Recent Advances in Cervical Cancer

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Disclosures

No conflicts
Objectives

• To discuss the scope of cervical cancer burden and strategies to reduce incidence
• To describe advances and ongoing trials in management of cervical cancer
  – Post-operative setting
  – Locally advanced disease
Epidemiology

- 3rd most common gyn cancer
- Incidence in 2014: 12,360
- Deaths in 2014: 4,020
- Incidence of oropharynx cancer (OP) in men > cervix ca

Chaturvedi JCO 2011
Worldwide Burden

- 530,000 cases and 275,000 deaths annually
- #1 cause of cancer mortality in women in Africa and Central America

[Map showing incidence and mortality]
Human Papilloma Virus

- HPV detected in 99.7% of cervix ca
- Infection is common -> most cleared
- 8 high-risk genotypes cause 95% of cervix ca
  - HPV-16/18 responsible for 70%

Persistent HPV infection

↓

CIN III

↓

Invasive cancer

15 years

Cofactors:
High-risk genotype
Smoking
OCPs
HIV
Immunosuppression
Micronutrient deficiency
Mechanism of HPV Carcinogenesis

E6 binds p53, E7 affects RB
Landscape of genomic alterations in cervical carcinomas

79 SCC
24 adenoca
Mexico, Norway

PIK3CA 14%
PTEN 6%
TP53 5%
EP300 16%
FBXW7 15%
HLA-B 9%
MAPK1 8%

AI Ojesina Nature 2013
HPV screening guidelines

• USPSTF, ACS, ACOG (2012)
• \textit{Reduce colposcopy and biopsy}

• Cytology only for 21-29 yo every 3 years
• HPV co-testing for women 30+ years every 5 yrs
• Stop at age 65 years if recent negative
• More frequent screening: HIV, immunosuppression, \textit{in utero} DES exposure
HPV vaccine

- Quadrivalent: HPV-6/11/16/18
- Bivalent: HPV-16/18

- Uptake in U.S. for females aged 13-17:
  - 54% of at least 1 dose and 33% for 3 doses
- No immunity against HPV types responsible for 30% of cervical cancers

CIN, VAIN, VIN
Genital warts
Oral infection
AIN in males
<table>
<thead>
<tr>
<th>Histology</th>
<th>Squamous cell ca (69%)</th>
<th>Adenocarcinoma/Adenosquamous (25%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• HPV-16 (59%)</td>
<td>• HPV-18 (37%)</td>
</tr>
<tr>
<td></td>
<td>• HPV-18 (13%)</td>
<td>• HPV-16 (36%)</td>
</tr>
<tr>
<td>Other (6%):</td>
<td></td>
<td>• Incidence increasing</td>
</tr>
<tr>
<td>Small cell/</td>
<td></td>
<td>• Higher rates of LN involvement</td>
</tr>
<tr>
<td>Neuroendocrine ca</td>
<td></td>
<td>• Higher rates of ovarian involvement</td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
<td>• Worse prognosis</td>
</tr>
<tr>
<td>Sarcoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Staging

## Permitted by FIGO

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colposcopy</td>
<td></td>
</tr>
<tr>
<td>Endocervical curettage</td>
<td></td>
</tr>
<tr>
<td>Hysteroscopy</td>
<td></td>
</tr>
<tr>
<td>Cystoscopy (biopsy)</td>
<td></td>
</tr>
<tr>
<td>Proctoscopy (biopsy)</td>
<td></td>
</tr>
<tr>
<td>Barium enema</td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>only assessment of hydronephrosis, ureteral obstruction</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td></td>
</tr>
<tr>
<td>Skeletal radiographs</td>
<td></td>
</tr>
<tr>
<td>Intravenous pyelography</td>
<td></td>
</tr>
</tbody>
</table>

*If disagreement in clinical exam, lower stage used*
FIGO 2009 Staging Modification

- Stage IIA1: upper 2/3 vagina with size ≤ 4cm
- Stage IIA2: upper 2/3 vagina with size > 4cm
Advanced imaging modalities

MRI
• More sensitive than exam to detect parametrial involvement

PET-CT
• Approved by Medicare for baseline staging and post-treatment surveillance
PET in cervical cancer

- Nodal status most important prognostic factor

- Post-therapy PET is predictive of survival

Kidd JCO 2010
Schwarz JAMA 2007
Dose escalation to PET+ nodes

- 53 pts with EF-IMRT to median 54 Gy
- 7% acute (3/46) and 7% (3/46) late g3+ GI toxicity
- V55< 5cc small bowel

Poorvu IJROBP 2013
Dose escalation to para-aortics

- 105 pts with gross N+ of para-aortics
- IMRT to elective nodal volume to 45-50.4 Gy with boost to 60-66 Gy
- 3-yr duodenal toxicity:
  - V55> 15 cc 49%
  - V55< 15 cc 7%

Verma IJROBP 2013
Predictive Value of Response

- MRI pre-RT, week 2, week 4-5, 1-2 months post-RT
- Tumor volume and regression ratio correlated with LR/DSS

Pre-RT vol $>$ 40cc and V3/V1 $>$ 20% strongest predictors of outcome

Wang Cancer 2011
## Principles of Therapy

<table>
<thead>
<tr>
<th>Surgical Therapy</th>
<th>Radiation therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1A</strong></td>
<td><strong>1B1</strong></td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>Definitive RT + concurrent chemotherapy</td>
</tr>
<tr>
<td>Laser/CK Cone</td>
<td></td>
</tr>
<tr>
<td>LEEP</td>
<td></td>
</tr>
<tr>
<td>Trachelectomy</td>
<td></td>
</tr>
<tr>
<td>Simple hysterectomy</td>
<td></td>
</tr>
<tr>
<td><strong>1B1</strong></td>
<td><strong>1B2-IVA</strong></td>
</tr>
<tr>
<td>Trachelectomy (&lt; 2 cm)</td>
<td>Definitive RT + concurrent chemotherapy</td>
</tr>
<tr>
<td>Radical hysterectomy</td>
<td></td>
</tr>
</tbody>
</table>
## Post-op RT: Intermediate Risk

277 pts Radical HYS + pelvic LND

<table>
<thead>
<tr>
<th>LVSI</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>&gt;2 cm</td>
</tr>
<tr>
<td>Positive</td>
<td>Superficial 1/3</td>
<td>&gt;5 cm</td>
</tr>
<tr>
<td>Negative</td>
<td>Deep or middle 1/3</td>
<td>&gt; 4 cm</td>
</tr>
</tbody>
</table>

- **Observation**
- **Pelvic RT**
  - 46 Gy/23 fx
  - 50.4 Gy/28 fx

GOG 92
Post-op RT: GOG 92

- 46% ↓ recurrence risk (HR 0.54, p<0.01)
- 30% ↓ risk of death (HR 0.7, p=0.06)
- Pronounced benefit for adeno histology
  - 9 vs. 44% RR
- 4.5% ↑ g3/4 toxicity

Sedlis Gyn Onc 1999
Post-op ChemoRT: High Risk

268 pts
FIGO stage 1A2/1B/II
1. Positive LN
2. Positive parametria
3. Positive margins

Pelvic RT
49.3 Gy/29 fx

Pelvic RT
49.3 Gy/29 fx
Cisplatin 70 mg/m2
CI 5FU 1000 mg/m2/d
x 4 cycles

GOG 109/SWOG 8797
Post-op RT: GOG 109/SWOG 8797

- PFS/OS HR 2.0
- 4-yr PFS: 63 vs 80%
- 4-yr OS: 71 vs. 81%

- Addition of chemo resulted in similar outcomes for adenocarcinoma
- 70% received 3-4 cycles chemo -> ↑ PFS/OS
- Impact of adjuvant chemo uncertain

Peters JCO 2000
## Post-op RT: Ongoing trials

<table>
<thead>
<tr>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GOG 263/KGOG 0801</strong></td>
<td><strong>RTOG/GOG 0724</strong></td>
</tr>
<tr>
<td>• Addition of weekly cisplatin to adjuvant pelvic RT</td>
<td>• Addition of outback carboplatin/paclitaxel (x4c) to weekly cisplatin/pelvic RT</td>
</tr>
<tr>
<td>• Endpoints:</td>
<td>• Endpoints:</td>
</tr>
<tr>
<td>– RFS</td>
<td>– DFS</td>
</tr>
<tr>
<td>– OS</td>
<td>– OS</td>
</tr>
<tr>
<td>– Toxicity profile</td>
<td>– Neuropathy/QOL</td>
</tr>
</tbody>
</table>
|  – QOL            | }
RTOG TIME-C trial

- Phase III study of conformal vs. IMRT Pelvic RT for post-op cervical/endometrial ca

  Stratified by:
  (1) Dose
  (2) Use of weekly chemo
  (3) Disease site

  Eligibility for cervix: Intermediate or high risk with –margins

- Primary endpoint: Acute GI toxicity at 5 weeks, patient reported by EPIC
Definitive Radiation Therapy
Stage IB₂/IIB – IVA

NCI Alert 1999

- Survival improved with concurrent chemotherapy in 6 of 7 randomized trials
- St IB₂/ IIB – IVA, >4 / >5 cm tumors
## Concurrent Chemotherapy Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>FIGO stage</th>
<th>No of Patients</th>
<th>Arms</th>
<th>Follow-up</th>
<th>HR</th>
<th>% Increase in Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 85</td>
<td>IIB–IVA</td>
<td>368</td>
<td>CF vs HU</td>
<td>8.7 yrs</td>
<td>0.7</td>
<td>10</td>
</tr>
<tr>
<td>RTOG 9001</td>
<td>IB (&gt;5cm) – IVA</td>
<td>388</td>
<td>CF vs None</td>
<td>6.6 yrs</td>
<td>0.59</td>
<td>15</td>
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<tr>
<td>GOG 120</td>
<td>IIB–IVA</td>
<td>526</td>
<td>C vs HU</td>
<td>35 mo.</td>
<td>0.61</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>IIB–IVA</td>
<td>526</td>
<td>CFHU vs HU</td>
<td>35 mo.</td>
<td>0.58</td>
<td>18</td>
</tr>
<tr>
<td>GOG 123</td>
<td>IB2 (&gt;4cm)</td>
<td>369</td>
<td>C vs None</td>
<td>36 mo.</td>
<td>0.54</td>
<td>9</td>
</tr>
<tr>
<td>NCI Canada</td>
<td>IB (&gt;5 cm) – IVA</td>
<td>253</td>
<td>C vs None</td>
<td>64 mo.</td>
<td>0.91</td>
<td>3</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>IB–IVA</td>
<td>3452</td>
<td>Chemo vs none</td>
<td>62 mo.</td>
<td>0.78</td>
<td>—</td>
</tr>
</tbody>
</table>
Meta-Analysis of Randomized Trials

- 15 trials 1987-2006, N=3,452
- Cisplatin-based, 3 non-platinum (FU, mitomycin)
- EBRT: 40-61.2 Gy
- OS HR 0.81 (5-yr 60 to 66%)
- LC ↑ Acute toxicity ↑

13 Trials comparing RT with RT + concurrent CT

△ 6% OS
Outback chemotherapy

• 515 pts with Stage IIB-IVA cervix ca
• RCT: concurrent and adjuvant cis/gemcitabine vs concurrent cis alone
• 3-year PFS 74% vs 65%, p=0.03
• OS HR 0.68, p=0.02
• Grade 3-4 toxicity:
  – 87% vs 46%

Dueñas-González A et al. JCO 2011
Stage III-IVA greatest benefit
OUTBACK Trial

- Multi-center GCIG
- Accrual goal: 780
- Eligible:
  - 1B1 with positive nodes, IB2, II, IIB, IVA
- Weekly cisplatin with pelvic RT +/- 4c carbo/tax

Arm A: Control Arm
Concurrent chemoRT

Arm B: Intervention Arm
Concurrent chemoRT ->
adjuvant chemo
GOG 240

- RCT in metastatic/recurrent cervical cancer
- 2x2 design to evaluate effectiveness of Bevacizumab and nonplatinum combination chemo (cis/taxol vs. topo/taxol)

OS HR 0.71
17.0 vs. 13.3 mo, p<0.01
Response rates 48% vs. 36%

Tewari NEJM 2014
Mutational landscape

- High-throughput genotyping
- *KRAS* mutations exclusively in adenoca (17.5%)
- *PIK3CA* mutations in 31%
  - Across histologic subtypes
  - Associated with decreased survival (67 vs 90 months)
- *EGFR* mutations only in SCC

Wright Cancer 2013
Novel therapeutic strategies

- Small molecular inhibitors
  - Ribonucleotide reductase, PARP, PI3K inhibitors
- Anti-angiogenics
  - Bevacizumab (RTOG 0417)
- Immunotherapy
  - Ipilimumab, ADXS