Cervical Cancer Screening, Prevention, and Management:

*It’s a Brave New World*

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University of Alabama at Birmingham

Objectives

1) Primary HPV Screening and the Impact of Vaccination on Screening

2) New US Colposcopy Standards and Risk Based Colposcopy

3) New, upcoming Risk-based Treatment Guidelines for Cervical Abnormalities

4) MIS and Cervical Cancer: The Ongoing Debate
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It started here... Village of Kimi, Island of Evia, Greece
George Nicholas Papanicolaou (1883-1962)

May 13, 2008: Celebration of 125 years of the birth of Papanicolaou, the developer of the oldest medical test

How good is Pap cytology in cervical cancer screening?

- Duke Report (Nanda et al., 2000): sensitivity 51%, specificity 98%
- Pooled analysis of European and Canadian studies (Cuzick et al., 2006): sensitivity 53%, specificity 96%
- Cytology screening programs have to compensate for the low sensitivity by requiring 2-3 annual Pap tests before screening can be done less frequently
Other Issues to Consider with Cytology

- Highly subjective test: substantial inter-laboratory (as well as intra-laboratory) variability and limited reproducibility
- Unable to identify those women who are at future risk of developing cervical cancer precursors
- Unclear how cytology will perform as HPV vaccination rates increase in the US

Cumulative incidence of CIN3+ according to baseline test results in European sites (excluding Denmark and Tubingen).

RCTs of HPV testing in screening

- POBASCAM study: The Netherlands (Meijer et al., Int J Cancer 2004; Bulkmans et al, Lancet 2007)
- Indian Trial (Osmanabad) (Sankaranarayanan et al. NEJM 2009)
- ARTISTIC trial: UK (Kitchener et al. Lancet Oncol 2009)
- NTCC Italian Study (Ronco et al., Lancet Oncol, 2006; JNCI 2006)
- SWEDESCREEN: Swedish trial (Elfström et al. AJOG 2005; Naule et al., NEJM 2007; JNCI 2009)
- Finnish RCT (Kallioniemi et al., BJC 2005; Eur J Cancer 2008; IJC 2008; Leinonen et al., JNCI 2009)
- CCCaST study: Canada (Mayrand et al., IJC 2006; NEJM 2007)
- BC RCT (HPV FOCAL): Canada (Ogilvie et al, BJC 2012)
- ATHENA Trial: United States
CCCaST Study: First Screening Round Results

<table>
<thead>
<tr>
<th>Indices</th>
<th>Screening test</th>
<th>Estimate (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>Pap</td>
<td>55.4 (33.6-77.2)</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>94.6 (84.2-100)</td>
</tr>
<tr>
<td>Specificity</td>
<td>Pap</td>
<td>96.8 (96.3-97.3)</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>94.1 (93.4-94.8)</td>
</tr>
<tr>
<td>PPV</td>
<td>Pap</td>
<td>7.1 (4.8-10.3)</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>6.4 (5.0-8.0)</td>
</tr>
<tr>
<td>NPV</td>
<td>Pap</td>
<td>99.8 (99.7-99.9)</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>100 (98.6-100)</td>
</tr>
</tbody>
</table>

* 10,171 women in Montreal and St. John’s, aged 30-69 years, randomized to Pap or HPV as primary screening method; detection of CIN2+, estimates corrected for verification bias.

(Mayrand et al., NEJM 2007)

Influence of laboratory performing the test on Pap and HPV testing performance (CCCaST Study)

(Mayrand et al., unpublished data)

Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials
FDA NEWS RELEASE

For Immediate Release: April 21, 2014

Media Inquiries: Robert Lamb, 301-796-9086, media.lamb@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA approves first human papillomavirus test for primary cervical cancer screening

The U.S. Food and Drug Administration today approved the first FDA-approved HPV DNA test for women 25 and older that can be used alone to help a health care professional decide the need for a woman to undergo additional diagnostic testing for cervical cancer. The test also can provide information about a patient’s risk for developing cervical cancer in the future.

Guidelines

Use of Primary High Risk Human Papillomavirus Testing for Cervical Cancer Screening

Interim Clinical Guidance

Werner K. Jakob, MD, Kevin A. Aff, MD, David Chiloso, MD, Diane D. Davy, MD, Robert G. Grant, MD, Francisco A. R. Genero, MD, MD, Walter K. Knies, MD, L. Stewart Mesaud, MD, Edward J. Meyers, MD, Debbie Stites, MD, Mark Seligman, MD, MD, Nicolas Wientzen, MD, MD, Hervé-L. Lhomme, MD, and Mark H. Eisner, MD, MD
The ‘Candidate’ Algorithm

Candidate Screening Algorithm
HPV with 16/18 Genotyping and Reflex Cytology

Why Start at 25 years of Age?

Why Start at 25 years of Age?

Why Start at 25 years of Age?
HPV DNA primary screening
Progress around the world

New cervical cancer screening recommendations include more options
By Nancie Wulsie, CNN
August 21, 2018

New cervical cancer guidelines start making Pap smears obsolete
Women over 30 can cut the years between tests if they get the HPV test, a panel of experts says.

Screening for Cervical Cancer
US Preventive Services Task Force Recommendation Statement
US Preventive Services Task Force
Is Screening Needed After Vaccination?*

Yes!!!
- Vaccines protect against HPVs 16 and 18 which cause at most 75% of all cervical cancers
- Vaccination is for pre-exposure prophylaxis; most women will continue to rely on screening

But How?

*2018: FDA Approved Gardasil 9 up to 45 years of age
What are Vaccination Rates in the US and Worldwide

Are we making a Difference?

- One of the highest HPV vaccination rates in the world: ~75% for the 3rd dose in 12-13 year olds
- From 2007 to 2011
  - Women <21 years old, 93% reduction in genital warts!
  - Women 21-30 years old, 73% reduction in genital warts
  - No significant decline in women >30 years old


What are Vaccination Rates in the US and Worldwide

Are we making a Difference? What About Men?

- From 2007 to 2011
  - Substantial decline in warts in men, 50-80%, depending on age group (i.e., herd immunity)
  - No real decline seen in men (>30 years old)


High-grade cervical abnormalities in young Victorian women, by age group, 2003–2010
Influence of prevalence of cervical lesions on the positive predictive value (PPV) and negative predictive value (NPV) of using HPV as a primary screening test. Sensitivity and specificity held constant at 70% and 98%, respectively. The values of PPV and NPV were calculated using 1000 simulations using each of the parameter combinations in hypothetical populations of 10,000 women. (Franco et al., Arch Med Res 2009)

The Interval Debate

Current Commentary
Increased Cervical Cancer Risk Associated With Screening at Longer Intervals
Walter Kinney, MD, Thomas C. Wright, MD, Helen E. DiDonato, MD, Mark DeFrancisco, MD, J. Thomas Cox, MD, and Werner Hub, MD

Objectives
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Establishing U.S. Standards for Colposcopy Terminology and Practice

Colposcopy is Central to ASCCP Guidelines

Context for Colposcopy Standards

- Colposcopy has not been standardized previously
- IFCPC standard terminology exists, not adopted in U.S.
  - Complex
  - Terminology is not familiar to many U.S. settings
- British standards are stringent
  - Training at accredited center
  - Certification through BSCCP/RCOG including case logs
  - Annual minimum volume (50 new cases/yr)
  - Triennial case review/recertification
  - Ongoing CME
- Depends on central payor: currently not feasible in U.S.
U.S. Colposcopy: Why Change?

- Clinician experience/skill declining with
  - Shift to screening q3-5y
  - Deferring start to age ≥21
- Lesions have changed
  - Colpo threshold shifted from Pap III to ASCUS/persistent HPV+
    →Smaller, more subtle, lack classic appearance

Colposcopy in the U.S.

- Hundreds of thousands colposcopies performed every year
- Performed by Ob/Gyn, Family Practice, Internists, NPs, PAs
- Large country, many remote areas that need coverage but have low volumes
  - In 2016 ASCCP survey, many respondents did <60 cases/yr
- No nation-wide integrated healthcare system, no screening or precancer registries

Colposcopy in the U.S.

- Reproducibility is poor
- Sensitivity is low
- Training is highly inconsistent: Residency, courses (e.g. ASCCP), mentorship training, self-education
- No formal certificate of colposcopy competence
- No formal colposcopy guidelines/standards
Goals

- Develop colposcopy standards for the U.S. setting
- Evidence-based, expert consensus
- Simplification: Clear message in training, wide outreach
- Harmonization with international standards as much as possible

Colposcopy Standards Working Groups

Working Group 1: Role of colposcopy, Benefits and Harms and Terminology
(Michelle Khan/ Warner Huh/ Mark Schiffman)

Working Group 2: Risk-based Colposcopy and Biopsy
(Nicolas Wentzensen/ L. Stewart Massad)

Working Group 3: Colposcopy procedures and Adjuncts
(Alan Waxman/ Candy Tedeschi/ Christine Coraypes)

Working Group 4: Quality Control
(E.J. Mayeaux/ Mark Einstein)

Working Group 2: Risk-Based Colposcopy

Chairs: Nicolas Wentzensen and L. Stewart Massad
Members: Mark Schiffman, Michelle Khan, Rebecca Perkins, Katie Smith, Julia Gage, Michael Gold, Michelle Silver
Working Group 2: Risk-Based Colposcopy

- WG2 was charged with evaluating how findings before colposcopy together with colposcopic impression may modify the colposcopy process
  - Biopsy number
  - Immediate treatment
  - Non-targeted biopsy
  - Will assess ECC at later iteration

Risk-Based Approach to Colposcopy (Example ALTS)

Risk-Based Colposcopy-Biopsy Practice

Liu et al., ASCCP talk 2016

Risk-Based Colposcopy

- Biopsy Practice
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Screening detects CIN3 (“pre-cancer”)

Treating CIN3 prevents cancer

Goal of screening is to detect CIN3 and prevent cervical cancer

Risk of cervical cancer with untreated CIN3 over 30 years

Untreated CIN3: 30% (95% CI 22.7-42.3) chance of developing invasive cancer over the next 30 years

Treated CIN3: <1% (95% CI 0.3-1.9) chance of developing cancer

Based on data from the National Women’s Hospital, Auckland, New Zealand, where treatment of CIN3 was withheld from a substantial number of women between 1965 and 1974

MR McCredie et al, Lancet Oncol. 2008 May;9(5):425-34
Existing screening and management guidelines treat all women the same way

But past history predicts future risk

Upcoming ASCCP guidelines for the management of abnormal results will incorporate history AND test result to determine the next step in a woman's care

Schiffman et al, JLGTD, 2016

Examples of Risk Modifiers that predict CIN3+ risk

HPV vaccination reduces risk of CIN2+

Note that women who remain positive for HPV16/18 have up to 40% risk of high grade precancer or cancer in 3-10 years!
Multiple negative HPV tests predict very low cancer risk

Cancer risk fell from 9.2/100,000 after first negative HPV tests to 1.5/100,000 after 3rd consecutive negative HPV test

New HPV infection confers lower CIN3+ risk

- 331,818 women over 2003-2009
- Risk of CIN3+ at 3 years
  - 5% with unknown prior HPV result
  - 3% with negative prior HPV result
- Prior negative HPV test reduced risk of CIN3 with a new HPV+ result

Prior HPV+ or unknown history is higher risk

- 26,799 women with a current positive HPV+ test and no prior CIN2+
- Cumulative CIN3+ incidence rates over 4 years among women with current HPV+/Pap neg screen
  - Prior HPV positive: 4.36
  - Prior HPV negative: 1.32
  - Prior HPV unknown: 4.67
- Note prior HPV+ have the same risk as women with an unknown screening history

Castle et al, Annals of Internal Medicine, 2018
Long-term persistent HPV is especially high risk

- 8656 women age 20-29 underwent co-testing years 1 & 3
- Followed for 12 years for CIN3+
- Risk of CIN3+
  - 47% persistent HPV16+
  - 19% persistent HC2
  - HPV neg 2%
- HPV history is an important risk modifier


All women with persistent HPV develop CIN2+
195 women pap neg/HPV+ at start, 40 remained HPV+ for 7 years and all developed CIN2+

Elfgren, AJOG, 2017

Treated CIN2+ has a high risk of recurrence within 5 years of treatment

- 8-16% risk after treated CIN3/AIS
- 5-10% risk after treated CIN2
- 0.08% risk after neg/neg co-test

- Thus history of CIN2/3 denotes 100-fold CIN2+ risk over negative co-testing, even after treatment

Why revise ASCCP management guidelines to include risk data?

1. Detect and treat more precancer
2. Decrease testing and treatment that won’t prevent cancer and may cause reproductive harm

*Risk-based testing should allow better precancer detection in high risk women, and fewer procedures in low-risk women*

THE NEXT GENERATION OF RISK-BASED MANAGEMENT

Consensus process led by ASCCP with >26 organizations including professional societies for physicians and mid-level providers, research and education groups, and patient organizations
New ASCCP risk-based guidelines

- Patient’s current test results and past history
- Risk matrix is used to calculate her risk of CIN2/3
- Computer program generates risk score
- Recommends next step in management

Clinical trials
High quality observational studies
Medical record data
Clinical consensus

Risk strata
Risk now
1-year risk
2-year risk
3-year risk
4-year risk
5-year risk

HPV and cytology
Biomarkers
Screening history
Vaccination data
Other variables

Risk matrix:
Calculating risk of CIN2+/CIN3+ for all meaningful combinations

Setting risk-action thresholds

Consortium, including ASCCP, CISNET, DCCPS, others

Clinical recommendations

Reducing complexity for providers

Data entry
Recommendation

A 42 year old woman with LSIL cytology and HPV16 has a n% risk of CIN3+, which is above the colposcopy referral threshold of m%.

Recommendation

Patient: Doe, Jane
Age: 42
HPV: Pos
Genotype: 16
Cytology: LSIL
Vaccine: No
Last screen: Negative
Prior LEEP: No

Recommendation

Enter risk data
Show details

Show recommendation

Reducing complexity for providers
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Background

• Laparoscopic radical hysterectomy shows reduction in blood loss, postoperative complications, and hospital stay compared to open approach. No significant difference in 5-year DFS and OS. (N=1,539)

• Robotic radical hysterectomy is associated with less blood loss, lower transfusion rates, lower wound-related complications, and shorter hospital stay compared to open radical hysterectomy. (N=4,013)
  Shaddy S, Murad M, Dowdy S, Godbout B, Famuyide A. Gyn Oncol 2016

• Disease recurrence and survival not different between robotic radical hysterectomy and open radical hysterectomy. (N=491)
  Sert BM, Boggs JS, Ahmad S, Jackson AL, Stavitski NM, Dahl AA, Holloway RW EJSO 2016
Phase III Randomized Trial of Laparoscopic or Robotic Radical Hysterectomy vs. Abdominal Radical Hysterectomy in Patients with Early-Stage Cervical Cancer: LACC Trial

Pedro T. Ramirez, Michael Frumovitz, Rene Parraja, Aldo Lopez, Marcelo Vieira, Reniel Ribeiro, Alessandro Buda, Xiaojian Yan, Krisly P Robledo, Val Gabiski, Robert L Coleman, Andreas Obermair

Primary Objective
LACC Trial

Compare disease-free survival at 4.5 years amongst patients who underwent a total laparoscopic or robotic radical hysterectomy (TLRH/TRRH) vs. a total abdominal radical hysterectomy (TARH) for early stage cervical cancer.
**Study Schema**

Open: June 2008  
Accrual: 631  
Closed: June 2017

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

RANDOMIZE

<table>
<thead>
<tr>
<th>Total Abdominal Radical Hysterectomy</th>
<th>N= 312</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Laparoscopic/Robotic Radical Hysterectomy</td>
<td>N= 319</td>
</tr>
</tbody>
</table>

*Recommendation of study termination by DSMC*

**Inclusion Criteria**

**Participating Sites**

- Submission of 10 cases of TLRH/TRRH to Trial Management Committee
  - Age
  - BMI
  - Stage
  - OR time
  - EBL
  - LOS
  - Intracop and postop complications (<30 days)
  - Transfusion rates
- Total of 2 unedited videos of TLRH/TRRH
- Independent Review 2 members of Trial Management Committee

**Primary Outcome: DFS at 4.5 years**

<table>
<thead>
<tr>
<th>Intention to Treat</th>
<th>TARH (95% CI)</th>
<th>TLRH/TRRH (95% CI)</th>
<th>Non-inferiority boundary (1.24)</th>
<th>P-value for non-inferiority (2-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>86.5 (96.7 - 89.4)</td>
<td>86.0 (79.7 - 90.4)</td>
<td>87.1 (81.3 - 91.3)</td>
<td>0.87</td>
<td>0.35</td>
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</tbody>
</table>

Favors TARH  
Favors TLRH/TRRH
**Disease-Free Survival (DFS)**

HR: 3.74 (95% CI 1.63 - 8.58), p=0.002

Events/N
- TARH: 7/312
- TLRH/TRRH: 27/319

**Progression-Free Survival (PFS)**

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

Events/N
- TARH: 8/312
- TLRH/TRRH: 32/319

**Cumulative Local/Regional Recurrence**

HR: 4.26 (95% CI 1.44 - 12.6), p=0.009
Conclusions

- Disease-free survival at 4.5 years for minimally invasive radical hysterectomy was inferior compared to the open approach.
- Minimally invasive radical hysterectomy was associated with higher rates of loco/regional recurrences.
- Results of the LACC Trial should be discussed with patients scheduled to undergo radical hysterectomy.
**Surgery by Randomized Treatment**

<table>
<thead>
<tr>
<th></th>
<th>TARH</th>
<th>TLRH/TRRH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized patients</td>
<td>312</td>
<td>319</td>
</tr>
<tr>
<td>• TARH</td>
<td>274 (88%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>• TLRH/TRRH</td>
<td>8 (3%)</td>
<td>289 (91%)</td>
</tr>
<tr>
<td>• Withdrawn prior to surgery</td>
<td>19 (6%)</td>
<td>12 (4%)</td>
</tr>
<tr>
<td>• Surgery abandoned</td>
<td>11 (4%)</td>
<td>16 (5%)</td>
</tr>
<tr>
<td>Surgery performed as randomized</td>
<td>274 (88%)</td>
<td>289 (91%)</td>
</tr>
</tbody>
</table>

**Method of TLRH/TRRH**

- Laparoscopic
  - N=8
  - 7 (88%)
  - 1 (13%)
- Robotic
  - N=289
  - 244 (84%)
  - 45 (16%)

**MIS converted to Laparotomy**

- 1 (0.3%)
- 10 (3%)

**Postoperative Histopathology**

<table>
<thead>
<tr>
<th>Histopathology</th>
<th>TARH</th>
<th>TLRH/TRRH</th>
<th>P-value</th>
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<tbody>
<tr>
<td></td>
<td>282</td>
<td>291</td>
<td></td>
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<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>146 (52%)</td>
<td>152 (52%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>58 (21%)</td>
<td>59 (20%)</td>
<td></td>
</tr>
<tr>
<td>Adenosquamous</td>
<td>12 (4%)</td>
<td>12 (4%)</td>
<td></td>
</tr>
<tr>
<td>No residual disease</td>
<td>59 (21%)</td>
<td>60 (21%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>7 (2%)</td>
<td>8 (3%)</td>
<td></td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>29 (10%)</td>
<td>32 (11%)</td>
<td>0.98</td>
</tr>
<tr>
<td>2</td>
<td>111 (40%)</td>
<td>115 (40%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>61 (22%)</td>
<td>61 (21%)</td>
<td></td>
</tr>
<tr>
<td>Not Reported</td>
<td>81 (29%)</td>
<td>83 (29%)</td>
<td></td>
</tr>
<tr>
<td>Invasion</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Superficial</td>
<td>61 (22%)</td>
<td>83 (29%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Middle</td>
<td>72 (26%)</td>
<td>50 (17%)</td>
<td></td>
</tr>
<tr>
<td>Deep</td>
<td>56 (20%)</td>
<td>64 (22%)</td>
<td></td>
</tr>
<tr>
<td>Not Reported</td>
<td>94 (33%)</td>
<td>94 (32%)</td>
<td></td>
</tr>
</tbody>
</table>

**Additional Food for Thought**

- Clinical practice has already change based on a non-published, randomized clinical trial
- Majority of cases are laparoscopic
- All were done outside of the United States
- How many open radicals did our fellows do at UAB last year?
  - 19 Total
  - 6 Open Cases
- What about tumor size, grade?
- Do we throw the baby out with bath water?
Final Thoughts/Conclusions:

- All future cervical cancer screening should incorporate HPV testing (either by itself or with cytology)
- Eventually cytology will transition away
- Colposcopy: take more biopsies and preceding cytology/HPV results do make a difference
- Next generation treatment guidelines: its going to get a lot more complicated yet simpler at the same time
- The future of MIS in cervical cancer is truly uncertain
- Randomized surgical trials are really hard to do
- Change practice on published literature (not a presentation)
Thank you!
Questions?

It's a common misconception that noting kids' feet off the floor means definitely it's a Bert disease.