Management of Cervical Cancer

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• No disclosures
Outline

• The Problem
• Management of Early Stage Cervical Cancer
• Prevention
• The hysterectomy
• Fertility Sparing
• Ovaries
• Sentinel lymph nodes
Cervical Cancer

Squamous Cell Carcinoma

Adenocarcinoma
Cervical cancer – USA stats

- 2019 American Cancer Society estimates:
  - 13,170 new cases (13,240 in 2018)
  - 4,250 deaths (4,170 in 2018)

- 0.68% lifetime risk (1/147 women in USA)

<table>
<thead>
<tr>
<th></th>
<th>All stages</th>
<th>Local</th>
<th>Regional</th>
<th>Distant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td>68</td>
<td>91</td>
<td>57</td>
<td>16</td>
</tr>
<tr>
<td>Uterine</td>
<td>82</td>
<td>95</td>
<td>68</td>
<td>17</td>
</tr>
<tr>
<td>Ovary</td>
<td>44</td>
<td>92</td>
<td>72</td>
<td>27</td>
</tr>
</tbody>
</table>
The Global Problem

“It is unacceptable that every two minutes one woman dies of cervical cancer in a world where we have the proven solutions to prevent and treat this disease” says WHO Assistant Director-General for Noncommunicable Diseases and Mental Health, Dr Svetlana Axelrod

WHO Worldwide stats (2012)

• 4th Most common cancer in women
  • Breast > Colorectal > Lung > Cervical > Stomach
  • 7.9% of female cancers
  • 530,000 new cases

• 4th leading cause of cancer death in women
  • Breast > Lung > Colorectal > Cervical > Stomach
  • >300,000 deaths
  • 85% in low to middle income countries
### Why is it such a problem?

**Early detection is key!**

<table>
<thead>
<tr>
<th>Stage</th>
<th>5 Year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA1</td>
<td>97.5</td>
</tr>
<tr>
<td>IA2</td>
<td>94.8</td>
</tr>
<tr>
<td>IB1</td>
<td>89.1</td>
</tr>
<tr>
<td>IB2</td>
<td>75.7</td>
</tr>
<tr>
<td>IIA</td>
<td>73.4</td>
</tr>
<tr>
<td>IIB</td>
<td>65.8</td>
</tr>
<tr>
<td>IIIA</td>
<td>39.7</td>
</tr>
<tr>
<td>IIIB</td>
<td>41.5</td>
</tr>
<tr>
<td>IVA</td>
<td>22.0</td>
</tr>
<tr>
<td>I VB</td>
<td>9.3</td>
</tr>
</tbody>
</table>

Risk Factors for Cervical Cancer:

- **Demographic Factors**
  - Age
  - Race (black, Hispanic, American Indian)
  - **Low socioeconomic status**
  - Low educational level
- **Behavioral and Sexual Factors**
  - Number of sexual partners
  - **Early age at first coitus**
  - **Cigarette Smoking**
  - Long-term contraceptive use
  - Diet low in folate, carotene
- **Medical/Gynecological**
  - **Infection with High-risk HPV**
  - Multiparity
  - **Early age at first pregnancy**
  - **History of sexually transmitted disease** (HSV/HPV-associated lesions)
  - **Lack of routine cytologic screening**
  - **Immunosuppression** (HIV, steroids, Fanconi anemia, transplant)
  - Specific HLA-DR haplotypes
Symptoms of Cervical Cancer

- **Most common presentation of invasive cervical cancer:**
  - Abnormal vaginal bleeding
  - Post-coital bleeding
  - Vaginal discharge

- **Advanced disease symptoms**
  - Pelvic pain
  - Difficulty urinating/defecating
  - Metastatic: back pain, leg swelling (unilateral)

- **PE:** abnormal lesion on cervix, necrotic/friable.
  - Staging is clinical, include RVE
  - **Biopsy** confirmation
Early detection = The Pap Smear

- Drs. Papaniculaou & Traut (published 1941)
  - Became available in many countries in 1950s
  - Research showed treating precancerous lesions prevented development of cancer
  - USA incidence cervical cancer in 1975 was 14.8/100K → 6.5/100K (2006)

- Conventional:
  - Sensitivity HSIL: >90%

- Liquid-based:
  - Sensitivity HSIL: >95%
  - Allows for reflex HPV testing
  - Disadvantage higher cost

- Future: HPV testing → reflex PAP
Normal

Low N:C
Abundant cytoplasm
Well defined borders
Small non-descript Nuclei

LG-SIL: CIN I

Low N:C
Abundant cytoplasm
Large irregular nuclei
Viral Factories

HG-SIL

High N:C
Scant cytoplasm
Large Atypical Nuclei
Big/Dark/Irregular

HG-SIL

Slide Courtesy of Dr. Ajit Paintal
Abnormal PAP → Colposcopy

• Low-power (3x-15x) binocular
• Evaluate Cervix/Vulva/Vagina
• Focus on Transformation Zone (TZ)
  • Area between normal columnar epithelium & mature squamous epithelium
• Acetic Acid (3-5%)
  • Look for areas of acetowhite change
• Lugol Iodine Solution
  • Look for areas that do not absorb iodine
• Satisfactory colposcopy
  • Complete visualization of TZ and entire lesion
  • **BAD things:**
    • raised, gray, non-arborizing blood vessels, extension beyond TZ
• Biopsy: Taken to confirm colposcopist impression
• Colposcopic **Sensitivity to detect CIN 3** approx 70%. (ALTS)
  • Increased when 2 or more biopsies taken
  • Did not matter level of training: NP, Generalist, Gyn Onc Fellow, Gyn Onc
Primary Prevention: the best management of early stage cervical cancer!

- HPV Vaccination: HPV most common STD
  - HPV 16,18 → 80% cervical cancer cases
  - HPV 31,33, 45, 52, 58 also oncogenic
  - HPV 6,11 → 90% genital warts

- Who: everyone age 9-45 years old, CDC recommends age 11-12

- What: 2 shots <15 years old, 3 shots >15 years old
The HPV Vaccine

- Recombinant Non-infectious Viral Like Particle
  - Capsid alone (L1) → neutralizing antibody response

- Gardasil (Merck)
  - HPV 6,11,16,18 → Garadasil 9 (31, 33, 45, 52, 58)
  - Immunity 10 years → at least 6 years with Gardasil 9
  - CIN3/AIS prevention efficiency > 93%

- Cervarix (GlaxoSmithKline)
  - HPV 16,18
  - Immunity at least 9 years
  - CIN3/AIS prevention efficiency > 93%

- WHO supports use of either

- Treatment CIN3 and ok to get if h/o HPV
Early Stage Cervical Cancer

- What is it?
“Old” Staging - Clinical

• **FIGO**
  • H&P
    • vaginal and rectal exam
    • nodal exam (neck/supraclavicular and inguinal)
  • EUA, cystoscopy, hysteroscopy, proctoscopy,
  • CXR
  • IV pyelogram

• **USA** – Nodal status very important!
  • PET/CT skull to midthigh
  • Pelvic MRI

• **3 Categories**
  • Cervix Confined, tumor <4cm = Surgery
  • Locally advanced = Radiation
  • Distant mets (lung, liver, supracaclvicular node) = Chemotherapy
Cervical Cancer Staging

**microscopic**

**visible lesion**

- **IA**
  - IA1
  - IA2
  - Upper vagina
  - Parametia + (not to sidewall)

- **IB1**
  - Lower 1/3 vagina

- **IB2**
  - Pelvic side wall

- **IIA**
  - Upper vagina

- **IIB**
  - Pelvic side wall

- **IIIA**
  - Lower 1/3 vagina

- **IIIB**
  - Pelvic side wall
  - Hydronephrosis

- **IVA**

- **IVB**
  - Bladder/rectal mucosa
  - Beyond true pelvis
  - Distant mets

Carcinoma of Cervix: Staging

**Stage I** The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)
- **IA** Invasive carcinoma which can be diagnosed only by **microscopy**, with deepest invasion ≤ 5 mm and largest extension ≥ 7 mm, dx on LEEP/CKC or Hysterectomy Specimen
  - **IA1** stromal invasion of ≤ 3.0 mm in depth and extension of ≤ 7.0 mm
  - **IA2** stromal invasion of > 3.0 mm and not > 5.0 mm with an extension of not > 7.0 mm
- **IB** Clinically **visible** lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA*
  - **IB1** Clinically visible lesion ≤ 4.0 cm in greatest dimension
  - **IB2** Clinically visible lesion > 4.0 cm in greatest dimension

**Stage II** Cervical carcinoma invades **beyond the uterus**, but not to the pelvic wall or to the lower third of the vagina
- **IIA** Without parametrial invasion
  - **IIA1** Clinically visible lesion ≤ 4.0 cm in greatest dimension
  - **IIA2** Clinically visible lesion > 4 cm in greatest dimension
- **IIB** With obvious **parametrial invasion**

**Stage III** The tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney**
- **IIIA** Tumor involves **lower third of the vagina**, with no extension to the pelvic wall
- **IIIB** Extension to the **pelvic wall and/or hydronephrosis** or non-functioning kidney

**Stage 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 of the growth to **adjacent organs, mucosa of the bladder or rectum**
- **IVB** Spread to **distant organs**
New Staging! 2018

Box 1 FIGO staging of carcinoma of the cervix uteri (2018).

Stage I:
The carcinoma is strictly confined to the cervix uteri (extension to the 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

Stage 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

Stage III:
The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or paraaortic lymph nodes
- IIIA 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 non-functioning kidney (unless known to be due to another cause)

- IIIIC Involvement of pelvic and/or paraaortic lymph nodes, irrespective of tumor size and extent (with r and p notations)*
  - IIIIC1 Pelvic lymph node metastasis only
  - IIIIC2 Paraaortic lymph node metastasis

Stage IV:
The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bulblous edema, as such, does not permit a case to be allotted to stage IV
- IVA Spread of the growth to adjacent organs
- IVB Spread to distant organs

*Imaging and pathology can be used, when available, to supplement clinical findings with respect to tumor size and extent, in all stages.
*The involvement of vascular/lymphatic spaces does not change the staging. The lateral extent of the lesion is no longer considered.
*Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to stage III. For example, if imaging indicates pelvic lymph node metastasis, the stage allocation would be stage III1C1r and, if confirmed by pathological findings, it would be Stage III1C1p. The type of imaging modality or pathology technique used should always be documented. When in doubt, the lower staging should be assigned.

- Big Changes
  - lateral spread removed
  - IB (1,2,3)
  - IIIC (1,2, r, p)
<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA1 (neg LVSI):</td>
<td>CKC, simple hysterectomy</td>
</tr>
<tr>
<td>IA2:</td>
<td>Modified Radical hysterectomy + PLND ± PALND</td>
</tr>
<tr>
<td>IB1, IB2:</td>
<td>Radical hysterectomy + PLND ± PALND</td>
</tr>
<tr>
<td>IB3 – IVA:</td>
<td>Chemo/XRT</td>
</tr>
<tr>
<td>IVB:</td>
<td>cisplatin/paclitaxel +/- bevacizumab, +/- palliative XRT</td>
</tr>
</tbody>
</table>
## “old IB1” Surgery = XRT

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>Radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Survival</strong></td>
<td>91%</td>
<td>89%</td>
</tr>
<tr>
<td><strong>Serious complications</strong></td>
<td>Urologic Fistula (1-2%)</td>
<td>Intestinal and Urinary strictures and fistulae (1.4 -5.3%)</td>
</tr>
<tr>
<td><strong>Vaginal function</strong></td>
<td>Initially shortened</td>
<td>Fibrosis and stenosis</td>
</tr>
<tr>
<td><strong>Ovarian function</strong></td>
<td>Conserved</td>
<td>Destroyed</td>
</tr>
<tr>
<td><strong>Chronic effects</strong></td>
<td>Atonic bladder (3%)</td>
<td>Radiation enteritis (6-8%)</td>
</tr>
</tbody>
</table>

NB: ovarian transposition is not generally supported → oocyte/embryo freezing and HRT, there are grants to help with fertility preservation costs for cancer patients, NW has a program

XRT if IB1 but not surgical candidate, often VTE, AMI (on plavix)
IB, IIA (old) can be cured with XRT (EBRT and brachytherapy) or surgery, toxicity and morbidity differ

- Prospective RCT
- Adjuvant tx in 62/114 (<4cm tumor), 46>55 (>4cm tumor)

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>XRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>170</td>
<td>167</td>
</tr>
<tr>
<td>5yr OS</td>
<td>83%</td>
<td>74%</td>
</tr>
<tr>
<td>Recurrence</td>
<td>42 (25%)</td>
<td>44 (26%)</td>
</tr>
<tr>
<td>Severe Morbidity</td>
<td>48 (28%)</td>
<td>19 (12%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type I</th>
<th>Name</th>
<th>Vagina</th>
<th>Bladder</th>
<th>Ureter</th>
<th>Uterine Artery</th>
<th>Parametria</th>
<th>Uterosacral Ligament</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Extrafascial (Simple)</td>
<td>Minimal</td>
<td>Partially Mobilized</td>
<td>Not Mobilized</td>
<td>At the uterus</td>
<td>Minimal</td>
<td>At the uterus</td>
</tr>
<tr>
<td>II</td>
<td>Modified Radical</td>
<td>Upper 1-2 cm removed</td>
<td>Partially Mobilized</td>
<td>Unroofed in parametrial tunnel</td>
<td>Medial to ureter</td>
<td>Medial to ureter</td>
<td>At midpoint</td>
</tr>
<tr>
<td>III</td>
<td>Radical</td>
<td>Upper 1/3 – 1/2 removed</td>
<td>Completely mobilized</td>
<td>Dissected until entry into bladder</td>
<td>At the origin (internal iliac/superior vesical)</td>
<td>At Pelvic Side Wall</td>
<td>At distal attachment</td>
</tr>
<tr>
<td>IV</td>
<td>Extended Radical</td>
<td>Upper 3/4</td>
<td>Completely mobilized</td>
<td>All peri-ureteral tissue removed</td>
<td>At origin (and ligation of sup. Vesical)</td>
<td>As Class III</td>
<td>As Class III</td>
</tr>
<tr>
<td>V</td>
<td>Partial Exenteration</td>
<td>As Class IV</td>
<td>Portion of bladder resected</td>
<td>Distal Ureter removed</td>
<td>As Class IV</td>
<td>As Class III</td>
<td>As Class III</td>
</tr>
</tbody>
</table>
Radical Hysterectomy

• 1895!

Spaces

- Parametria = cardinal and uterosacral ligaments, free the ureter and transect uterine artery
Pelvic LAD

- Important prognostic information!
Para-aortic LAD

Vena cava

Right ureter

Renal a. & v.

Inferior mesenteric artery

Aorta

Right ovarian artery and vein

Mid portion of common iliac a.
3 hours later...
Complications of radical surgery

• GU
  • Voiding dysfunction
  • 2.1% fistula
  • urine retention
    • Foley or Suprapubic catheter

• Anal dysfunction
Surgical Approach

• MIS = Open
LACC: laparoscopic approach to cervical cancer

- Phase III prospective international, multicenter non-inferiority RCT of laparoscopic or robotic vs abdominal radical hysterectomy in patients with early stage cervical cancer

- Well designed with good surgical technical validity

- Is DFS with MIS not inferior to open? In early stage SCC, adeno, or adenosquamous (IA1 LVSI → IB1)
  - 90% power to declare non-inferiority at 4.5yrs with 7.2% margin

- Mean age 46yo, 91% IB1
LACC

- **MIS (84.4% lpsc, 15.6% robotic)**
- **Open**

<table>
<thead>
<tr>
<th></th>
<th>MIS</th>
<th>Open</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>319</td>
<td>312</td>
</tr>
<tr>
<td>4.5yr DFS</td>
<td>86%</td>
<td>96.5%</td>
</tr>
<tr>
<td>3yr DFS</td>
<td>91.2%</td>
<td>97.1%</td>
</tr>
<tr>
<td>3yr OS</td>
<td>93.8%</td>
<td>99%</td>
</tr>
<tr>
<td>HR death from any cause</td>
<td>6 (1.77-20.3)</td>
<td></td>
</tr>
</tbody>
</table>
A cohort study of Stage IA2 or IB1 cervical cancer from 2010-2013

To determine effect of MIS on all cause mortality of women undergoing radical hysterectomy

Median f/u 45 months

1225/2461 (49.8%) had MIS
4yr relative survival rate of early stage cervical cancer tx with radical hyst: Annual % change

<table>
<thead>
<tr>
<th></th>
<th>Open</th>
<th>MIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000-2006</td>
<td>0.3%</td>
<td></td>
</tr>
<tr>
<td>2006-2010</td>
<td></td>
<td>Decline 0.8% per year after 2006</td>
</tr>
</tbody>
</table>
ASCO 2018, Abstract #5502: outcomes and costs of open, robotic, and laparoscopic radical hysterectomy for stage IB1 cervical cancer

- SEER 2010-2013 IB1 SCC or adenocarcinoma of the cervix s/p radical hysterectomy: open = 982, MIS = 910,

- Tumor ≥ 2cm 5yrOS: MIS 81.3% (75.6-87.3%) vs open 90.8% (87.7-93.9%),

- HR: 2.14 (95%CI) (1.36-3.38), p <0.001

- Cost: Open ($12,080) > Robotic ($11,562) > Lpsc ($9,649)
Radical hysterectomy with bilateral pelvic lymph node dissection (with or without SLN mapping) is the preferred treatment for FIGO stage IA2, IB1, IB2 and select IB3-IIA1 lesions when fertility preservation is not desired. Radical hysterectomy results in resection of much wider margins compared with a simple hysterectomy, including removal of parts of the cardinal and uterosacral ligaments and the upper 1–2 cm of the vagina; in addition, pelvic and sometimes para-aortic nodes are removed. The Querleu and Morrow classification system\(^1\) is a modern surgical classification that describes degree of resection and nerve preservation in three-dimensional (3D) planes of resection.\(^2\) Procedural details for the most commonly used types of hysterectomy are described in Table 1 (see CERV-C 5 of 7).

The standard and historical approach for radical hysterectomy is with an open abdominal approach. Previous iterations of the guidelines indicated that radical hysterectomy could be performed via open laparotomy or minimally invasive surgery (MIS) laparoscopic approaches, using either conventional or robotic techniques. However, several key contemporary reports have questioned the presumed therapeutic equivalency of open vs. MIS approaches. A prospective randomized trial\(^3\) demonstrated that minimally invasive radical hysterectomy was associated with lower rates of DFS and OS than open abdominal radical hysterectomy. Moreover, two recent epidemiologic studies also demonstrated that minimally invasive radical hysterectomy was associated with shorter OS than open surgery among women with stage IA2-IB1 cervical cancer.\(^4,5\) See Discussion for additional details.

Given recently presented findings of significantly poorer survival outcomes with the minimally invasive approach compared to the open approach in a randomized controlled trial of women with early-stage cervical cancer, women should be carefully counseled about the short-term versus long-term outcomes and oncologic risks of the different surgical approaches.\(^3-5\)
Abstract #5504
Recurrence rates in cervical cancer patients treated with abdominal versus minimally invasive radical hysterectomy: A multi-institutional analysis of 700 cases.

- Retrospective multi-institutional review
- Stage IA1, IA2, IB1 from 2010-2017
- N=704
- Multivariate analysis:
  - MIS OR recurrence 2.37 (p=0.031)
    - (race, comorbidities, preop tumor size, histology, grade, smoking, LVSI, vaginal margin status, adjuvant tx)

<table>
<thead>
<tr>
<th></th>
<th>Open</th>
<th>MIS – 90% robotic</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>185 (26.3%)</td>
<td>519 (73.7%)</td>
<td></td>
</tr>
<tr>
<td>recurrence</td>
<td>13/185 (7%)</td>
<td>42/519 (8.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>death</td>
<td>10/185 (5.4%)</td>
<td>26/519 (5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Recurrence rate tumor &lt;= 2cm</td>
<td>5/121 (4.1%)</td>
<td>25/415 (6%)</td>
<td>0.34</td>
</tr>
</tbody>
</table>
Abstract #5504

- <2cm MIS may be ok but data not consistent, and surgeon correct about lesion size <2cm only 75%
- Uterine manipulator?...likely not the culprit

<table>
<thead>
<tr>
<th></th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>No vaginal manipulator</td>
<td>0/26</td>
</tr>
<tr>
<td>Intra-uterine: (Vcare, Zumi, Rumi)</td>
<td>19/270 (7%)</td>
</tr>
<tr>
<td>Vaginal manipulator: (EEA, colpo probe)</td>
<td>22/210 (11%)</td>
</tr>
</tbody>
</table>

- # rad hysts on decline, resource effort: is open rad hyst that bad vs put effort into vaccination and prevention
Today: Data vs emotion
Fertility Preservation

• 40% early stage cervical cancer <40yo

• HB 2617 – active now
  • IL is the 5th state to do this
  • mandates IL insurance cover oncofertility and fertility preservation
  • Oocyte, sperm, embryo preservation

• Patient resources
  • Kristin Smith: Chicago
    • ksmith@nm.org
  • Jennifer Elvikis: West suburbs,
    • jelvikis@nm.org
    ▪ Oak Brook office
Fertility Sparing Surgery

- Stage IA1 without LVSI
  - Conization
    - SEER database study (n = 1409)
      - Age ≤40 years with stage IA1 cervical cancer
      - No significant difference in 5 yr survival between those who underwent conization versus hysterectomy (98 vs 99%)
Fertility Sparing Surgery: Radical trachelectomy (Plante)

- <40yo, no impaired fertility, lesion <2cm, stage IA-IB1 (old), negative upper endocervical margin (at least 5mm), negative nodes
- 2-4% recur
- 2-6% mortality
- 70% of attempts at pregnancy are successful with 50% term delivery rate
- 16% 1st trimester miscarriage, 4% 2nd trimester loss
Reproductive outcomes of patients undergoing radical trachelectomy for early-stage cervical cancer


a Department of Surgery, Gynecology Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA
b Department of Psychiatry and Behavioral Sciences, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

- N=105, 2001-2010 with IB1 (75%) tx with radical trachelectomy, PLND, cerclage
- Median age 32
- 1st trimester miscarriage: 4% (N=1)
- 2nd trimester miscarriage: 11% (N=3)
- 74% conceptions → live 3rd trimester births
  - 32-36 weeks: 35%
  - 37 weeks: 65%
OB outcomes (Kim, et al)

- 35/105 attempted conception 6 months after surgery
- 23/35 (66%) were successful in conceiving
- 4 patients had 2 pregnancies
  - 2nd all delivered 32-36 weeks
- 20 live births → all deliveries C-section
- ART use (N=18): 10 cervical stenosis
- Route of trachelectomy did not matter
- Preterm and 2nd trimester loss due to cerclage disruption
Fertility Sparing: Unique IB1 or less Big CKC and Pelvic lymphadenectomy

- **Stage IA1 with LVSI, IA2, or IB1**
  - Squamous carcinoma or adenocarcinoma histology
  - Lesion size ≤2 cm with limited endocervical extension as assessed by colposcopy and MRI
  - No evidence of lymph node metastasis

- **Less is More?**
  - recurrence (4.4 %)
  - mortality (2.1 %)

- Prospective study of 32 women <40 with Stage IA2 (9.28%), IB1 (21, 66%), IB2 (2, 6%) tx with CKC and pelvic LAD (30) or SLN (2)
- Median f/u 75 months
- DFS 94%, OS 97%
- Safe, but 1/5 needed more treatment
Pregnancy outcome, Bogani et al

- 11/16 (69%) who attempted to conceive became pregnant
- Important because trachelectomy associated with more OB complications than CKC

OB outcomes:
Term = 8
Preterm (32 week) = 1
2\textsuperscript{nd} trimester miscarriage = 1
Early pregnancy = 1
Ovaries

- SCC, <1% ovary mets
- Stage IB adenocarcinoma 1.3-7.7% ovary mets, higher for higher stages
- transposed ovaries fail 20% if unirradiated, 42% with irradiation
- benign adnexal mass after RT up to 4%
SLN ( Sentinel Lymph Nodes)

- Lymph node most important prognostic factor
- PLND → 20% lymphedema
Sentinel lymph nodes

- Blue dye (**isofulfan blue**) CI: sulfa allergy
- Technetium 99 (Tc99)
- Near infrared (**ICG**: indocyanine green) water soluble CI: iodine/shellfish allergy (requires FIREFLY technology)
- Ultrastaging: IHC for pancytokeratin AE1 and AE3, cytokeratin
- Macro met: >2mm foci or mets, micro mets: 0.2-2.mm tumor, isolated tumor cells: <2mm or individual cells
Photos firefly, blue dye
SLN - Cervix

- Still investigational, but included in NCCN guidelines
- Sensitivity 92%, NPV 98%
- Tumor ≤ 2cm
  - Detection 95.4%, Sensitivity 100%
- Tumor >2cm
  - Detection 80.1%, Sensitivity 89.3%

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLN</td>
<td>91%</td>
<td>100%</td>
</tr>
<tr>
<td>PET</td>
<td>75%</td>
<td>98%</td>
</tr>
<tr>
<td>MRI</td>
<td>56%</td>
<td>93%</td>
</tr>
<tr>
<td>CT</td>
<td>58%</td>
<td>92%</td>
</tr>
</tbody>
</table>
Adjuvant XRT after surgery

- Sedlis and Peters criteria

<table>
<thead>
<tr>
<th>LVSII</th>
<th>Stromal Invasion</th>
<th>Tumor Size (cm) (determined by clinical palpation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>Deep 1/3</td>
<td>Any</td>
</tr>
<tr>
<td>+</td>
<td>Middle 1/3</td>
<td>≥2</td>
</tr>
<tr>
<td>+</td>
<td>Superficial 1/3</td>
<td>≥5</td>
</tr>
<tr>
<td>-</td>
<td>Middle or deep 1/3</td>
<td>≥4</td>
</tr>
</tbody>
</table>

LVSII: Lymphovascular space invasion
Locally advanced Cervix

- Med Onc, Rad Onc, GYN Onc
- Cisplatin
- If toxicity, carbo AUC 2 weekly
- Main treatment XRT based
- Stage IIB, III, IVA (locally advanced)
- XRT vs XRT cis vs XRT cis/5FU/hydroxyurea vs XRT hydroxyurea
- Chemo improved all outcomes and cisplatin based chemo regimens best
- Less toxicity in cisplatin alone

<table>
<thead>
<tr>
<th></th>
<th>Cis</th>
<th>Cis/5FU/hydroxy</th>
<th>Hydroxy</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR progression</td>
<td>0.57 (0.42-0.78)</td>
<td>0.55 (0.4-0.71)</td>
<td>Baseline</td>
</tr>
<tr>
<td>RR death</td>
<td>0.61 (0.44-0.85)</td>
<td>0.58 (0.41-0.81)</td>
<td>baseline</td>
</tr>
</tbody>
</table>
NCCN alert

- Feb 1999
- Concomitant chemotherapy and radiation should be considered in all cervix cancer patients
Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis

John A Green, John M Kirwan, Jayne F Tierney, Paul Symonds, Lydia Fresco, Mandy Collingwood, Christopher J Williams

- 10% survival benefit with addition of chemo to XRT
- Meta-analysis (N=4580)
- chemoXRT improves OS , HR 0.71
Outback Chemo

- Outback Trial, GOG 274: awaiting results, carbo/taxol after cis/XRT
- RTOG 0724: enrolling, carbo/taxol after adjuvant chemo/XRT for high risk patients
Other Highlights

- No indication for completion hysterectomy in locally advanced cervix
- NACT → rad hyst → postop XRT vs XRT worse DFS, toxicity and no change in OS
- Cis/gem concurrent with XRT followed by outback cis/gem significantly more toxicity
Metastatic (Tewari et al)

- Phase III RCT with 90% power to detect 30% reduction in risk of death
- Cisplatin 50mg/m² + paclitaxel 135 or 175mg/m² IV +/- bevacizumab 15mg/kg q21 days
- Topotecan 0.75mg.m² IV D1-3 + paclitaxel 175mg/m² +/- bevacizumab 15mg/kg q21days
- Until toxicity, progression, complete response

Final Overall Survival of the Phase III Randomised Trial of Chemotherapy with and without Bevacizumab for Advanced Cervical Cancer: An NRG Oncology/Gynecologic Oncology Group Study

*Lancet. 2017 October 07; 390(10103):*
- Topo/taxol not superior to cis/taxol (HR 1.2)
- Addition of bev to chemo increased OS from 13 to 17 months (4-month increase OS), HR death 0.71, higher response rates
- Bev side effects: HTN, VTE, GI fistula
Tewari Final Update

- Improved OS and PFS with bev
- Bev improved OS and PFS with either chemo regimen

<table>
<thead>
<tr>
<th></th>
<th>No Bev (n=225)</th>
<th>Bevacizumab (n=227)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>178 (79)</td>
<td>170 (75)</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>13.3</td>
<td>16.8</td>
</tr>
<tr>
<td>HR=0.77 (95% CI, 0.62–0.95)</td>
<td><strong>P=0.0068</strong></td>
<td></td>
</tr>
<tr>
<td>RR, %</td>
<td>36</td>
<td>49</td>
</tr>
<tr>
<td>P=0.0032</td>
<td></td>
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</tr>
</tbody>
</table>

OS: overall survival
HR: hazard ratio
CI: confidence interval
Bev: bevacizumab

PFS: progression-free survival
RR: response rate
HR: hazard ratio
CI: confidence interval
Bev: bevacizumab
Recurrent (Chemo vs Surgery)

**Surgery** = anterior or posterior of total pelvic exenteration.
- isolated central pelvic recurrence with negative surgical margins.

**Chemo**: based on toxicity
- platinum/taxane +/- bev preferred initial tx
  - cisplatin preferred if platinum naïve
- taxol/avastin
- Pembrolizumab becoming more prime time
- gem, topotecan, single agent avastin
### SYSTEMIC THERAPY REGIMENS FOR CERVICAL CANCER

**Chemoradiation**

#### Preferred Regimens
- Cisplatin
- Carboplatin if patient is cisplatin intolerant

#### Recurrent or Metastatic Disease

<table>
<thead>
<tr>
<th>First-line combination therapy&lt;sup&gt;b,c&lt;/sup&gt;</th>
<th>Possible first-line single-agent therapy&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Second-line therapy&lt;sup&gt;6&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred Regimens</strong></td>
<td><strong>Preferred Regimens</strong></td>
<td><strong>Preferred Regimens</strong></td>
</tr>
<tr>
<td>• Cisplatin/paclitaxel/bevacizumab&lt;sup&gt;d,1&lt;/sup&gt; (category 1)</td>
<td>• Cisplatin&lt;sup&gt;3&lt;/sup&gt;</td>
<td>• Pembrolizumab for PD-L1-positive&lt;sup&gt;f&lt;/sup&gt; or MSI-H/dMMR tumors&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>• Carboplatin/paclitaxel/bevacizumab&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td>(All agents listed here are category 2B unless otherwise noted)</td>
</tr>
<tr>
<td><strong>Other Recommended Regimens</strong></td>
<td><strong>Other Recommended Regimens</strong></td>
<td>• Bevacizumab&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>• Cisplatin/paclitaxel&lt;sup&gt;2,3&lt;/sup&gt; (category 1)</td>
<td>• Carboplatin&lt;sup&gt;f&lt;/sup&gt;</td>
<td>• Albumin-bound paclitaxel</td>
</tr>
<tr>
<td>• Carboplatin/paclitaxel&lt;sup&gt;4,5&lt;/sup&gt; (category 1 for patients who have received prior cisplatin therapy)</td>
<td>• Paclitaxel&lt;sup&gt;8,9&lt;/sup&gt;</td>
<td>• Docetaxel</td>
</tr>
<tr>
<td>• Topotecan/paclitaxel/bevacizumab&lt;sup&gt;d,1&lt;/sup&gt; (category 1)</td>
<td></td>
<td>• Fluorouracil</td>
</tr>
<tr>
<td>• Topotecan/paclitaxel&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td>• Gemcitabine</td>
</tr>
<tr>
<td>• Cisplatin/topotecan&lt;sup&gt;6&lt;/sup&gt;</td>
<td></td>
<td>• Ifosfamide</td>
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<tr>
<td></td>
<td></td>
<td>• Irinotecan</td>
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<tr>
<td></td>
<td></td>
<td>• Mitomycin</td>
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<tr>
<td></td>
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<td>• Pemetrexed</td>
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<tr>
<td></td>
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<td>• Topotecan</td>
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<tr>
<td></td>
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<td>• Vinorelbine</td>
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</table>

**Useful in Certain Circumstances**
- Larotrectinib or entrectinib for NTRK gene fusion-positive tumors (category 2B)

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<sup>1</sup> FDA approval for cervical cancer.

<sup>2</sup> Not FDA approved for cervical cancer.

<sup>3</sup> FDA approval for cervical cancer.

<sup>4</sup> FDA approval for cervical cancer.

<sup>5</sup> FDA approval for cervical cancer.

<sup>6</sup> FDA approval for cervical cancer.

<sup>7</sup> FDA approval for cervical cancer.

<sup>8</sup> FDA approval for cervical cancer.

<sup>9</sup> FDA approval for cervical cancer.

<sup>10</sup> FDA approval for cervical cancer.

<sup>11</sup> FDA approval for cervical cancer.

<sup>12</sup> FDA approval for cervical cancer.

**See Evidence Blocks on CERV-F (EB-1) and CERV-F (EB-2)**
Clinical trials

- Listeria injections
Thanks!

Questions