Cervical Cancer

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Incidence and Mortality in 2006

3rd most common gynecological cancer in the U.S

- **Worldwide**
  - Incidence = 466,000
  - Mortality ~ 232,000

- **US (projected)**
  - Incidence = 9,710
  - Mortality = 3,700

- Bimodal peak from ages 35-39 and 60-64
Etiology

HPV - 1st etiologic agent in 99% tumors
- HPV 16, 18 most common; 35, 45 and others-less common

Risk factors include:
- HPV
- Smoking
- Early frequent sexual activity with multiple partners
- OCP use
- Multiparity
Diagnosis and Screening

Diagnosis
- Pap smear
- HPV DNA test
- Colposcopy
- Biopsy

Symptoms
- Abnormal vaginal discharge or bleeding
- Pelvic pain
- Leg edema
- Anemia
- Asymptomatic – abnormal Pap smear
Pathology

Histology: ~90% of invasive tumors are SCC, 10% are adenocarcinoma, and 1% clear cell

Progression of Disease in 90% of disease
- CIN1 → CIN2 → CIN3 → CIS in 5-10 years
- CIS → invasive cancer in 3-10 years

Spread
- Local extension into other pelvic structures
- Sequentially along LN chains
- Hematogenous spread to lung, bone, liver, and brain
Staging

IA - max depth of 5mm from base of epithelium and a horizontal spread of 7.0mm or less
IA1 - 3.0 or less in depth and 7.0 mm or less horizontal
IA2 - more than 3-5 mm with 7.0 mm or less horizontal

IB - Clinically visible lesion
IB1 - clinically visible lesion 4 cm or less
IB2 - clinically visible lesion more than 4 cm

Staging is clinical!

AJCC 7th ed., 2010/FIGO 2008
Staging

- **IIA** - Tumor w/o parametrial invasion
  - IIA1 - Clinically visible lesion 4cm or less
  - IIA2 - Clinically visible lesion more than 4cm

- **IIB** - Tumor with parametrial invasion

- **IIIA** - Tumor extends to lower third of vagina, no pelvic wall extension

- **IIIB** - Tumor extends to pelvic wall and/or affecting the kidney

- **IVA** - Tumor invades mucosa of bladder or rectum, and/or extends beyond the true pelvis

- **N1=IIIB** (regional lymph node metastasis)

- **M1=IVB** (distant metastasis)
Stage IA and IB1: Early stage
- Radical hysterectomy or radiation therapy
- 5 year survival = 80-90%

Stage IB2-IVA: Locally advanced disease
- Radiation or combined chemoradiation
- 5 year survival ~ 65%

Late stage and recurrent disease
- Palliative chemotherapy novel agents
- 5 year survival <5%

Brachytherapy is a component of radiation treatment at any stage
<table>
<thead>
<tr>
<th>Stage</th>
<th>Pelvic Node +</th>
<th>Overall Survival</th>
<th>Overall Survival Pelvic +</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB</td>
<td>15%</td>
<td>85-90%</td>
<td>50-60%</td>
</tr>
<tr>
<td>IIB</td>
<td>30%</td>
<td>60-65%</td>
<td>30%</td>
</tr>
<tr>
<td>IIIB</td>
<td>45%</td>
<td>30-40%</td>
<td>10-15%</td>
</tr>
<tr>
<td>IVA</td>
<td>50-70%</td>
<td>5-10%</td>
<td>0%</td>
</tr>
</tbody>
</table>
ASSESSING LYMPH NODE INVOLVEMENT:

- Lymphangiography
- Surgery
- CT/MRI
- PET
Lymph Nodes of the Pelvis
Conventional pelvic fields planned on bony landmarks as an indication of lymph node location have been used for several decades. Locoregional rates or relapse remain high, especially in lymph node regions. Need optimization of radiation field parameters.
Lymphangiogram

Pendlebury et al. (1993)

- Bipedal angiogram
- 87 patients with Stage II or III carcinoma treated with RT retrospectively reviewed
- 62% of the patients with angiogram had radiation fields altered from a standard portal
- Conclusion: standard fields may result in a geographic miss in some patients
Fig. 1. Simulator films: "Standard" field size. (a) Postero-anterior field; (b) Lateral field (note: antero-posterior dimension shown in full width).
Bony landmarks are not an adequate substitute for lymphangiography in defining pelvic LN location for cervix cancer/Bonin (Fox Chase) IJROBP 34(1):167-172, 1996

Fig. 1. The reference points from which lymph node positions were measured and the range of their location with regard to that reference point on A/P simulation films.

Fig. 2. The reference points from which lymph node positions were measured and the range of their location with regard to that reference point on LAT simulation films.
Greer et al. (1990)

- 100 patients had intraoperative retroperitoneal measurements to examine anatomic basis during radical surgery.
- Structural measurements of pelvic/paraaortic arterial branches made in reference to lumbosacral prominence.
- Mean level of aortic bifurcation = 6.7 cm above lumbosacral prominence, common iliac artery = 1.7 cm right, 1.4 cm left.
- Conclusion: place superior border at L4-5 interspace to encompass the mid-common iliac nodes consistently.
FIG. 1. Illustration of the lumbosacral prominence and the radiographic sacral promontory. The lumbosacral prominence is the surgical landmark that defines the anteroinferior lip of the L5 vertebral body.
FIG. 3. Illustration of the posterior extension of the uterosacral and cardinal ligaments to the level of the sacral hollow. The rectangle indicates current conventional lateral pelvic radiotherapy fields with a superior border of L5–S1 and a posterior border at the S2–S3 interspace, which provides inadequate coverage of volume at risk.
CT vs. conventional pelvic fields

Finlay et al 2006 - Canada
N= 43, FIGO Stages II-III
Pelvic arteries contoured on CT, hidden
Conventional pelvic fields outlined
Superiorly- 34 (79%) had inadequate coverage, AP margins inadequate in 20.9%, LAT margins inadequate in 69.8%.
Conclusion: conventional fields based on bony landmarks do not provide optimal lymph node coverage. May include excess tissue
Grigsby et al 2001: CT vs. FDG-PET

N-101 patients

CT: 20% abnormal pelvic nodes, 7% paraaortic; PET: 67% abnormal pelvic nodes, 21% paraaortic

2y PFS: 64% paraaortic in CT-/PET-, 18% in CT-/PET+, 14% in CT+/PET+ (p<0.0001)

This study demonstrates that FDG-PET detects abnormal lymph node regions more often than does CT and that the findings on PET are a better predictor of survival than those of CT in patients with carcinoma of the cervix.
Defining CTV for pelvic nodes..

- Determination of target volumes and organs at risk not well standardized
- Need optimal lymph node field coverage; guidelines to optimize the delivery of EBRT

- Consensus guidelines defining CTV for pelvic LN in EBRT for uterine cervical cancer
  - RTSG of the JCOG (2010)
Table 1. Clinical target volume definition on pelvic nodes related to anatomic landmarks for cervical cancer

<table>
<thead>
<tr>
<th>Node chains</th>
<th>Cranial margin</th>
<th>Caudal margin</th>
<th>Anterior margin</th>
<th>Posterior margin</th>
<th>Lateral margin</th>
<th>Medial margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common iliac</td>
<td>Aortic bifurcation or L4-5 space</td>
<td>Common iliac a bifurcation</td>
<td>7 mm anterior to a/v</td>
<td>L5—sacrum (adequately involve adipose connective tissue between lateral surface of vertebral body and psoas m&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>7 mm lateral to a/v (expanding to psoas major m)</td>
<td>—</td>
</tr>
<tr>
<td>External iliac</td>
<td>Common iliac a bifurcation</td>
<td>Superior aspect of femoral head</td>
<td>7 mm anterior to a/v (connecting to obturator region)</td>
<td>7 mm posterior to a/v (connecting to obturator region)</td>
<td>7 mm lateral to a/v (expanding to psoas major m or iliacus m)</td>
<td>7 mm medial to a/v uterus, ovary, bowel, ureter or bladder</td>
</tr>
<tr>
<td>Internal iliac</td>
<td>Common iliac a bifurcation</td>
<td>Cranial section of coccygeus m, spine of ischium or uterine a/v (connecting to parametrial region)</td>
<td>Cranial level: wing of sacrum</td>
<td>Cranial level: psoas m, iliacus m or lateral edge of sacroiliac joint</td>
<td>Middle-caudal level: anterior edge of piriformis m or inferior gluteal a/v</td>
<td>Middle level: Iliac bone, psoas m or medial edge of iliacus m</td>
</tr>
<tr>
<td>Abdominal</td>
<td>Caudal section of sacroiliac joint (connecting to internal iliac region)</td>
<td>Superior part of obturator foramen</td>
<td>Cranial-middle level: connecting to external iliac region</td>
<td>Cranial-middle level: connecting to internal iliac region</td>
<td>Obturater internus m, iliacus m, psoas m or iliac bone</td>
<td>Caudal level: obturator internus m or piriformis m</td>
</tr>
<tr>
<td>Presacral</td>
<td>Common iliac a bifurcation</td>
<td>Lower level of S2 or cranial section of piriformis m</td>
<td>10 mm anterior to sacrum</td>
<td>L5—sacrum</td>
<td>Piriformis m (connecting to external or internal iliac region)</td>
<td>—</td>
</tr>
</tbody>
</table>

<sup>a</sup> artery; a/v, artery and vein; m, muscle.

<sup>Even in patients with low adipose connective tissue in this space, posterior margin should also extend to posterior edge of vertebral body.</sup>
Figure 1. An atlas of clinical target volume for pelvic lymph nodes for uterine cervical cancer
LN CTV defined as area encompassed by a 7mm margin around the pelvic vessels

The bones and muscle were excluded, however the bowel routinely was not

For the common iliac region, two definitions exist; based on blood vessel and bone anatomy

External iliac region defined as the level of the superior border of the femoral head

Modifications were made in each nodal area to cover adjacent adipose tissues at risk for microscopic nodal metastases.
What does this guideline provide?

- It provides standard definitions for nodal CTV in cervical cancer to aid in treatment planning.

- Can be used in multi-institutional clinical trials to avoid variation in CTV determination.
ROLE OF SURGERY IN CERVICAL CANCER:

- As a diagnostic procedure – to obtain tissue
- As a “curative” procedure
- To indicate the need for adjuvant therapy
TYPES OF SURGERY:

- Total (extrafascial) abdominal hysterectomy
  - Removal or cervix, small rim or vaginal cuff and outside of the pubocervical fascia
- Modified radical hysterectomy
  - Unroofing of the ureters to resect parametrial and paracervical tissue medial to ureters and vaginal cuff
- Radical hysterectomy
  - Mobilization of the ureters, bladder and rectum to remove parametrial tissue to pelvic sidewall and vaginal cuff
- Extended radical hysterectomy
  - Same as above with full mobilization of the ureters
- Total pelvic exenteration
  - This operation removes the bladder, urethra, rectum, anus, and supporting muscles and ligaments, together with the reproductive organs
Generally speaking, for gross disease in cervical cancer requires higher doses of radiation in the vicinity 60+ Gy.

**TD 5/5:**
- Kidney- 23 Gy
- Bladder- 65 Gy
- Rectum- 60 Gy
- Spinal Cord- 47 Gy
- Small intestine- 40 Gy
Brachytherapy

- Prescribed to a point
- Other tumor sites prescribed to a volume
- LDR: Low dose intracavitary brachytherapy. 15-20 Gy × 2 fx. It is temporary and usually takes 1 to 4 days.
- HDR: To an increasing extent, low-dose-rate intracavitary brachytherapy is being replaced by high-dose-rate intracavitary therapy. 6 Gy × 5 fx or 7 Gy × 4 fx
Uterine Implants

- Prescribe to Point A = 2 cm superior to the external os and 2 cm lateral to central canal.

- Point B = 3 cm lateral to Point A, represents parametrial nodes

- Bladder point = posterior to surface of Foley balloon

- Rectal point = 5 mm behind posterior vaginal wall.
Chemoradiotherapy is widely used in treating women with cervical cancer.

How did it first come about.....all due to the findings of 5 trials.
Phase III trials with concurrent chemo-radiotherapy in stage IB2-IVa Cervical Cancer

- Advanced clinical stage (IIB, III, IVA)
  - GOG 85, RTOG 90-01, GOG 120

- Bulky stage IB (IB2)
  - GOG 123

- Stage IA2, IB with positive margins, positive nodes, paramererial extension
  - SWOG 8797 (GOG 109)
### Ca Cervix: Relative Risk of Death in Five Clinical Trials of Concurrent CT/RT

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
<th>Control</th>
<th>Comparison</th>
<th>Survival Benefit</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB2 (GOG123)</td>
<td>RT</td>
<td>RT+ wkly Plat</td>
<td>9%</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>IIB-IVA (GOG120)</td>
<td>RT+HU</td>
<td>RT+ wkly Plat</td>
<td>18%</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT+ wkly Plat, FU, HU</td>
<td>12%</td>
<td>0.58</td>
<td></td>
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<tr>
<td>IB-IVA (RTOG9001)</td>
<td>Ext field RT</td>
<td>RT+ wkly Plat, FU</td>
<td>12%</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>IB2-IVA (GOG85)</td>
<td>RT+HU</td>
<td>RT+ wkly Plat, FU</td>
<td>10%</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>IB-IIA SWOG8789/GOG109</td>
<td>RT</td>
<td>RT+ wkly Plat, FU</td>
<td>10%</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>
Survival by treatment group
GOG 85
IIB,III,IVA (Negative para-aortic Lymph nodes).

55% vs. 43%

Whitney C W et al. JCO 1999;17:1339-1339
GOG 120
Kaplan-Meier Estimates of Overall Survival
IIB, III, IVA (Negative para-aortic Lymph nodes).

RTOG 9001
Stages IB2-IVA or stage IB or IIA (with a tumor > 4cms or involvement of pelvic lymph nodes)

73% vs. 58%

GOG 123
Kaplan-Meier Estimates of Overall Survival in Patients with Cervical Cancer Given Radiotherapy and Cisplatin or Radiotherapy Alone (and adjuvant hysterectomy)
Stage IB2 (tumor ≥ 4 cm in diameter)


83% vs. 75%
Concomitant chemoradiation improve absolute survival and DFS whether or not platinum was used with absolute benefit of 6% and 8% respectively.
Decreasing relative effect of chemoradiotherapy on survival with increasing tumor stage; size of benefit may vary.
Chemoradiation appears to reduce local and distant recurrence.
Cervical Cancer: Standard Treatment locoregional disease/locally advanced: IB2-IVA

2/22/1999: NCI Clinical Announcement:

Five different large, randomized clinical trials showed women benefited from the use of radiation therapy and chemotherapy given together. The findings of this trials are remarkably consistent. They are likely to change the standard of care: Concomitant Chemoradiotherapy.
Systematic reviews by Green et al (2001, 2005) and Lukka et al (2002) found that interpretation of the benefits was complicated.

Difficult to distinguish any interaction between the treatment effect and patient characteristics.

Concluded that IPD meta-analysis required to obtain more reliable estimates of effect in patient subgroups

Chemotherapy for Cervical Cancer Meta-Analysis Collaboration

To assess the effect of chemoradiotherapy on all outcomes
<table>
<thead>
<tr>
<th>Main analysis</th>
<th>Trial Period</th>
<th>Stage</th>
<th>Affected Para-aortic Nodes Excluded?</th>
<th>Comparison</th>
<th>Concomitant CT (dose in mg/m²)</th>
<th>No. of Cycles</th>
<th>Frequency (weeks)</th>
<th>RT (Gy to point A)</th>
<th>RT Duration (days)</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Thomas (a)</em></td>
<td>1987-1995</td>
<td>lb (&gt;5 cm) to Ila</td>
<td>No</td>
<td>RT v CTRT</td>
<td>IV FU 32 mg/m²</td>
<td>2</td>
<td>3</td>
<td>50</td>
<td>&lt; 56</td>
<td>116</td>
</tr>
<tr>
<td><em>Thomas (b)</em></td>
<td>1987-1995</td>
<td>lb (&gt;5 cm) to Ila</td>
<td>No</td>
<td>Hyperfractionated RT v CTRT</td>
<td>IV FU 32 mg/m²</td>
<td>2</td>
<td>3</td>
<td>50</td>
<td>&lt; 56</td>
<td>118</td>
</tr>
<tr>
<td><em>Lorvidhaya (a)</em></td>
<td>1997-1994</td>
<td>lb, IIIb to Iva</td>
<td>No</td>
<td>RT v CTRT</td>
<td>MMC 10 mg/m²</td>
<td>2</td>
<td>4</td>
<td>50</td>
<td>28</td>
<td>49-56</td>
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<tr>
<td><em>Lorvidhaya (b)</em></td>
<td>1997-1994</td>
<td>lb, IIIb to Iva</td>
<td>No</td>
<td>RT + Adj CT + CTRT</td>
<td>MMC 10 mg/m², FU (oral 4,200 mg)</td>
<td>2</td>
<td>4</td>
<td>50</td>
<td>28</td>
<td>49-56</td>
</tr>
<tr>
<td>Onishi *44</td>
<td>1989-1995</td>
<td>lb to IV</td>
<td>No</td>
<td>RT v CTRT</td>
<td>Adj FU 6,800 mg/loral CTRT</td>
<td>3</td>
<td>4</td>
<td>50</td>
<td>24</td>
<td>45-55</td>
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<tr>
<td>Roberts *19</td>
<td>1991-2001</td>
<td>lb2, II to Iva</td>
<td>No</td>
<td>RT v CTRT</td>
<td>MMC 30 mg/m²</td>
<td>2</td>
<td>6</td>
<td>II-IVB: 40 Gy</td>
<td>45-55</td>
<td>Not specified</td>
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<td>Petras *6,16</td>
<td>SWOG 8797</td>
<td>laa to Ila</td>
<td>No</td>
<td>RT v CTRT</td>
<td>CDDP 70 mg/m²</td>
<td>4</td>
<td>3</td>
<td>49.3</td>
<td>None</td>
<td>42</td>
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<tr>
<td>Pearcy *23</td>
<td>1991-1996</td>
<td>lb-lla (&gt; 4 cm) to III to Iva</td>
<td>No</td>
<td>S + RT v S + CTRT</td>
<td>CDDP 0 mg/m²</td>
<td>5</td>
<td>1</td>
<td>45</td>
<td>24-35</td>
<td>46-66</td>
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<tr>
<td>Keys *6, 123</td>
<td>1997-1997</td>
<td>lb (bulky)</td>
<td>Yes</td>
<td>S + RT v S + CTRT</td>
<td>CDDP 40 mg/m²</td>
<td>6</td>
<td>1</td>
<td>45</td>
<td>&lt; 70</td>
<td>374</td>
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<tr>
<td><em>Chen (a)</em> 23</td>
<td>1993-1994</td>
<td>lb to III</td>
<td>No</td>
<td>RT + hyperthermia v CTRT</td>
<td>CDDP 60 mg/m²</td>
<td>3</td>
<td>3</td>
<td>40</td>
<td>50</td>
<td>49</td>
</tr>
<tr>
<td>Pras *23</td>
<td>1995-1999</td>
<td>lb to lla &gt;4 cm to lla</td>
<td>Yes</td>
<td>CTRT v hyperthermia</td>
<td>CDDP 300 mg/m²</td>
<td>4</td>
<td>3</td>
<td>45</td>
<td>35</td>
<td>&gt; 56</td>
</tr>
<tr>
<td>Leborgne *48</td>
<td>1995-2004</td>
<td>lb2 to IVb</td>
<td>No</td>
<td>RT v CTRT</td>
<td>CDDP 80 mg/m²</td>
<td>2</td>
<td>4</td>
<td>40</td>
<td>42</td>
<td>40</td>
</tr>
<tr>
<td>Garnpasoglu *46</td>
<td>1996-1997</td>
<td>lb, lla</td>
<td>No</td>
<td>RT v CTRT</td>
<td>CDDP 120 mg/m²</td>
<td>2</td>
<td>3</td>
<td>46-50</td>
<td>20</td>
<td>61-62</td>
</tr>
<tr>
<td>Kantardzic *46</td>
<td>1996-1999</td>
<td>lb, lla + CTRT</td>
<td>No</td>
<td>RT v CTRT</td>
<td>CDDP 40 mg/m²</td>
<td>6</td>
<td>3</td>
<td>46</td>
<td>25-30</td>
<td>56-60</td>
</tr>
<tr>
<td>*Lanciano (a) *55</td>
<td>1997-1998</td>
<td>lb, lla, Iva</td>
<td>Yes</td>
<td>RT v CTRT</td>
<td>CDDP 40 mg/m²</td>
<td>6</td>
<td>1</td>
<td>45</td>
<td>30 (HDR) or 40 (LDR)</td>
<td>&lt; 56</td>
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<tr>
<td>*Lanciano (b) *55</td>
<td>1997-1998</td>
<td>lb, lla, Iva</td>
<td>Yes</td>
<td>RT v CTRT</td>
<td>CDDP 40 mg/m²</td>
<td>6</td>
<td>1</td>
<td>45</td>
<td>30 (HDR) or 40 (LDR)</td>
<td>&lt; 56</td>
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<tr>
<td>Lalikos *47</td>
<td>2000-2006</td>
<td>II to IV</td>
<td>No</td>
<td>RT v CTRT</td>
<td>CDDP 38 mg/m²</td>
<td>6</td>
<td>1</td>
<td>46</td>
<td>18</td>
<td>63</td>
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<tr>
<td>Cicotri *47</td>
<td>2002-2003</td>
<td>lb to lla</td>
<td>No</td>
<td>RT v CTRT</td>
<td>CDDP 40 mg/m²</td>
<td>5</td>
<td>1</td>
<td>46</td>
<td>30</td>
<td>20</td>
</tr>
</tbody>
</table>

**Sensitivity analysis**

| *Whitney* *19, GOG 906 | 1986-1990 | lb to Iva | Yes | RT + HU v CTRT | CDDP 50 mg/m² | 2 | 4 | 40.8 | 40 | > 70 | 306 |
| *Morris* *17, RTOG 9401* | 1990-1997 | lb to lla (>4 cm or positive pelvic nodes) to lla | No | RT v CTRT | CDDP 75 mg/m² | 3 | 3 | 45 | 40 | < 56 | 403 |
| *Rose (a) *9, GOG 115 | 1992-1997 | lb to Iva | Yes | RT + HU v CTRT | CDDP 40 mg/m² | 6 | 1 | 40.8 | 40 | 70 | 304 |
| *Rose (b) *9, GOG 175 | 1992-1997 | lb to Iva | Yes | RT + HU v CTRT + HU | CDDP 50 mg/m² | 2 | 4 | 40.8 | 40 | < 56 | 383 |

**Abbreviations:** CT, chemotherapy; RT, radiotherapy; BRT, brachytherapy; CTRT, chemoradiotherapy; IV, intravenous; FU, fluorouracil; MMC, mitomycin; Adj, adjuvant; CDDP, cisplatin; CDBC, carboplatin; S, surgery; VCR, vincristine; BLM, bleomycin; HDR, high-dose rate; LDR, low-dose rate; HU, hydroxyurea; GOG, Gynecologic Oncology Group; RTOG, Radiation Therapy Oncology Group.

*Three-arm and four-arm trials were analyzed as two separate trials.

†After 673 patients were randomly assigned, FU was given 300 mg/day loral Monday through Friday for duration of external-beam radiotherapy.

‡With or without 8- to 10-Gy parametrial boost.

§Extended-field external-beam radiotherapy (to para-aortic nodes) given on the control arm.
Fig 1. (A) Hazard ratio (HR) plot for survival

Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration
J Clin Oncol; 26:5802-5812 2008
Fig 2. (A) Survival & (B) DFS by Tumor Stage (main group of 13 trials only)

Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration  
*J Clin Oncol;* 26:5802-5812 2008
**Fig 3. A)** Hazard ratio (HR) plot for survival (sensitivity analysis)

**B)** Kaplan-Meier curves for survival (sensitivity analysis; O-E, observed minus expected events

Main group of trials: HR = 0.81 (95% CI, 0.71 to 0.91)

Trials using HU on control arms: HR = 0.63 (95% CI, 0.54 to 0.74)

Trials using additional radiotherapy (RT) on control: HR = 0.50 (95% CI, 0.37 to 0.67)
Conclusions

- Main analysis: adding chemotherapy to RT improves both survival and DFS
- Benefit associated with non PT based chemoradiotherapy
- CTRT benefits women with all stages of cervical cancer
- Larger benefits seen for the trials in which additional chemotherapy was administered after chemoradiotherapy
RTOG/GOG combined study for high-risk, early stage cervical carcinoma

RTOG-0724
RTOG 0724/GOG-0724

Why is this study being done?

To determine if adjuvant systemic chemotherapy following chemoradiation therapy will improve disease free and overall survival compared to chemoradiation therapy alone in patients with high-risk, early-stage cervical carcinoma found to have +nodes and/or +margins, and/or + parametria after a radical hysterectomy.

Who is eligible to participate?

- At least 18 years old
- No more than 10 weeks since radical hysterectomy
- No distant metastases
- No previous chemotherapy for this cancer
Radical Hysterectomy: + LNs

Randomize

ARM 1
- XRT 45 vs 50.4 Gy
- Cisplatin 40 mg/m² wkly

ARM 2
- XRT 45 vs 50.4 Gy
- Cisplatin 40 mg/m² wkly
- Carboplatin AUC 5
- Paclitaxel 135 mg/m², q3wks ×4

Estimated enrollment: 400
Endpoints

Primary objective:
- Disease-free survival

Secondary objective:
- Toxicity
- Overall survival
- To collect fixed tissue to identify tumor molecular signatures that may be associated with patient outcomes
- To collect blood from serum and plasma
What needs improvement in managing cervical cancer?

- We need to find ways to improve the outcomes of bulky locally advance cervical cancer
- Important to have patients adequately staged with PET, CT
- Stratify by risk of disease, then incorporate RT, chemotherapy
- Need for more prospective studies to evaluate quality of life, survival.
- Adjuvant therapy for high risk cervical cancer
- Neoadjuvant chemotherapy?
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QUESTIONS???

Thank you