Management of Cervical Cancer

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University of Pennsylvania
Learning Objectives

• Discuss the state of the art treatments for cervical cancer

• Identify basic competencies needed to perform gynecologic IMRT
Global Statistics

• 2nd most common cancer in the developing world
• ~500,000 new cases worldwide
• AIDS defining in the setting of HIV
• ~10,500 new cases per year in US
Transient HPV infection

CIN 1

CIN 2

CIN 3

Invasive Cervical Cancer

>90% Clearance

Progression/regression

Cofactors for Persistence:
Smoking
Increasing age
HPV type
Mutagens
Immunosuppression
Inflammation
Hormones
Genetic Factors

Kahn J, NEJM 2009; 361:271-278
HPV

• High Risk Types:
  – 16 and 18 (responsible for 70% of cervical cancers)
  – 31 and 45 (responsible for 10%)
  – Others: 33, 35, 39, 51, 52, 56, 58, 59, 68, 73, and 82

• Low risk types:
  – 6 and 11 (genital warts)
HPV Vaccine

• Gardasil (Merck): HPV 6, 11, 16, 18
  – 6, 11 cause 90% of genital warts
    • 16, 18 cause 70-80% of cervical cancers, and 20-25% H&N cancers, as well as vaginal, penile, anal

• Cervarix (GSK): HPV 16, 18
  – Approved 2009

• Timing:
  – FDA approved for women age 9-26
  – Extended to boys 9-26 in 9/09
  – Seeking approval for women aged 27-45
  – Given in 3 injections at 0, 2, and 6 months

• 32% of women eligible have received all 3 doses

*Cancer Epidemiology Biomarkers Prev 2012 May 3*
Histologic Subtypes

- Squamous cell carcinoma (85%)
- Adenocarcinoma (10%)
- Clear cell carcinoma (associated with in utero DES exposure) 1%
- Other (rare)
  - Sarcoma
  - Lymphoma
  - Small cell carcinoma
  - Neuroendocrine carcinoma
Prognostic Factors

- **Treatment related:**
  - Overall treatment time
  - Use of brachytherapy
  - Chemotherapy

- **Patient related**
  - Hgb status
  - Smoking

- **Tumor related**
  - Posthysterectomy (LVSI, size, stromal invasion)
  - Nodal status
Staging and Workup
FIGO Clinical Staging

• Pelvic exam-under anesthesia
• Cystoscopy
• Proctoscopy
• Chest Xray
• Intravenous Pyelogram
• Skeletal Survey
FIGO Clinical Staging-Not allowed

- CT
- MRI
- PET/CT
- Exploratory Surgery
FIGO Staging
FIGO Staging 2009 Updates

- Stage IIA1: upper 2/3rds vaginal involvement with size \( \leq 4 \) cm

- Stage IIA2: upper 2/3 vaginal involvement with size \( > 4 \) cm
Patterns of Spread

- **Direct Extension**
  - Vaginal mucosa
  - Myometrium of lower uterine segment and corpus (endocervical lesions)
  - Parametria

- **Lymph Nodes:**
  - Obturator LNs, Int/Ext/common Iliacs, Para-aortic LNs, and inguinals (vaginal disease)

- **Late disease**
  - Distant metastases to bone, lung or liver, supradiaphragmatic LN disease
Determining Extent of Primary Tumor

• Pelvic examination
  – Staging Accuracy: 47%
    • Bipat et al, Gyn Onc 2003

• MRI vs CT
  – Staging Accuracy: 86%
  – MR is superior to CT for detecting uterine body involvement/PM invasion (ACRIN 6651/GOG 183)
    • JCO 2006
  – MR superior in detecting vaginal extension
Determining Extent of LN/Distant Metastases: Role of FDG-PET/CT
# Risk of Lymph Node Metastases

<table>
<thead>
<tr>
<th>Stage</th>
<th>Pelvic LN</th>
<th>PA LN</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA1</td>
<td>&lt;1%</td>
<td></td>
</tr>
<tr>
<td>IA2</td>
<td>6-7%</td>
<td>&lt;3%</td>
</tr>
<tr>
<td>IB</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>IIB</td>
<td>30%</td>
<td>20%</td>
</tr>
<tr>
<td>III</td>
<td>45%</td>
<td>30%</td>
</tr>
</tbody>
</table>
FDG PET/CT Nodal Status

Kidd et al, JCO 2010

RFS ALL

DSS Stage I

DSS Stage II

DSS Stage III

Kidd et al, JCO 2010
Treatment

• Surgery

• Radiation Therapy

• Chemotherapy
Surgical Management: Early stage IA

- LEEP (Loop electrosurgical excision procedure)
- Conization
- Cryotherapy
- Radical trachelectomy
  - 3-6% recurrence rate when limited to <2 cm (-nodes, -LVSI)
- Radical hysterectomy: IA2
Surgery

- Radical Hysterectomy:
  - Class II hysterectomy generally sufficient
  - Lymphadenectomy:
    - Stage IA2 or small IB1:
      - low risk of node + (2-8%)  
      - pelvic LN resection only (no
        Exception: pelvic + paraaortic LN
        resection if PET/CT data that they
        may be positive.

- Partial mobilization of the ureters:
  - Uterine vessels ligated medial to ureters.
  - Uterosacral ligaments ligated midway b/t uterus and sacrum
  - Partial mobilization of the ureters

- Medial half of cardinal ligament excised
- Upper third of vagina excised
Treatment for Stage IB

- Radical hysterectomy and pelvic +/- PA LND
- Radiotherapy
  - EBRT and brachytherapy: 80 Gy to point A
Primary radiotherapy vs Radical Hysterectomy

469 Pts 1986-1991
Stages IB-IIA

Radical surgery
Class III rad hyst

RT 40-53 Gy
1.8-2 Gy
ICI x1
Pt A dose 70-90 Gy

Stage pT2b/+LN/+SM

Adj XRT
50.4 Gy to pelvis
PA to 45 Gy if PA nodes +

Landoni et al, Lancet 1997
Primary radiotherapy vs Radical Hysterectomy
Landoni et al, Lancet 1997

- Median follow-up 87 months
- No difference in survival/LC
- Adjuvant RT
  - 64% of patients overall
  - IB1 54%, IB2 88%
  - Higher rates of urologic complications with combined surgery/adjuvant RT
Role of Adjuvant Radiotherapy
GOG 92: LN Negative
Role of adjuvant post-operative radiotherapy

277 Pts Stage IB
1988-1995
Rad Hyst & LND
>1/3 stromal invasion/LVSI/LTD*

RT 46-50.4 Gy pelvis
23-28 fx 1.8-2.0 Gy
(No brachy)

No Further Therapy

* Pts with LN not eligible

Sedlis et al, Gyn Onc 1999
## GOG 92 Eligibility Criteria

<table>
<thead>
<tr>
<th>CLS</th>
<th>Stromal Invasion</th>
<th>Tumor Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Deep 1/3</td>
<td>Any</td>
</tr>
<tr>
<td>Positive</td>
<td>Middle 1/3</td>
<td>≥2 cm</td>
</tr>
<tr>
<td>Positive</td>
<td>Superficial 1/3</td>
<td>≥5 cm</td>
</tr>
<tr>
<td>Negative</td>
<td>Deep or middle 1/3</td>
<td>≥4 cm</td>
</tr>
</tbody>
</table>

Need 2 of 3 factors: Positive CLS, Middle 1/3, ≥ 4 cm

Sedlis et al, Gyn Onc 1999
## GOG 92: Sites of Failure

<table>
<thead>
<tr>
<th></th>
<th>Radiotherapy</th>
<th>No Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local</strong></td>
<td>13%</td>
<td>19%</td>
</tr>
<tr>
<td><strong>Distant</strong></td>
<td>2%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Sedlis et al, Gyn Onc 1999
GOG 92: Update

• Median f/u: 10 years
• PFS: 46% reduction in HR
• Overall survival:
  – 30% improvement (p=0.074)
• Grade 3/4 toxicity:
  – 6.6% (RT) vs 2.1% (obs)
• Adenocarcinoma and adenosquamous recurrence rate:
  – 8.8% (RT) vs 44% (obs), p=0.019

Rotman et al, IJROPB 2006
Radiation vs Radiation and Concurrent and Adjuvant Cisplatin/5FU after Hysterectomy
GOG 109
Role of concurrent chemotherapy as adjuvant therapy in high risk pts in post-operative setting

243 Pts Stage IA2, IB, IIA
1991-1996
Rad Hyst & LND

RT only
49.3 Gy / 29 fx

RT + CT
CDDP 70 mg/m²
5-FU 4,000 mg/m²
Days 1, 22, 43, 66

Peters et al, JCO 2000
Eligibility Criteria

• Positive Pelvic Lymph Nodes

• Positive Parametrial Involvement

• Positive Surgical Margins
GOG 109/SWOG 8797

• 4 year PFS
  – 80% CT+RT vs. 63% RT alone

• 4 year OS:
  – 81% CT+RT vs. 71% RT alone
Treatment of Locally Advanced Cervical Cancer
## Concurrent weekly CDDP/RT

<table>
<thead>
<tr>
<th></th>
<th>GOG 120</th>
<th>NCIC</th>
<th>GOG 123</th>
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</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
<td>IIB-IVA</td>
<td>IA – IIA, &gt; 5cm</td>
<td>IB2</td>
</tr>
<tr>
<td><strong>Arms</strong></td>
<td>WPRT/B/HU</td>
<td>WPRT/B</td>
<td>WPRT/B + SH</td>
</tr>
<tr>
<td></td>
<td>WPRT/B/cis/5FU/HU</td>
<td>WPRT/B + wkly cis</td>
<td>WPRT/B/wkly cis + SH</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>47%</td>
<td>62%</td>
<td>74%</td>
</tr>
<tr>
<td></td>
<td>65% (3 year)</td>
<td>58% (5 year), p = NS</td>
<td>83% (3 year)</td>
</tr>
<tr>
<td><strong>LR</strong></td>
<td></td>
<td></td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>37%</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>↓toxicity with cis or HU alone</td>
<td>Non-surgical staging of nodes</td>
<td>↑pCR with chemo (52 vs 41%)</td>
</tr>
</tbody>
</table>
## Concurrent CDDP/5FU and RT

<table>
<thead>
<tr>
<th>Stage</th>
<th>RTOG 90-01 Morris, 1999</th>
<th>SWOG 8797 Peters, 2000</th>
<th>GOG 85 Whitney, 1999</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>IIB – IVA</td>
<td>IA2-IIA (posthys)</td>
<td>IIB-IVA</td>
</tr>
<tr>
<td></td>
<td>IB-IIA &gt; 5cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LN +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arms</td>
<td>EFRT/B</td>
<td>WPRT</td>
<td>WPRT/B /HU</td>
</tr>
<tr>
<td></td>
<td>WPRT/B + cis5FU</td>
<td>WPRT + cis/5FU x 4 cycles</td>
<td>WPRT/B/cis/5FU</td>
</tr>
<tr>
<td>OS</td>
<td>41%</td>
<td>71%</td>
<td>43%</td>
</tr>
<tr>
<td></td>
<td>67% (8 year)</td>
<td>81% (4 year)</td>
<td>55% (3 year)</td>
</tr>
<tr>
<td>LR</td>
<td>35%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notes</td>
<td>NS ↑ PAN failures in CRT arm</td>
<td>Postop (+LN, +PM, +margins)</td>
<td>Late complications 16% (equivalent)</td>
</tr>
</tbody>
</table>
What was the 5 year overall survival benefit of concurrent chemo observed in the meta-analysis published in 2008 (JCO) by the Chemoradiotherapy for Cervical Cancer Meta-analysis collaboration?

1. 20%
2. 15%
3. 12%
4. 6%
Chemo-radiotherapy Meta-analysis

- 15 randomized trials of CT+RT vs RT
  - 11 Platinum based
  - 3 Nonplatinum
- 3452 pts
- CT+RT vs RT
  - 8% absolute improvement in DFS (50% to 58%)
    - Also for locoregional DFS and distant metastases free survival
  - Overall survival benefit of 6% (60% to 66%) for CT+RT vs RT
- CT+RT → CT vs RT alone
  - Two trials
  - 19% absolute OS improvement (60% to 79%)
Should we be giving outback chemo?

515 Pts Stage IIB-IVA
KPS ≥ 70

EBRT 50.4 Gy/1.8 Gy fx
Brachy 30-35 Gy in 96 hours
Cisplatin weekly 40 mg/m2

EBRT+brachy
Cis 40 mg/m2 and gem 125 mg/m2 weekly
Outback: Cis 50 mg/m2 and gem 1000 mg/m2
Q21 day cycles x 2

Duenas-Gonzalez, JCO 2011
Should we be giving outback chemo?

• Use of cisplatin plus gemcitabine resulted in
  • An improvement in progression free survival compared to cisplatin alone (3 year PFS 74% versus 65%)
  • An improvement in overall survival
  • Significantly more serious (grade ¾) toxicities (87% versus 46%) and rate of hospitalizations (30% versus 11%)

Duenas-Gonzalez A et al, JCO 2011
Treatment of Locally advanced IB2-IVA cervical cancer

- EBRT 45 Gy (1.8 Gy fx)
  - 3D CRT, AP/PA, 4 fields
  - Boost to parametrial or sidewall disease
- Brachytherapy 80-90 Gy
- Concurrent chemotherapy
  - (weekly CDDP 40 mg/m2)
Radiation Therapy
RT Fields
FDG PET/CT and MR simulation
FDG PET/CT Simulation
Use of IMRT for Intact Cervix: Controversies

• Contouring

• Organ Motion

• Simulation/Setup/IGRT
CONSENSUS GUIDELINES FOR DELINEATION OF CLINICAL TARGET VOLUME FOR INTENSITY-MODULATED PELVIC RADIOTHERAPY FOR THE DEFINITIVE TREATMENT OF CERVIX CANCER

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CATHERYN YASHAR, M.D.,∥∥∥ SUSHIL BERIWAL, M.D.,∥∥∥ AARON WOLFSON, M.D.,∥∥∥
ALEXANDRA TAYLOR, F.R.C.R.,∥∥∥ WALTER BOSCH, PH.D.,∥∥∥ ISAM EL NAQA, PH.D.,∥∥∥
AND ANTHONY FYLES, M.D.* FOR THE GYN IMRT CONSORTIUM.

- http://www.rtog.org/CoreLab/ContouringAtlases/GYN.aspx
IMRT for Intact Cervix Cancer

Lim et al, IJROBP 2011
How much margin is needed?
Every Patient is Unique...

Van den Bunt et al, Radio and Onc 2008
IMRT Considerations for Intact Cervix Cancer

- Simulation: bladder full and bladder empty
- MRI pretreatment or at the time of simulation
- Margins:
  - CTV→PTV margins for primary CTV: 1.5-2 cm
  - CTV→PTV margins for nodal CTV: 7 mm
- Daily soft tissue IGRT
Uses for IMRT

• PA nodes

• Inguinal nodes

• Boost
  – Nodal boost
  – Sidewall boost
Contouring PA Nodes

Upper 1/3 4%
Middle 1/3 36%
Lower 1/3 60%

Left Paraaortic - 51%
Aortocaval - 44%
Right Paracaval - 4%
Contouring Inguinal nodes: How much margin is necessary?

- Margin on nearest femoral vessel required to encompass ≥90% of the positive nodes:
  - anteromedial ≥35 mm
  - anterior ≥23 mm
  - anterolateral ≥25 mm
  - medial ≥22 mm
  - posterior ≥9 mm
  - lateral ≥32 mm

Kim et al, PRO 2012
PET Defined Nodal Boost
Brachytherapy
Brachytherapy

• Type: LDR v HDR
  – fractionation

• Sequencing

• Choice of instrumentation:
  – Interstitial
  – Tandem and (ovoid/ring)

• Image-guided treatment planning
  – Xray vs CT vs MRI
Classical & Revised Manchester System

Revised Pt A - may fall in the high dose gradient next to the ovoid
Normal Tissue Dose Points

- **Bladder**
  - ICRU Bladder pt<75 Gy
  - D2cc <90 Gy

- **Rectum**
  - ICRU Rectal pt<70 Gy
  - D2cc: 70-75 Gy

- **Vagina:**
  - Upper: 120-140 Gy
  - Lower: 90 Gy
MRI for Image Guided Brachytherapy
Treatment Schema

<table>
<thead>
<tr>
<th>Week</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBRT (40-45 Gy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Boost</td>
</tr>
<tr>
<td>Chemo (CDDP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDR Brachy</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDR Brachy</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
# 45 Gy Pelvis EQD2

<table>
<thead>
<tr>
<th>Fx #</th>
<th>Dose</th>
<th>EQD2 Tumor</th>
<th>EQD2 Normal tissue (90% PD)</th>
<th>EQD2 Normal tissue (70% of PD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>7 Gy</td>
<td>83.9 Gy</td>
<td>90.1 Gy</td>
<td>74.2 Gy</td>
</tr>
<tr>
<td>5</td>
<td>6 Gy</td>
<td>84.3 Gy</td>
<td>88.6 Gy</td>
<td>73.4 Gy</td>
</tr>
<tr>
<td>6</td>
<td>5 Gy</td>
<td>81.8 Gy</td>
<td>83.7 Gy</td>
<td>70.5 Gy</td>
</tr>
<tr>
<td>5</td>
<td>5.5 Gy</td>
<td>79.8 Gy</td>
<td>82.6 Gy</td>
<td>69.6 Gy</td>
</tr>
</tbody>
</table>
Summary

• Concurrent chemoradiotherapy for locally advanced cervical cancer
• Role of outback chemotherapy in the locally advanced setting is an open question
• IMRT may be reasonable, but must consider:
  – Contouring
  – Organ motion/Margins
  – Image guidance/daily IGRT