the two surgical approaches in that context.

THIS IS NOT a CONFIRMATORY study
NOTHING more than a retrospective DB study

MIS cervix DB study

Cancer-specific survival – true scale

MIS cervix DB study

Time interrupted analyses - OS

What exactly were we doing from 2000-06 that would even account for this “increasing survival rate”?

LACC Trial

Is an internally valid trial!

• Appropriate statistical design
• Appropriate randomization trial
• Cohorts are of the same characteristics
• Majority of the surgeons are respected GYN ONC
• Surgeries were appropriately radical
• Appropriately stopped early by DSMB
• Analyzed appropriately
• RCTs only enroll a fraction of the eligible population
Ecological Fallacy falsely assumes that every surgeon’s outcomes are poor, since the average outcome in the class is poor.

I acknowledge....

- The many “confirmatory” studies
  - ALL retrospective
  - ALL prone to the same issue that may have led to LACC results
  - Only those “confirming” LACC results seem to be best?
- The 2 cm cutoff
- The many news and press releases
- The societal and guideline statements

RBT vs OPEN rad hysts

*Swedish Quality Register of Gynaecologic Cancer*

- SQRGC
- Cervical cancer centralized to only 7 university centers
- All women treated are registered in this register
- Robotic platform introduced in 2005 in Sweden
- Only few GYN ONCs at each center perform rad hysts
- Uterine manipulators not used
- 236 OPEN; 628 ROBOTIC


**SQRGC - DFS**

- Overall 5-yr DFS
  - OPEN: 84%
  - RBT: 89%
- Propensity matched 5-yr DFS
  - OPEN: 85%
  - RBT: 84%
  - HR: 1.08 (95%CI:0.66-1.78); P=0.8

RBT vs OPEN rad hysts

*Netherlands Cancer Registry – IPTW adjusted*

- LRS v OPEN rad hysts
  - 2010-2017
  - 9 specialized centers
  - IA2-IIA1


**LRS v OPEN rad hysts**

- 5-yr PFS
  - 90.2% LRS/89.4% OPEN
- 5-yr OS
  - 95.5% LRS/95.2% OPEN
  - **P=0.01** [95%CI:0.00-0.02]
**Stage IA cervical cancer**

*Netherlands Cancer Registry*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparotomy</td>
<td>1.00</td>
<td>1.00-1.00</td>
</tr>
<tr>
<td>Sterilization</td>
<td>0.00</td>
<td>0.00-100.00</td>
</tr>
<tr>
<td>Byselysis</td>
<td>0.00</td>
<td>0.00-200.00</td>
</tr>
<tr>
<td>Beviation</td>
<td>0.00</td>
<td>0.00-141.00</td>
</tr>
<tr>
<td>Beviation</td>
<td>0.00</td>
<td>0.00-141.00</td>
</tr>
<tr>
<td>Beviation</td>
<td>0.00</td>
<td>0.00-141.00</td>
</tr>
<tr>
<td>Beviation</td>
<td>0.00</td>
<td>0.00-141.00</td>
</tr>
<tr>
<td>Beviation</td>
<td>0.00</td>
<td>0.00-141.00</td>
</tr>
<tr>
<td>Beviation</td>
<td>0.00</td>
<td>0.00-141.00</td>
</tr>
<tr>
<td>Beviation</td>
<td>0.00</td>
<td>0.00-141.00</td>
</tr>
<tr>
<td>Beviation</td>
<td>0.00</td>
<td>0.00-141.00</td>
</tr>
</tbody>
</table>

Weighted Cox regression analysis with propensity score, based on IPTW

**Stage IA cervical cancer**

*Netherlands Cancer Registry*

- **Weighted Cox regression analysis with propensity score, based on IPTW**

**Stage IB and <2 cm**

*Four C DB (China)*

- **Med F/U (months)**
  - LRH: 42
  - ARH: 48
  - *P*-value: 0.5

**Stage IB2-IB2**

*The CIRCOL Group Study (Brazil - multicenter)*

- **Radiotherapy for stage IB2-IB2**
  - Radiotherapy for stage IB2-IB2
  - Radiotherapy for stage IB2-IB2

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparotomy</td>
<td>1.00</td>
<td>1.00-1.00</td>
</tr>
<tr>
<td>Sterilization</td>
<td>0.00</td>
<td>0.00-100.00</td>
</tr>
<tr>
<td>Byselysis</td>
<td>0.00</td>
<td>0.00-200.00</td>
</tr>
<tr>
<td>Beviation</td>
<td>0.00</td>
<td>0.00-141.00</td>
</tr>
<tr>
<td>Beviation</td>
<td>0.00</td>
<td>0.00-141.00</td>
</tr>
<tr>
<td>Beviation</td>
<td>0.00</td>
<td>0.00-141.00</td>
</tr>
<tr>
<td>Beviation</td>
<td>0.00</td>
<td>0.00-141.00</td>
</tr>
<tr>
<td>Beviation</td>
<td>0.00</td>
<td>0.00-141.00</td>
</tr>
<tr>
<td>Beviation</td>
<td>0.00</td>
<td>0.00-141.00</td>
</tr>
<tr>
<td>Beviation</td>
<td>0.00</td>
<td>0.00-141.00</td>
</tr>
<tr>
<td>Beviation</td>
<td>0.00</td>
<td>0.00-141.00</td>
</tr>
<tr>
<td>Beviation</td>
<td>0.00</td>
<td>0.00-141.00</td>
</tr>
</tbody>
</table>

Weighted Cox regression analysis with propensity score, based on IPTW
2018 IA2-IB2
The CIRCOL Group Study (Brazil - multicenter)


Median F/U (mo): 59.1 OPEN vs 39.3 MIS (P<0.001)
Median time to recur: 19 vs 21.1 (P=0.89)

MIS: 37 mo
OPEN: 40 mo

More IB1
More adenoca
More tumors >2cm
More LVSI
Less LN mets

SO, if desires fertility...

OK to do MIS radical tracheectomy

BUT...

If not, same patient has to be OPEN radical hysterectomy?
ConCerv: a prospective trial of conservative surgery for low-risk early-stage cervical cancer

- FIGO 2009 stage IA2-IB1
- SCC (any grade), adenocarcinoma (G1 or 2)
- Tumor <=2cm by exam and/or imaging
- NO LVS
- No mets on CT scan, MRI and/or PET
- DOI <=10mm
- Cone margins and ECC negative for cancer or high-grade dysplasia
- Repeat cone allowed

ConCerv: a prospective trial of conservative surgery for low-risk early-stage cervical cancer

- Fertility sparing – LN assessment alone
- Not desiring fertility – Simple hyst + LN assessment
- Also allowed cases that underwent an "inadvertent" hysterectomy – taken back for LN assessment
- Would be an infeasible approach if the immediate failure rate (residual in uterus) exceeded 3%
- Additional stopping rule if 2 or more patients recurred

MSKCC Radical Hysterectomy

Cases

280 rad hyst cases:

196 cases for analysis

MIS rad hyst at MSKCC

All cases outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>IA %</th>
<th>OPEN %</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-yr DFS (%)</td>
<td>87.0 (3.4)</td>
<td>86.6 (4.5)</td>
<td>0.92</td>
</tr>
<tr>
<td>5-yr OS (%)</td>
<td>96.5 (2.6)</td>
<td>87.4 (4.9)</td>
<td>0.15</td>
</tr>
<tr>
<td>5-yr DSS (%)</td>
<td>96.5 (2.6)</td>
<td>93.9 (3.5)</td>
<td>0.93</td>
</tr>
</tbody>
</table>


MIS rad hysts at MSKCC
IA1-IB1 SCC, adeno, adenosq (>2cm)

<table>
<thead>
<tr>
<th>Variable</th>
<th>MI S</th>
<th>OPEN</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-yr DFS (%)</td>
<td>86.3 (5.8)</td>
<td>76.9 (8.4)</td>
<td>0.44</td>
</tr>
<tr>
<td>5-yr OS (%)</td>
<td>93.7 (2.0)</td>
<td>79.3 (9.4)</td>
<td>0.23</td>
</tr>
<tr>
<td>5-yr DSS (%)</td>
<td>93.7 (4.4)</td>
<td>83.8 (8.8)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

No recurrences in IA1(LVI)-IA2 (N=18)
No recurrences if no residual in uterus (N=37)

What is the mechanism for surgical approach impacting recurrence when there is absolutely no cancer left in the organ??

MIS rad hysts at MSKCC
IB1 with residual in uterus

<table>
<thead>
<tr>
<th>Variable</th>
<th>MI S</th>
<th>OPEN</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-yr DFS (%)</td>
<td>82.1 (4.8)</td>
<td>85.0 (5.0)</td>
<td>0.55</td>
</tr>
<tr>
<td>5-yr OS (%)</td>
<td>95.2 (2.7)</td>
<td>86.1 (5.3)</td>
<td>0.28</td>
</tr>
<tr>
<td>5-yr DSS (%)</td>
<td>95.2 (2.7)</td>
<td>93.2 (3.8)</td>
<td>0.88</td>
</tr>
</tbody>
</table>

MIS group recurrences with patient who declined adj Rx and one with glassy cell

LACC Trial results
My humble thoughts

- A random error rate of 16% (Power was 84%)
  - Outcomes among the best ever in the OPEN arm
  - Basis of statistical sampling natural error and RCT natural error
  - This justifies need for another RCT to either validate or refute LACC findings

Rad hysterectomy
DFS in OPEN cohorts

LACC was a non-inferiority design—all other analyses are superiority

LACC Trial results
My humble thoughts

- Possible inappropriate case selection
  - No preoperative MRI
  - Patients undergoing surgery who shouldn't have
  - Do rectal cancer patients have surgery based on a digital rectal exam alone?
- Technique
  - Not a radicality issue
  - Not a CO2 issue
  - Technique error in MIS in larger tumors truly IB1 (2-4 cm) and in tumors that weren't truly IB1
  - Lack of tumor containment

Cervical cancer – newly diagnosed
MSKCC post-LACC

- Abdominal approach is an appropriate option for all cases
- MIS (robotic only) approach is also an appropriate option for “select” cases
- Preop MRI on all cases
- Preop CT scan (+/-PET) on select cases

Cervical cancer – newly diagnosed
MIS not appropriate

- Stage IB2 (FIGO 2008) or greater
  - No MIS
  - Probably best for chemoradiation

MIS radical hysterectomy
Tumor containment methods

- Stapled colpotomy
- Vaginal colpotomy after robotic radical dissection
- Vaginal mucosal incision and oversewn over tumor prior to colpotomy
- Vaginal "cerclage" intracorporeally
Stapled colpotomy

Radical Hysterectomy at MSKCC

**Prospective QA Program**

- Initiated January 1, 2017
- All clinics screened for new cervical cancer patients
- Clinical FIGO IA1(LVI)-IB2
- All cases undergoing radical hysterectomy tracked and outcomes assessed every 6 months
- Dedicated research fellow, research assistant
- Supervised and reviewed by faculty member
- Primary rad hysts (include inadvertent simple hysts)
- Planned rad trachs that converted to hyst intraop
- Exclude neoadjuvant cases
- Exclude clear cell, gastric, small cell neuroendocrine histologies

Prospective QA – 1/1/17 to 6/16/21

<table>
<thead>
<tr>
<th>MIS</th>
<th>N (%)</th>
<th>OPEN</th>
<th>N (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>51</td>
<td>54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIGO</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA1(LVI)</td>
<td>1 (2.0)</td>
<td>0 (0.0)</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>IA2</td>
<td>12 (23.5)</td>
<td>12 (22.2)</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>IB1</td>
<td>36 (70.6)</td>
<td>36 (66.7)</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>IB2</td>
<td>2 (3.9)</td>
<td>2 (3.7)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCC</td>
<td>26 (51.0)</td>
<td>26 (48.1)</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>Adenoca</td>
<td>24 (47.1)</td>
<td>24 (44.4)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Adenosquamous</td>
<td>1 (2.0)</td>
<td>1 (1.9)</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>Margin positive</td>
<td>41 (80.4)</td>
<td>41 (75.9)</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>LVSI</td>
<td>21 (41.2)</td>
<td>21 (41.2)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Residual in uterus</td>
<td>41 (80.4)</td>
<td>41 (75.9)</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>Tumor ≥ 2 cm at hyst</td>
<td>21 (41.2)</td>
<td>21 (41.2)</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

**MIS**

- LN assessment
- LND only
- SLN algorithm
- SLN+LND
- None

- Node positive**: 13/47 (27.7) vs 5/51 (9.8), P=0.02
- LN met type
  - ITC
  - Micromet
  - Macromet
  - Carcinoma, NOS

- Adjuvant RX given 23 (45.1) vs 17 (31.5), P=0.15

**Recurred 4 (7.8) vs 5 (9.3), P=1.0**
**Died 0 vs 0**
**Med F/U 39.4 (0.43-53.13) vs 20.7 (0.5-52.1), P<0.001**

2-yr PFS: 92.9% (MIS) vs 88.3% (OPEN), P=0.22
GOG 3043: A Randomized Controlled Trial of Robotic* versus Open Radical Hysterectomy for Cervical Cancer (ROCC trial)

(*with tumor containment prior to colpotomy)

PI: Kristin Bixel, MD
Co-PI: Mario Leitao, MD; Leslie Randall, MD

Funding: Unrestricted research grant awarded to GOG Partners from the Intuitive Foundation

IA2-IB2 (FIGO 2018)

- Histology: SCC, adeno, adenosquamous
- MRI required
- Uterus <12 cm and amenable to vaginal delivery of specimen

Open radical hysterectomy + LN assessment (N=420)
Robotic radical hysterectomy* + LN assessment (N=420)

*Tumor containment methods:
1) Vaginal colpotomy following radical dissection
2) Vaginal closure prior to intracorporeal colpotomy

Primary outcome: 3 year DFS
Secondary outcomes:
- DSS/OS
- Patterns of recurrence
- Intra-op/Post-op comps
- PRO’s
- Lymphedema

Randomized 1:1
83/90 (92%) sites “interested” in enrolling

We must be illuminated by the LACC trial and learn

NOT... All or none!

This is an opportunity to improve our MIS approach with better patient selection and adherence to sound oncologic principles...

Not simply abandoning MIS

THANK YOU!
A “LACC” of Prior Data: Why We Should Reconsider MIS in Early-Stage Cervical Cancer

Amanda Nickles Fader, MD
Professor and Vice Chair of GYN Surgical Operations
The Kelly Gynecologic Oncology Service
Johns Hopkins Medicine

Disclosures

• I have no financial disclosures.

• ~65% of my cases are minimally invasive, and MIS is a clinical and academic passion.

• I have no affiliation with the LACC trial.

My Esteemed Debate Opponent

Objectives

• Critically appraise the contemporary surgical literature on management of early-stage cervical cancer

• Demonstrate with compelling evidence that MIS radical hysterectomy in this setting is harmful to women

• Discuss unanswered questions

ORIGINAL ARTICLE

Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer

Pedro T. Ramires, M.D., Michael Frumovitz, M.D., Rene Pueyo, M.D., Aldo Lopez, M.D., Mariano Vena, M.D., Reitan Riboni, M.D., Alessandro Ruda, M.D., Xiaojian Yan, M.D., Xia Shuchong, M.D., Neville Cherry, M.D., David Iara, M.D., Mariano Tamura, M.D., Tao Zhu, M.D., Kingsley P. Bafetila, Ph.D., Val Gelinski, M.S., Rebecca Asher, M.S., Vanessa Bohan, B.S.N., James L. NcKlin, M.D., Robert L. Coleman, M.D., and Andreas Obermair, M.D.
Trial Conclusions

- Disease-free survival at 4.5 years for minimally invasive radical hysterectomy was inferior (86%) compared to the open surgery (96.5%)
- The 4-year mortality was 9.1% among women who underwent minimally invasive radical hysterectomy and 5.3% among those who underwent open surgery (p=0.002)

Challenges of a Surgical Trial

- Identifying appropriate outcome
- Number of cases required
- Consistency of care
- Surgeon and patient variables
- Assessment of surgical intervention
- Funding

A Problematic Premise and Surgeon Bias

- Literature demonstrates that surgeons/physicians are more likely to be skeptical and to distrust an outcome from a study when it is not aligned with their core beliefs or personal experiences!
- The experimental study arm (MIS) is the dominant method of performing radical hysterectomy in most countries!
High-volume cervical cancer surgeons

- Submission of 10 cases of MIS to Trial Management Committee
  - Age
  - BMI
  - Stage
  - Intraop and postop complications (<30 days)
  - OR time
  - Transfusion rates
- Total of 2 un-edited videos of MIS
- Independent Review 2 members of Trial Management Committee

National Cancer Database Study
Hospital cancer registries that cover 70% of new cancer diagnoses in the U.S.

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%)

Premier Cohort (2010-2015)
43,629 women with cervical cancer
2,830 had a radical hysterectomy
1,277 (49%) Open Radical Hysterectomy (ORH)
1,481 (56%) Robotic Radical Hysterectomy (RRH)
169 (6%) Laparoscopic Radical Hysterectomy (LRH)

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)

Overall Survival by Tumor Size

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.,
Minimally invasive surgery versus open surgery for radical hysterectomy as a primary treatment in patients with stage IB1-IIA2 cervical cancer (Abstract 12539)

- 5yr PFS*: 84.9% vs. 80.2%
- Less proportion of IB1-IIA2 and parametrial invasion in MIS than in open arm

- *adjusted HR = 2.160, 95% CI 1.371–3.404, P = 0.001
- Fewer IIA2 and parametrial invasion cases in MIS than in open arm
- No difference in LR population (<2cm tumor size at pre-op MRI, pre-op conization)
- No difference in MIS receiving Intracorporeal vs Vaginal Colpotomy

Impact of surgical approach on survival outcomes in women undergoing radical hysterectomy for cervical cancer: a population based cohort (Abstract 12677)

- 5yr PFS: 89.2% vs. 87.2%
- 5yr OS: 92.9% vs. 91.8%
- *2x higher HR for recurrence and death in Stage IB receiving MIS

Criticism #2: “The open hysterectomy outcomes are TOO good; the data is unexpected and not aligned with prior publications.”

Preponderance of data SURGICAL and NOT based on long-term clinical or SURVIVAL outcomes

- 96%+ of articles are retrospective report on surgical/perioperative outcomes ONLY and omit data on long-term clinical or survival outcomes
- Randomized and non-randomized data can be divergent in direction as well as magnitude.
- 2/3 prior RCTs in early-stage cervical cancer enriched by patients at intermediate or high risks of recurrence

Criticism #3: There is missing patient data and post-surgery treatment wasn’t standardized.

Missing Data in the LACC Trial

- Surgical cohorts well balanced for:
  - All demographic variables
  - Age
  - Stz
  - Ov
  - Nv
  - Pn
  - Mi

- 5-8% missing data considered acceptable in RCTs as long as well balanced in the treatment arms.

- Some “missing” data was not missing at all, it pertained to women who had no residual tumor post-hysterectomy, and therefore, did not have tumoral variables to report.

Adjuvant Treatment by Randomized Treatment

<table>
<thead>
<tr>
<th>Eligible patients</th>
<th>TARH</th>
<th>MIS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients treated with <strong>either</strong> chemo or radiotherapy</td>
<td>86 (28%)</td>
<td>92 (29%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Total patients treated with <strong>at least one cycle of chemotherapy</strong></td>
<td>66 (21%)</td>
<td>72 (23%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Total patients treated with <strong>at least one dose of radiotherapy</strong></td>
<td>73 (23%)</td>
<td>81 (25%)</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>Time to initiation of adjuvant therapy(days)</strong></td>
<td>46 (33-70)</td>
<td>41 (31-57)</td>
<td></td>
</tr>
</tbody>
</table>

LACC trial has flaws…but all other data on the matter is more flawed

- Flaws of retrospective data
  - Sequential comparisons
  - Unbalanced groups
  - Lack of focus on oncologic outcomes

“Early trial closure strongly recommended given the findings of worse mortality in the MIS arm.”
  - The LACC Trial DSMB

Criticism #4: The trial closed early with only 85% of participants enrolled. Was the primary study endpoint met and are the statistics valid?
Primary Outcome: DFS at 4.5 years (expected 90%)

- **HR**: 3.74 (95% CI 1.63 - 8.58), p=0.002
- **Events/N**
  - TARH: 7/312
  - MIS: 27/319

Statistics reviewed by:
- Two NEJM Statisticians
- Two National Cancer Institute Senior Statisticians
- One Trials Statistician at Johns Hopkins

Criticism 5: “Few patients were enrolled each year from each site.”

Criticism #6: The surgical-related morbidity and mortality will be worse in the laparotomy arm.
Summary of Complications

<table>
<thead>
<tr>
<th></th>
<th>Open (n = 257)</th>
<th>MIS (n = 279)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-operative complications</td>
<td>26 (10%)</td>
<td>34 (12%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Early post-operative morbidity</td>
<td>82 (32%)</td>
<td>93 (33%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Delayed morbidity</td>
<td>43 (17%)</td>
<td>53 (19%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Major Adverse Events</td>
<td>45 (17.5%)</td>
<td>46 (16.5%)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

In Summary....

• Surgical trials challenging to conduct and interpret.

• Surgeons have invested years in perfecting MIS techniques and hospitals, in technologies to help them get there.

• Retrospective, single or multi-site institution data **DOES NOT** trump international, multi-site RCT and epidemiologic data demonstrating worse survival outcomes in cervical cancer with MIS radical hysterectomy.

• More data needed to determine which patients may potentially be safely offered MIS but certainly not for IB tumors.

• But in the setting of cervical cancer...these are young and middle-aged women diagnosed with an **EARLY-STAGE** and **CURABLE** malignancy.

How Are We Going to Counsel Our Patients?

• No major difference in intraoperative complications

• No difference in long-term morbidities

• Almost 4x more likely to recur with MIS radical hysterectomy

• 6x more likely to die after MIS radical hysterectomy

We must balance surgical innovation with good science!

Oncologic neutrality **MUST** be demonstrated!

Mario, there’s no escaping the data...

Thank you!
Assembly Bill 1195 was signed into law on July 1, 2006 requiring local CME providers, such as the AAGL, to assist in enhancing the cultural and linguistic competency of California’s physicians (researchers and doctors without patient contact are exempt). This mandate follows the federal Civil Rights Act of 1964, Executive Order 13166 (2000) and the Dymally-Alatorre Bilingual Services Act (1973), all of which recognize, as confirmed by the US Census Bureau, that substantial numbers of patients possess limited English proficiency (LEP). It is the intent of the Legislature to encourage physicians and surgeons, continuing medical education providers located in California, and the Accreditation Council for Continuing Medical Education to meet the cultural and linguistic concerns of a diverse patient population through appropriate professional development.

Linguistic Competence: Providing readily available, culturally appropriate oral and written language services to limited English proficiency (LEP) members through such means as bilingual/bicultural staff, trained medical interpreters, and qualified translators.

Cultural Competence: A set of congruent behaviors, attitudes, and policies that come together in a system or agency or among professionals that enables effective interactions in a cross-cultural framework.1

Cultural and Linguistic Competence: The ability of health care providers and health care organizations to understand and respond effectively to the cultural and linguistic needs brought by the patient to the health care encounter.

Cultural competence requires organizations and their personnel to:
• Value diversity.
• Assess themselves.
• Manage the dynamics of difference.
• Acquire and institutionalize cultural knowledge.
• Adapt to diversity and the cultural contexts of individuals and communities served.

California Business & Professions Code §2190.1(c)(3) states that associations that accredit continuing medical education courses shall develop standards before July 1, 2006, for compliance with the cultural competency requirements. The associations may update these standards, as needed, in conjunction with an advisory group that has expertise in cultural and linguistic competency issues. Cultural competency means a set of integrated attitudes, knowledge, and skills that enables a health care professional or organization to care effectively for patients from diverse cultures, groups, and communities. At a minimum, cultural competency is recommended to include the following: (A) Applying linguistic skills to communicate effectively with the target population. (B) Utilizing cultural information to establish therapeutic relationships. (C) Eliciting and incorporating pertinent cultural data in diagnosis and treatment. (D) Understanding and applying cultural and ethnic data to the process of clinical care, including, as appropriate, information pertinent to the appropriate treatment of, and provision of care to, the lesbian, gay, bisexual, transgender, and intersex communities.

Title VI of the Civil Rights Act of 1964 prohibits recipients of federal financial assistance from discriminating against or otherwise excluding individuals on the basis of race, color, or national origin in any of their activities. In 1974, the US Supreme Court recognized LEP individuals as potential victims of national origin discrimination. In all situations, federal agencies are required to assess the number or proportion of LEP individuals in the eligible service population, the frequency with which they come into contact with the program, the importance of the services, and the resources available to the recipient, including the mix of oral and written language services. Additional details may be found in the Department of Justice Policy Guidance Document: Enforcement of Title VI of the Civil Rights Act of 1964 http://www.usdoj.gov/crt/cor/pubs.htm.

Executive Order 13166, “Improving Access to Services for Persons with Limited English Proficiency”, signed by the President on August 11, 2000 http://www.usdoj.gov/crt/cor/13166.htm was the genesis of the Guidance Document mentioned above. The Executive Order requires all federal agencies, including those which provide federal financial assistance, to examine the services they provide, identify any need for services to LEP individuals, and develop and implement a system to provide those services so LEP persons can have meaningful access.

Dymally-Alatorre Bilingual Services Act (Assembly Bill 305) requires that state agencies that serve a substantial number of non-English-speaking people employ a sufficient amount of bilingual persons in order to provide certain information and render certain services in a language other than English.