Recent Updates in Cervical Cancer

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Chairperson, FIGO Committee for Gynecologic Oncology (2015-18)
Secretary-General, IFCPC; Council Member, ASGO
Past President, AOGIN; Past President, AGOI
What is new in CaCx in 2018-19?

• GLOBOCAN 2018
• Revised FIGO Staging of CaCx 2018
• LACC trial and its implications
• National Program for Screening for Oral, Breast and Cervical Cancer
• HPV vaccination programs – Punjab, Sikkim, Delhi
• Updates in HPV vaccination
• WHO Call for Elimination of Cervical Cancer by 2030
Number of new cases in 2018, both sexes, all ages

- Lung: 2,093,876 (11.6%)
- Breast: 2,088,849 (11.6%)
- Colorectum: 1,849,518 (10.2%)
- Prostate: 1,276,106 (7.1%)
- Stomach: 1,033,701 (5.7%)
- Breast: 569,847 (3.2%)
- Oesophagus: 572,034 (3.2%)
- Liver: 841,080 (4.7%)

Total: 18,078,957 cases

Number of deaths in 2018, both sexes, all ages

- Lung: 1,761,007 (17.8%)
- Colorectum: 880,792 (8.9%)
- Cervix uteri: 311,365 (3.2%)
- Prostate: 358,989 (3.6%)
- Pancreas: 432,242 (4.4%)
- Oesophagus: 506,585 (5.2%)

Total: 9,555,027 deaths

Data source: GLOBOCAN 2018
Graph production: IARC (http://gco.iarc.fr/today)
World Health Organization

Cervical cancer – an avoidable NCD with gross inequities (GLOBOCAN 2018)

Estimated age-standardized incidence rates (World) in 2018, cervix uteri, all ages

Globally 569,847 new cases annually
India 96,9222
Globally 311,365 deaths annually
India 60,078
REVISED FIGO STAGING
Cervical cancer was the first cancer to be assigned a staging system!
FIGO’s perspective on staging

• FIGO is sensitive to different resources in various parts of the world and the need for equal participation and access from less resourced countries
• In endometrial and ovarian cancers, where the mainstay of treatment is surgery, changed to surgico-pathological staging (last revision in 2009 and 2014 respectively)
• Cervical cancer, mainly a disease of low resource regions, with radiation an important treatment option, continued to be staged clinically (last revision in 2009).
Changes in scenario since 2009

- Imaging capability increased significantly globally
  - Though significantly lacking in many regions that bear the burden of cervical cancer, advanced imaging technology is available in many parts of LMICs also
  - Image-guided FNA also being practiced at several centers
- Advances in minimally invasive surgery (MIS)
  - Increased practice of “surgical staging” even without MIS.
- Increasing use of fertility-sparing surgery (radical trachelectomy)
  - Data on correlation of size of tumor with outcomes
Cervical cancer staging – Questions

☒ Should it continue to be clinical?
✓ Should we include lymph node status and pathological findings on tumor size in staging?
✓ Should we include imaging in staging?
☒ Should we have different staging for different resource settings?
Stage wise survival in cancer cervix

Accuracy of clinical staging of CaCx

• 24%–39% error rate in staging by clinical exams$^{1,2,3}$
• Without cross-sectional imaging, poor evaluation of deep pelvic invasion
• Accuracy in early stage$^{4,5}$
  • IA1-IB1 85%
  • IIA 35%
  • IIB 21%

Clinical staging – Lacunae

- Significant prognostic factors are not assessed
  - Tumor volume
  - Nodal metastasis
  - Stromal invasion
  - Lower uterine segment involvement
- Data collection is incomplete for further research when based only on clinical staging
Prognostic value of nodal metastases

• Meta-analysis by Gynecologic Oncology Group (GOG)

• Studied 626 patients from GOG protocols 24, 56, and 59 with cervical carcinoma

• Para-aortic node status and pelvic node status were significantly associated with progression-free survival

Prognostic value of tumor size

Risk of Parametrial Spread in Small Stage I Cervical Carcinoma

Pathology Review of 223 Cases With a Tumor Diameter of 20 mm or Less

Boris Vranes, MD,* Svetlana Milenkovic, MD,† Milos Radojevic, MD,* Ivan Soldatovic, MD,‡ and Vesna Kesic, MD, PhD*

Conclusions: Risk of parametrial spread of 0.45% for tumors less than 20 mm in diameter, no LVSI, and a depth of invasion within the inner third.

Int J Gynecol Cancer 2016 Feb;26(2):416-21 (Belgrade, Serbia)
Advantages of Imaging

• Obviates the use of invasive procedures such as cystoscopy and proctoscopy, especially when there is no sign of local extension

• Identify important prognostic factors such as lesion volume and metastatic lymph nodes
  • Can upstage or downstage disease
  • Avoid multi-modality management
    • especially needed with increased screening and early detection
  • Less radiation side effects when planned without hysterectomy than as postoperative adjuvant RT

Incidence of cancer cervix

Estimated age-standardized incidence rate

The Global Voice for Women’s Health
Do we have adequate imaging facilities?

Number of Magnetic Resonance Imaging (MRI) units (per million population)

Status of OECD countries

The Global Voice for Women’s Health
“We probably have fewer than 400 radiologists working in South Africa for a population of 42 million, and the majority of them actually work in private practice. There are probably fewer than 50 radiologists working in the public health system, which caters to the needs of almost 65% of the population. Most hospitals in the public sector have never seen a radiologist.”
Dilemmas in including imaging for staging

- Enlarged nodes in imaging may be infective
  - Especially true in HIV endemic areas
- Stromal invasion not confirmatory by imaging
- PET-CT also not confirmatory
- Confirmation needed by cytology / histology
- Will further increase the need for resources
CaCx Staging Revision 2018 – Process

Presented at FIGO 2018, Rio de Janeiro
FIGO Cancer Report 2018

Published
https://doi.org/10.1002/ijgo.12749
CaCx Staging Revision 2018 – Salient Features

- Applicable to all resource levels
- Option of using clinical/imaging/pathological findings
- Additional cut-off at 2cm in Stage I (IB1, IB2, IB3)
- Any lymph node positive is Stage IIIC

Stage I

The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)

- **Stage IA** - Invasive carcinoma that can be diagnosed only by microscopy with measured deepest invasion < 5 mm \(^a\) (**lateral spread has been removed**)
  
  **Stage IA1** - Measured stromal invasion < 3.0 mm
  **Stage IA2** - Measured stromal invasion ≥ 3.0 mm and < 5.0 mm

\(^a\) The involvement of vascular/lymphatic spaces should not change the staging.
Stage I...

- **Stage IB** - Invasive carcinoma with measured deepest invasion \(\geq 5\) mm, limited to the cervix with size measured by maximum tumor diameter
  
  **Stage IB1** - Invasive carcinoma \(\geq 5.0\) mm depth of invasion and \(< 2\) cm in greatest dimension
  
  **Stage IB2** - Invasive carcinoma \(\geq 2\) cm and \(< 4\) cm in greatest dimension
  
  **Stage IB3** - Invasive carcinoma \(\geq 4\) cm in greatest dimension
The vaginal radical trachelectomy: An update of a series of 125 cases and 106 pregnancies

Marie Plante *, Jean Gregoire, Marie-Claude Renaud, Michel Roy

Recurrences: 6 / 125 (4.8%)
Deaths: 2 / 110 (1.6%)

Risk factor associated with recurrence

- Size of the lesion > 2 cm (p = 0.001)
- 10% of patients had lesions > 2 cm
- Represented 50% of the recurrences

Vaginal Radical Trachelectomy for early stage cervical cancer. Results of the Danish National Single Center Strategy

L. Hauerberg a,*, C. Høgdall a, A. Loft b, C. Ottosen a, S.F. Bjoern a, B.J. Mosgaard a, L. Nedergaard c, H. Lajer a

N=120
6 recurrences (5.1%); 2 deaths (1.7%)
7 patients had lesions >2 cm (5.8%)
3 recurrences (50%)
Long-Term Outcomes After Fertility-Sparing Laparoscopic Radical Trachelectomy in Young Women With Early-Stage Cervical Cancer: An Asan Gynecologic Cancer Group (AGCG) Study

JEONG-YEOL PARK, MD, PhD,1 WON DEOK JOO, MD, PhD,2 SUK-JOON CHANG, MD, PhD,3 DAE-YEON KIM, MD, PhD,1 JONG-HYEOK KIM, MD, PhD,1 YONG-MAN KIM, MD, PhD,1 YOUNG-TAK KIM, MD, PhD,1 AND JOO-HYUN NAM, MD, PhD1*

Evidence informing the change in Stage IB cut-offs


Controversial issues:

• Presence of vascular/lymph space invasion: Lymphovascular space invasion does not change the stage.

• Extension to the uterine corpus: Involvement of the uterine body does not change the stage.

Recommendations:

• The size and extent of the primary tumor can be assessed by clinical evaluation (pre- or intraoperative), imaging, and/or pathological measurement.
Stage II

Cervical carcinoma invades beyond the uterus, but not to the pelvic sidewall or to the lower third of the vagina

- **Stage IIA** Without parametrial invasion
  - *Stage IIA1* - Invasive carcinoma < 4 cm in greatest dimension
  - *Stage IIA2* - Invasive carcinoma ≥ 4 cm in greatest dimension

- **Stage IIB** With parametrial invasion
Controversial issues:

*Use of imaging for assessment of parametrial involvement:*

• The utility of imaging for evaluation of parametrium and upper vagina is less clear
• MRI performs better than CT scan for parametrial assessment
• False negative as well as false positive results have been reported especially when there is infection or with larger tumor size and stretching of the upper vagina by the growth
Stage III

The tumor extends to the pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or paraaortic nodes

**Stage IIIA** - Tumor involves lower third of the vagina, with no extension to the pelvic wall

**Stage IIIB** - Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney

**Stage IIIC** - Involves pelvic and/or paraaortic lymph nodes, irrespective of tumor size and extent (adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate to stage IIIC).

**Stage III C1** - Pelvic lymph node metastasis only

**Stage III C2** - Paraaortic lymph node metastasis

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*b* Example: Notation of r = imaging and p = pathology, e.g., imaging indicating pelvic lymph node metastasis would be Stage IIIIC1r and by pathological findings would be Stage IIIIC1p. When in doubt, the lower staging should be assigned.
Evidence informing the change – Imaging


MRI vs CT in cervix cancer staging?

Radiological Evaluation of Lymph Node Metastases in Patients With Cervical Cancer: A Meta-analysis

• 17 studies comparing CT, MRI and LAG
• LAG, CT, and MR imaging perform similarly in the detection of lymph node metastasis from cervical cancer
MRI vs CT vs PET in cervix cancer staging?

- 41 studies with histologic confirmation

PET or PET/CT had an overall higher diagnostic performance than CT or MRI in detecting metastatic lymph nodes in patients with cervical cancer

Lymph Node Staging by Positron Emission Tomography in Cervical Cancer: Relationship to Prognosis

Elizabeth A. Kidd, Barry A. Siegel, Farrokh Dehdashti, Janet S. Rader, David G. Mutch, Matthew A. Powell, and Perry W. Grigsby

N = 513

Lymph Node Staging by Positron Emission Tomography in Cervical Cancer: Relationship to Prognosis

Elizabeth A. Kidd, Barry A. Siegel, Farrokh Dehdashti, Janet S. Rader, David G. Mutch, Matthew A. Powell, and Perry W. Grigsby

Stage II

Stage III

Stage IV

# Comparison of MRI and High-Resolution Transvaginal Sonography for the Local Staging of Cervical Cancer

## TABLE 2
Diagnostic Accuracy of Disease Staging with MRI and TVS in the Detection of Stromal Invasion in 46 Women with Invasive Cervical Cancer

<table>
<thead>
<tr>
<th></th>
<th>Histopathologically Positive, n</th>
<th>Histopathologically Negative, n</th>
<th>Sensitivity, 80%</th>
<th>Specificity, 50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI positive</td>
<td>12</td>
<td>9</td>
<td>Positive predictive value, 57%</td>
<td></td>
</tr>
<tr>
<td>MRI negative</td>
<td>3</td>
<td>9</td>
<td>Negative predictive value, 75%</td>
<td></td>
</tr>
<tr>
<td>TVS positive</td>
<td>12</td>
<td>9</td>
<td>Kappa, 0.29 (“fair”)</td>
<td></td>
</tr>
<tr>
<td>TVS negative</td>
<td>3</td>
<td>9</td>
<td>Sensitivity, 80%</td>
<td>Specificity, 50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Positive predictive value, 57%</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Negative predictive value, 75%</td>
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<td></td>
<td></td>
<td></td>
<td>Kappa, 0.29 (“fair”)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: TVS performed by a dedicated gynecologic radiologist is a feasible and economic imaging modality with a diagnostic accuracy comparable to MRI.
Transrectal ultrasound and magnetic resonance imaging in staging of early cervical cancer


### Accuracy of MRI and TRUS in the identification of tumor ($P \leq 0.006$) in the whole group ($n = 95$) and in the subgroup of small tumors $\leq 1$ cm$^3$ ($P \leq 0.049$)

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
<th>PPV, % (95% CI)</th>
<th>NPV, % (95% CI)</th>
<th>Accuracy, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TRUS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95 patients</td>
<td>93.42 (85.31–97.83)</td>
<td>94.74 (73.97–99.87)</td>
<td>98.61 (92.50–99.96)</td>
<td>78.26 (56.30–92.54)</td>
<td>93.68 (86.76–97.65)</td>
</tr>
<tr>
<td>$\leq 1$ cm$^3$</td>
<td>72.00 (50.61–87.93)</td>
<td>97.14 (90.06–99.65)</td>
<td>90.00 (68.30–98.77)</td>
<td>90.67 (81.71–96.16)</td>
<td>90.53 (82.78–95.58)</td>
</tr>
<tr>
<td><strong>MRI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95 patients</td>
<td>82.89 (72.53–90.57)</td>
<td>84.21 (60.42–96.62)</td>
<td>95.45 (87.29–99.05)</td>
<td>55.17 (35.69–73.55)</td>
<td>83.16 (74.10–90.06)</td>
</tr>
<tr>
<td>$\leq 1$ cm$^3$</td>
<td>44 (24.40–65.07)</td>
<td>94.29 (86.01–98.42)</td>
<td>73.33 (44.90–92.21)</td>
<td>82.50 (72.38–90.09)</td>
<td>81.05 (71.72–88.37)</td>
</tr>
</tbody>
</table>

PPV, positive predictive value; NPV, negative predictive value.

### Accuracy of MRI and TRUS in the evaluation of parametrial involvement ($P \leq 0.219$)

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
<th>PPV, % (95% CI)</th>
<th>NPV, % (95% CI)</th>
<th>Accuracy, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TRUS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>83.33 (35.88–99.58)</td>
<td>100.00 (95.94–100)</td>
<td>100.00 (47.82–100)</td>
<td>98.89 (93.96–99.97)</td>
<td></td>
<td>98.95 (94.27–99.97)</td>
</tr>
<tr>
<td><strong>MRI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50.00 (11.81–88.19)</td>
<td>97.75 (92.12–99.73)</td>
<td>60.00 (14.66–94.73)</td>
<td>96.67 (90.57–99.31)</td>
<td></td>
<td>94.74 (88.14–98.27)</td>
</tr>
</tbody>
</table>

PPV, positive predictive value; NPV, negative predictive value.

THREE-DIMENSIONAL TRANSGINGINAL TOMOGRAPHIC ULTRASOUND IMAGING FOR CERVICAL CANCER STAGING

Xue-Song Han,* Chun-Ping Ning,† Li-Tao Sun,* Xiao-Ying Li,* Yan-Qing Peng,* and Mei-Zheng Dang*

- N=80
- Tomographic transvaginal US

Table 3. Comparison of clinical, US and MRI staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical staging</th>
<th>US staging</th>
<th>MRI staging</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Final staging</td>
<td>Accurate</td>
<td>Understaged</td>
</tr>
<tr>
<td>IA</td>
<td>5</td>
<td>5</td>
<td>—</td>
</tr>
<tr>
<td>IB</td>
<td>50</td>
<td>42</td>
<td>2</td>
</tr>
<tr>
<td>IIA</td>
<td>15</td>
<td>13</td>
<td>—</td>
</tr>
<tr>
<td>IIB</td>
<td>10</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

Accuracy
Comparisons
Clinical vs. US
US vs. MRI

\[ \chi^2 = 4.902, p = 0.022 \]
\[ \chi^2 = 2.686, p = 0.079 \]

US = ultrasound; MRI = magnetic resonance imaging.

Controversial issues in Stage III

• **Presence of isolated tumor cells (ITCs) or micrometastases:**
  • Metastases in lymph nodes have been graded as ITCs (<0.2 mm), micrometastases (0.2-2.0 mm) or macrometastases (>2.0 mm).
  • Presence of ITCs or micrometastases signifies low volume metastasis; their implication is not clear. Their presence may be recorded but does not change the stage.

• **Differentiating metastases from infection:**
  • Many countries with a high cervical cancer burden also have a high prevalence of tuberculosis and HIV. In these endemic areas, nodes may be enlarged without metastases. The assessment of metastatic lymph nodes versus infected lymph nodes does not have clear radiological criteria.
Controversial issues in Stage III

• **Sentinel lymph nodes:**
  • Sentinel lymph node dissection is commonly used in vulvar and endometrial cancer.
  • In cervical cancer, good sensitivity and specificity has been reported with acceptable false negative rates.
  • Following the protocol is essential for this procedure. Appropriate facilities and expertise should be available to validate and follow the protocol for the sentinel lymph node approach, which also requires good backup of pathology for ultrastaging and immunohistochemistry.
Recommendations

• Surgicopathological assessment of lymph node involvement, whether by conventional or MIS route, requires advanced surgical skills.
• 85% of cases occur in low resource settings, where the required professional skills and infrastructure facilities are presently not widely available.
• Pathological confirmation is the gold standard but imaging can be used to interpret disease extent.
• The choice of imaging modality for nodal evaluation has not been fixed by FIGO. It depends upon availability and patients’ affordability. Non-availability of an imaging modality should not be a reason for undue delay in initiation of treatment.
Recommendations (contd.)

• FIGO does not define criteria to discriminate between malignancy and inflammation / infection on imaging. The clinician must opine on whether these look suspicious enough to upstage the case or not.
• Clinical assessment of staging or use of other facilities as available is permissible.
• The best available technology should be used for assessment, and the lowest appropriate stage should be assigned, i.e., when in doubt assign the lower stage.
• The method of assigning the stage is to be recorded and reported.
Imaging & Pathology Recommendations

• FIGO recommends adding imaging and pathological findings, collection and analysis of these data.

• A parenthetical notation of ‘r” and ‘p’ would be added.
  • r = Radiological (imaging) findings
    • cross-sectional imaging, e.g., US, CT, MRI, PET, PET/CT scans
  • p = Pathological findings
    • biopsy and/or FNAC proven findings
Stage IV

The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum.

Stage IVA  Spread of the growth to adjacent organs
Stage IVB  Spread to distant organs
Summary of revisions (2018)

- Allowing the use of any imaging modality and/or pathological findings for allocating stage, in addition to the previous option of clinical staging. Recording ‘r’ or ‘p’ to indicate resource used.
- In stage I, amendments to microscopic pathological findings and size designations, and allowing the use of imaging and/or pathological assessment of the size of the cervical tumor.
- In stage II, allowing the use of imaging and/or pathological assessment of the size of the cervical tumor and parametrial invasion.
- In stages I through III, allowing assessment of retroperitoneal lymph nodes by imaging and/or pathological findings, and, if deemed metastatic, the stage is designated stage IIIC.
- Removing previous recommendations for routine investigations.
LACC TRIAL – MIS IN CaCx
Approach to Early Stage Cervical Cancer

• Is surgery or radiotherapy better?
• Landmark trial, Landoni et al
  • Randomized 343 patients, IB-IIA to either
    • Radical hysterectomy
    • External beam radiotherapy (pelvic RT)
  • 5-year outcome: no difference; Non-bulky: OS surgery 87% vs. RT 90% (NS), DFS surgery 80% vs. 82% (NS)
  • AdenoCA: significantly better outcomes with surgery; OS (70% vs. 59%), DFS (66% vs. 47%)
  • Complications (Grade 2-3): Surgery 28% vs RT 12% (SS). Severe leg edema surgery 0%, RT 1%, surgery + RT 9%


Key is identifying patients that have surgically resectable disease that done require adjuvant treatment
Minimally Invasive Surgery in Gyne Cancer

• Minimally invasive surgery is now an accepted and “standard of care” approach to endometrial cancer staging.

• Several studies have shown the benefit of using this technique for appropriate detection for advanced and occult metastatic disease.

• The LAP2 trial showed that a MIS surgery approach was appropriate for the detection of occult disease at that survival was similar to open methods with lower complication rates.
Minimally Invasive Radical Hysterectomy for Cervical Cancer Is Associated With Reduced Morbidity and Similar Survival Outcomes Compared With Laparotomy

Elisabeth Diver, MD, Emily Hinchcliff, MD, Allison Gockley, MD, Alexander Melamed, MD, Leah Contrino, PA-C, Sarah Feldman, MD, MPH, and Whitfield Growdon, MD*

Table 3

<table>
<thead>
<tr>
<th>Patient outcomes by surgical modality</th>
<th>MIS (n = 101)</th>
<th>XL (n = 282)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any chemotherapy, n (%)</td>
<td>17 (16.7)</td>
<td>60 (21.3)</td>
<td>.32</td>
</tr>
<tr>
<td>Any radiation therapy, n (%)</td>
<td>20 (19.8)</td>
<td>69 (24.5)</td>
<td>.28</td>
</tr>
<tr>
<td>Recurrence, n (%)</td>
<td>5 (5.0)</td>
<td>18 (6.4)</td>
<td>.86</td>
</tr>
<tr>
<td>Survival, yr, median</td>
<td>Not reached</td>
<td>Not reached</td>
<td>.29</td>
</tr>
</tbody>
</table>

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).
What about randomized data in cervical cancer?

• To answer this question in cervical cancer, a randomized trial similar to the LAP-2 data was needed

• Several constraints on examination of this data....
  • The development of new technologies as compared to LAP-2 trial (mainly l-scope and no robotic surgery)
  • The advent of sentinel lymph node mapping for staging in both endometrial and possibly cervical cancer
  • Centralized evaluation of the surgical technique
  • Is robotic surgery better than standard straight-stick approaches?
  • International spread of MIS technologies...
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.

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

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

Randomize

Total Abdominal Radical Hysterectomy
N= 312

Total Laparoscopic/Robotic Radical Hysterectomy
N= 319

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

*N= 312
Recommendation of study termination by DSMC
LACC Trial Objectives

Primary: Disease Free Survival
Secondary: Overall Survival

Patterns of Recurrence
Treatment-Associated Morbidity
Cost-Effectiveness
Pelvic floor Dysfunction
Feasibility of Sentinel Nodes
Quality of Life
## Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Open (n=312)</th>
<th>MIS (n=319)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yr (SD)</td>
<td>46.0 (10.6)</td>
<td>46.1 (11.0)</td>
</tr>
<tr>
<td>Mean BMI, kg/m² (SD)</td>
<td>26.2 (5.3)</td>
<td>27.2 (5.6)</td>
</tr>
<tr>
<td>Geographic Region, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>63 (20)</td>
<td>63 (20)</td>
</tr>
<tr>
<td>Australia/New Zealand</td>
<td>48 (15)</td>
<td>46 (14)</td>
</tr>
<tr>
<td>Europe</td>
<td>27 (9)</td>
<td>32 (10)</td>
</tr>
<tr>
<td>North America</td>
<td>49 (16)</td>
<td>45 (14)</td>
</tr>
<tr>
<td>South America</td>
<td>125 (40)</td>
<td>133 (42)</td>
</tr>
<tr>
<td>Type of incision, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertical midline</td>
<td>156 (50)</td>
<td></td>
</tr>
<tr>
<td>Low transverse</td>
<td>118 (38)</td>
<td></td>
</tr>
<tr>
<td>Did not undergo open surgery</td>
<td>38 (12)</td>
<td></td>
</tr>
</tbody>
</table>
Progression-Free Survival (PFS)

HR: 3.88 (95% CI: 1.79 - 8.41), p<0.001

Events/N
TARH: 8/312
TLRH/TRRH: 19/319

Years from randomization
Proportion of patients progression-free
Overall Survival (OS)

HR: 6.00 (95% CI 1.77 - 20.3), p=0.004

Proportion of Patients Alive

Years from randomization
Where does this leave MIS surgery in all of this?

- Randomized data now show both PFS and OS are impaired after MIS approach for cervical cancer.
- HR for PFS (recurrence) is nearly 4X with MIS approach.
- Risk of death from cervical cancer after MIS procedures is 6 times greater.
- This is a well done randomized trial
  - Centralized surgical review at top cancer institutes
  - Both groups appear to be equally balanced
  - Number of nodes and parametrial dissection appear to be equivocal
  - Blinded statistical evaluation
So why the discrepancy......

• Surgical technique: ? parametrial dissection not as extensive as in open techniques; Most surgeons do not undergo a centralized review of their parametrial dissection/margin (2 cm)
• Vaginal resection and margin: Did surgeons get an adequate surgical margin on the vaginal specimen?
• Internal prejudice in previous data - many retrospective, single institution data sets suffer from well known issues in retrospective studies (bias, inclusion/exclusion criteria, coding errors etc.)
• Lack of international participation in previous studies...
Conclusions after LACC....... 

- MIS approaches to cervical cancer appear to have increased risk of recurrence and decreased overall survival.
- Extensive discussion with patients about possible risks of MIS approaches over standard techniques must be had in the interest of ethics and patient autonomy.
- Many practitioners in the US and elsewhere have now switched back to open radical hysterectomy and the technique should be continued to be taught to trainees and future.
- Presently MIS to be performed in research settings only.
NATIONAL PROGRAMME
The National Programme for the Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS) scheme, launched in 2010, is being implemented as part of the National Health Mission (NHM).
85 countries introduced HPV vaccine by Oct. 2018
Progress in HPV vaccination

• Approved by NTAGI
• Delhi launched the vaccine program for school girls aged 11 years in 2016
  • Punjab launched in Nov 2016
    • CHC based program
    • Class 6 students
    • Allows opt-in approach
• Sikkim in 2018
Cost Rica Vaccine Trial: Vaccine efficacy by number of doses after 4-yrs FU

Women ages 18-25 years;

*Endpoint: HPV16/18 infections that persist for 6+ months*

<table>
<thead>
<tr>
<th># of Doses</th>
<th>Vaccine Arm</th>
<th># Women</th>
<th># (%) with endpoint</th>
<th>HPV16/18 VE (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Control</td>
<td>3010</td>
<td>229 (7.6%)</td>
<td></td>
<td>84% (77% to 89%)</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>2957</td>
<td>37 (1.3%)</td>
<td></td>
</tr>
<tr>
<td>2 Control</td>
<td>380</td>
<td>24 (6.3%)</td>
<td></td>
<td>81% (53% to 94%)</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>422</td>
<td>5 (1.2%)</td>
<td></td>
</tr>
<tr>
<td>1 Control</td>
<td>188</td>
<td>15 (8.0%)</td>
<td></td>
<td>100% (79% to 100%)</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>196</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

Kreimer AR et al JNCI, 2011

*p trend = 0.2*
IARC 2- vs 3- dose HPV Vaccine multi-centric clinical trial – Study Sites

World Health Organization (WHO)
International Agency for Research on Cancer (IARC)
Lyon, France

*In collaboration with*

- TMH-Mumbai
- NDMCH-Barshi
- JCDC-Pune
- CFCHC-Ambillikai
- GCRI-Ahmedabad
- AIIMS-New Delhi
- MNJ Institute of Oncology and RCC, Hyderabad
- Cancer Foundation of India (CFI), Kolkata

and

Rajiv Gandhi Centre for Biotechnology (RGCB), Trivandrum
German Cancer Research Institute (DKFZ), Heidelberg

Recruitment initiated in September 2009
No. of girls/women (10-18 year at recruitment) by Vaccine Dose Groups (All study sites) in the FU Study

- **Vaccinated**
  - N=17,064

- **Received 1 dose**
  - (day 1)
  - N=4672

- **Received 2 doses**
  - (days 1-60)
  - N=3300

- **Received 2 doses**
  - (days 1-180+)
  - N=4850

- **Received 3 doses**
  - (days 1-60-180+)
  - N=4242

- **Unvaccinated women recruited in 2012-15 as controls**
  - N=1460

- **Additional unvaccinated women recruited in 2017-18 as controls**
  - N=3104 (planned 3500)
Mean MFI values for HPV 16 and 18 L1 antibodies at different time points among girls who completed vaccination per protocol (vaccination days 1, 60 and 180 (3-dose group) or days 1 and 180 (2-dose group)), and those who received only a single dose of vaccination.

No difference in titres between 10-14 and 15-18 year olds

INCIDENCE of HPV infections  
(targeted & non-targeted types, N=9,000)

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Women assessed (N)</th>
<th>Incident HPV 16/18 infection N (%)</th>
<th>Incident HPV 31/33/45 infection N (%)</th>
<th>Incident non-targeted excluding HPV 31/33/45 infection N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All vaccinated</td>
<td>7516</td>
<td>149 (2.0)</td>
<td>327 (4.4)</td>
<td>1149 (15.3)</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>1484</td>
<td>120 (8.1)</td>
<td>132 (8.9)</td>
<td>339 (22.8)</td>
</tr>
<tr>
<td>3- dose (Days 1, 60 &amp; 180+)</td>
<td>1637</td>
<td>29 (1.8)</td>
<td>75 (4.6)</td>
<td>270 (16.5)</td>
</tr>
<tr>
<td>2- dose (Days 1 &amp; 180+)</td>
<td>1662</td>
<td>27 (1.6)</td>
<td>74 (4.5)</td>
<td>252 (15.2)</td>
</tr>
<tr>
<td>2- dose (Days 1 &amp; 60+)</td>
<td>1799</td>
<td>42 (2.3)</td>
<td>57 (3.2)</td>
<td>238 (13.2)</td>
</tr>
<tr>
<td>1- dose</td>
<td>2418</td>
<td>51 (2.1)</td>
<td>121 (5.0)</td>
<td>389 (16.1)</td>
</tr>
</tbody>
</table>
## PERSISTENCE of HPV infections
**(targeted & non-targeted types, N=6,259)**

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Women assessed (N)</th>
<th>Persistent HPV 16/18 infection N (%)</th>
<th>Persistent HPV 31/33/45 infection N (%)</th>
<th>Persistent non-targeted excluding HPV 31/33/45 infection N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All vaccinated</td>
<td>5017</td>
<td>6 (0.1)</td>
<td>24 (0.5)</td>
<td>136 (2.7)</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>1242</td>
<td>28 (2.3)</td>
<td>12 (1.0)</td>
<td>57 (4.6)</td>
</tr>
<tr>
<td>3- dose (Days 1, 60 &amp; 180+)</td>
<td>1056</td>
<td>1 (0.1)</td>
<td>4 (0.4)</td>
<td>31 (2.9)</td>
</tr>
<tr>
<td>2- dose (Days 1 &amp; 180+)</td>
<td>1055</td>
<td>1 (0.1)</td>
<td>8 (0.8)</td>
<td>31 (2.9)</td>
</tr>
<tr>
<td>2- dose (Days 1 and 180+)</td>
<td>1263</td>
<td>3 (0.2)</td>
<td>2 (0.2)</td>
<td>27 (2.1)</td>
</tr>
<tr>
<td>1- dose</td>
<td>1643</td>
<td>1 (0.1)</td>
<td>10 (0.6)</td>
<td>47 (2.9)</td>
</tr>
</tbody>
</table>
Conclusions – HPV Vaccination

• Emerging data suggest the two-dose schedule can be extended till 18 years age
• One-dose schedule may afford equivalent protection – RCT is under way
• Vaccination of older women is licensed though the protection will be less than for younger women
WHO Call for Elimination of Cervical Cancer .... By 2030
MAY 2018: WHO DIRECTOR-GENERAL’S CALL TO ACTION TO ELIMINATE CERVICAL CANCER
WHO LIFE COURSE APPROACH TO CERVICAL CANCER CONTROL

Primary Prevention
- Girls 9-14 years
  - HPV vaccination
- Girls and boys, as appropriate
  - Health information and warnings about tobacco use
  - Sexuality education tailored to age & culture
  - Condom promotion/provision for those engaged in sexual activity
  - Male circumcision

Secondary Prevention
- Women > 30 years of age
  - “Screen and treat” – single visit approach
    - Point-of-care rapid HPV testing for high risk HPV types
    - Followed by immediate treatment
    - On site treatment

Tertiary Prevention and Palliative Care
- All women as needed at any age
  - Treatment of invasive cancer:
    - Surgery
    - Radiotherapy
    - Chemotherapy
  - Palliative care
Reduction in incidence, prevalence, morbidity or mortality to a locally acceptable level

**of disease:** incidence reduced to zero in a defined geographical area

**of infection:** incidence of infection caused by a specific agent reduced to zero.

**as a public health problem:** achievement of clear and commonly agreed target definitions

---

**Eradication**

Permanent reduction to zero of the worldwide incidence of infection

---

**Continued intervention measures needed**

**Intervention measures no longer needed**
CERVICAL CANCER ELIMINATION: CONCEPTUAL FRAMEWORK

Current vaccination and screening

Intensive screening and vaccination

Intensive vaccination

Cervical cancer cases/100,000

2020  2030  2060  2120
THE ARCHITECTURE TO ELIMINATE CERVICAL CANCER:

VISION: A world without cervical cancer

THRESHOLD: All countries to reach < 4 cases 100,000 women-years

2030 CONTROL TARGETS

90% of girls fully vaccinated with HPV vaccine by 15 years of age

70% of women screened with a high precision test at 35 and 45 years of age

90% of women identified with cervical disease receive treatment and care

SDG 2030: Target 3.4 – 30% reduction in mortality from cervical cancer

The 2030 targets and elimination threshold are subject to revision depending on the outcomes of the modeling and the WHO approval process
Conclusions

• There is much progress in the cervical cancer space
• New staging system, new information on management strategies, powerful prevention strategies and political will to eliminate this cancer in the foreseeable future
• The time to act is NOW!
Dr. Srabani Mittal
Secretary, AOGIN-India, 2017-19