Quimio – Radioterapia en Cancer de Cervix

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CLINICAL DIRECTOR SCHNECK CANCER CENTER
Worldwide incidence of cervical cancer

2014, 12,360 cases

2014, 4,020 deaths

Global incidence in 2012, 528,000 new cases

Annual death rate in 2012, 266,000

Source: GLOBOCAN 2000; IARC
Early Stage Cervical Cancer Role of RT vs CT+RT
2009 FIGO Staging System

- **T1b** (IB): Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
- **T1b1** (IB1): Clinically visible lesion 4.0 cm or less in greatest dimension
- **T1b2** (IB2): Clinically visible lesion more than 4.0 cm in greatest dimension
- **T2** (II): Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina
- **T2a** (IIA): Tumor without parametrial invasion
- **T2a1** (IIA1): Clinically visible lesion 4.0 cm or less in greatest dimension
- **T2a2** (IIA2): Clinically visible lesion more than 4.0 cm in greatest dimension

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**IB1**: 85-90%

**IB2**: 80-85%

**IIA**: 75-80%
Results

- Median FU 87 m (57-120m)
- 5y survival: (83%) & DFS (74%) - same for S & RT
- Recurrence rate: 25% (S) vs 26% (RT)
- Rate of severe morbidity 28% (S) vs 12% (RT)
GOG 92: “Randomized trial of pelvic RT vs NFT in selected patients with pSt IB carcinoma of the cervix, with negative pelvic nodes, after radical hysterectomy and pelvic LND”

- 277 pts randomized:
  - 137 pts Pelvic RT (46-50.4 Gy) vs 140 pts NFT
  - Primary endpoint: Disease Recurrence

- Eligibility Criteria: Intermediate Risk Group
  - LVSI+ and one of the following
    - Deep third penetration, any tumor size 49% pts
    - Middle third penetration, T ≥ 2cm 26% pts
    - Superficial third penetration, T ≥ 5cm 1% pts
  - LVSI- and one of the following
    - Middle or deep third penetration, T ≥ 4cm 34% pts

Sedlis A et. al., Gynecol Oncol 73: 177-183, 1999
### Adjuvant RT or CT+RT in St I-IIA Cervical Cancer

<table>
<thead>
<tr>
<th>TRIAL RANDOMIZATION</th>
<th>RISK-GROUP # PTS</th>
<th>DFS</th>
<th>OVERALL SURVIVAL</th>
<th>RECURRENCE RATE</th>
<th>TOXICITY Grade 3-4</th>
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<tbody>
<tr>
<td><strong>GOG-92</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>140</td>
<td>79%</td>
<td>79%</td>
<td>28%</td>
<td>2%</td>
</tr>
<tr>
<td>S + RT</td>
<td>137</td>
<td>88%</td>
<td>87%</td>
<td>15%</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p= 0.008</td>
<td></td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td><strong>GOG-109</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery + RT</td>
<td>High Risk</td>
<td>4y</td>
<td>4y</td>
<td>34%</td>
<td>4%</td>
</tr>
<tr>
<td>S + RT + CT</td>
<td>243 pts</td>
<td>63%</td>
<td>71%</td>
<td>16%</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80%</td>
<td>81%</td>
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NCI – Clinical Trials, GOG-0263

Rational: ≈ 15% RR after RT in intermediate risk cervix cancer

SCHEMA

- Post-operative Stage I-IIA cancer of cervix with intermediate risk factors (IRF)
- Squamous cell carcinoma, adenosquamous carcinoma or adenocarcinoma histology
- GOG performance status 0-2

RANDOMIZE
Stratification factors: IRF, performance status, radiation modality, cooperative group

Regimen I (control arm)
Radiation Therapy:
(External pelvic standard radiation or IMRT)

Regimen II (CRT arm)
Concurrent Cisplatin and Radiation Therapy
(External pelvic standard radiation or IMRT)

Cisplatin 40mg/m² (max=70mg) IV over 1-2 hours weekly x 6 cycles with radiation therapy (see Regimen II Schedule below)
Adjuvant Chemo-Radiation in pSt I-IIA cervical cancer

- **GOG 109**: “Concurrent CT+Pelvic RT vs Pelvic RT alone as adjuvant Tx after radical surgery in high-risk early-stage cervical cancer”
  - Eligible pts: cSt IA2, IB and IIA treated with radical hysterectomy and pelvic LND with
    - (+) Pelvic nodes 85%
    - (+) Common iliac nodes 5% \(\Rightarrow\) **EFRT +/- CT**
    - (+) Parametrium 34%
    - (+) Margins 5%
  - Median FU = 43 months

*Peters WA et al, JCO 18: 1606-1613, 2000*
## Adjuvant RT or CT+RT in St I-IIA Cervical Cancer

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<tr>
<td><strong>GOG-92</strong></td>
<td>Intermediate</td>
<td>2y</td>
<td>2y</td>
<td>28%</td>
<td>2%</td>
</tr>
<tr>
<td>Surgery</td>
<td>Risk</td>
<td>79%</td>
<td>79%</td>
<td>15%</td>
<td>7%</td>
</tr>
<tr>
<td>Surgery + RT</td>
<td>277 pts</td>
<td>88%</td>
<td>87%</td>
<td></td>
<td></td>
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<tr>
<td><strong>GOG-109</strong></td>
<td>S+RT</td>
<td>63%</td>
<td>71%</td>
<td>34%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>S+RT+CT</strong></td>
<td>127</td>
<td>80%</td>
<td>81%</td>
<td>16%</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>P=0.03</td>
<td></td>
<td>P=0.07</td>
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- **DFS**: Disease-Free Survival
- **OVERALL SURVIVAL**: Overall Survival
- **RECURRENCE RATE**: Recurrence Rate
- **TOXICITY Grade 3-4**: Toxicity Grade 3-4
**GOG # 201: “Clinical Stage IB2: Radical hysterectomy and tailored CT+RT vs Primary CT+RT”**

<table>
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<th>FIGO Stage IB2 ≥ 4 cm, any histology</th>
<th>• GOAL 740 pts to detect a difference of 8% in PFS</th>
</tr>
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<td><strong>Objectives</strong></td>
<td>• PFS and survival, Toxicity and QOL</td>
</tr>
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</table>
| **If randomized to Radical Hysterectomy** | • Low risk factors: No adjuvant Tx  
• Intermediate/high risk factors (GOG #92 & 109): |
| Abandoned Rad Hyst (+ PA nodes, extracervical disease or unresectable pelvic nodes): CT+RT | • Pelvic +/- PA RT + ICB + weekly CDDP |

**Closed due to lack of accrual!!!**
RTOG-0724
Adjuvant therapy high risk patients after radical hysterectomy and pelvic LND

CDDP+RT (3DCRT or IMRT) +/- Vaginal brachytherapy

Adjuvant Chemotherapy
Observation
Role of EFH in Locally Advanced Cervical Cancer
**GOG 71: RT+EFH vs RT in IB2**

*Keys HM et. al., Gynecol Oncol 89: 343, 2003*

**PFS**
- 23% reduction in the risk of progression
- 5 y- LRR: RT alone, 27%; EFH, 14%
- Distant Failures: RT alone, 16%; EFH, 20%
- No difference in grade 3-4 toxicity (10%)

**Survival**
- No difference in overall survival
- 48% and 40% pts had no evidence or microscopic residual disease in the histological specimen, respectively

EFH: lower risk of progression and death for tumor sizes 6-7 cm

*No impact in OS for the entire group*

256 pts
T ≥ 4 cm
## CT+RT in Early Stage Cervical Cancer

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<tr>
<td>GOG-92</td>
<td>Intermediate Risk 277 pts</td>
<td>2y 79%, 88%</td>
<td>2y 79%, 87%</td>
<td>28%, 15%</td>
<td>2%, 7%</td>
</tr>
<tr>
<td>GOG-109</td>
<td>S+RT 127 / S+RT+CT 116</td>
<td>63%, 80% P=0.03</td>
<td>71%, 81% P=0.07</td>
<td>34%, 10%</td>
<td>4%, 17%</td>
</tr>
<tr>
<td>GOG-123</td>
<td>IB2 186 / IB2+CT 183</td>
<td>63%</td>
<td>74%</td>
<td>37%</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>IB2+CT+EFH 183</td>
<td>79% P&lt;0.001</td>
<td>83% P=0.008</td>
<td>21%</td>
<td>35%</td>
</tr>
</tbody>
</table>
Advanced Stage Cervical Cancer
5-year survival
Concurrent chemo-radiation therapy

- Results of five randomized trials led to NIH alert in 1999:
  
  "Strong consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer"

- However,
  
  - Only 1/3 trials in Advanced disease had a RT alone arm!!!

  RTOG 90-01
## CT+RT in Advanced Stage Cervical Cancer

<table>
<thead>
<tr>
<th>Trial, Author, Year Randomization</th>
<th>RISK-GROUP # PTS</th>
<th>Overall Survival</th>
<th>Recurrence Rate</th>
<th>Toxicity Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GOG-85 Whitney, 1999</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No RT alone arm!!</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT+ CF</td>
<td>177</td>
<td>68% CF</td>
<td>43%</td>
<td>16.2</td>
</tr>
<tr>
<td>RT+HU</td>
<td>191</td>
<td></td>
<td>53%</td>
<td>16.5</td>
</tr>
<tr>
<td>FIGO IIB- IVA 62% IIB</td>
<td></td>
<td>RR death: CF vs HU = 0.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late toxicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
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## CT+RT in Advanced Stage Cervical Cancer

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<th>Toxicity Grade 3-4 (%)</th>
</tr>
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<tbody>
<tr>
<td>GOG-120 Rose, 1999 No RT alone arm!!</td>
<td>FIGO IIB-IVA 52% IIB</td>
<td>RR of death: WC vs HU = 0.61</td>
<td>Local</td>
<td>Grade 3-4 toxicity more than double in the HFC group</td>
</tr>
<tr>
<td>WC HFC H</td>
<td>Median FU 35m</td>
<td>HFC vs HU = 0.58</td>
<td>19% 20% 30%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>66% WC</td>
<td>66% HFC</td>
<td></td>
</tr>
</tbody>
</table>
GOG-120: Long-Term Follow-up

Rose PG et al. JCO 2007; 25: 2804

526 pts with St IIB-IVA, median FU 8.5 years

“Improvement in PFS and OS for both Cisplatin-containing arms compared with HU
Similar results noted for St IIB and III disease”
# CT+RT in Advanced Stage Cervical Cancer

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<tr>
<th>Trial, Author, Year Randomization</th>
<th>RISK-GROUP # PTS</th>
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<th>Recurrence Rate</th>
<th>Toxicity Grade 3-4 (%)</th>
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<tbody>
<tr>
<td>GOG-165 Lanciano, 2005</td>
<td>FIGO IIB-IVA 65% IIB Median FU, 40.4m</td>
<td>4 years</td>
<td>LRR / Distant</td>
<td>Acute</td>
</tr>
<tr>
<td>RT alone</td>
<td>24 (CIs)</td>
<td>68%</td>
<td>16% / 18%</td>
<td>58%</td>
</tr>
<tr>
<td>Plv RT + CDDP</td>
<td>159</td>
<td>61%</td>
<td>14% / 29%</td>
<td>32%</td>
</tr>
<tr>
<td>Plv RT+PVI-5FU</td>
<td>157</td>
<td></td>
<td></td>
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</tr>
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</table>
"RTOG 90-01: “Phase III Randomized Study: Pelvic RT with concurrent chemotherapy vs Pelvic + Para-Aortic RT for high risk cervical carcinoma”

- Eligibility Criteria
  - FIGO Stage: IB, IIA (if size ≥ 5cm or positive pelvic lymph nodes), IIB, III & IVA. Negative PA - LN’s
    - 70% IIB

- Schema
  - Arm 1: Pelvic RT + Concurrent Chemotherapy
    - Pelvic RT: 45Gy in 25 fx’s, 180 cGy/fx
    - ICB: 1 or 2, ICI. Total dose Point A 85 Gy (EBRT+ICB)
    - Cisplatin (75 mg/m2/d, dys 1 & 22) + 5-FU (1000 mg/m2/d x 4 days, 2-5 & 23-26)
    - A third course of CT will be given if a second intracavitary implant is to be performed
  - Arm 2: Pelvic + Para-Aortic RT
    - EFRT: 45Gy in 25 fx’s, 180 cGy/fx + ICI

RTOG 90-01: “Phase III Randomized Study: Pelvic RT+CT vs EFRT for high risk cervical carcinoma”

5-year DFS
67% (pRT+CT) vs 40% (EFRT)

5-year survival
73% (pRT+CT) vs 58% (EFRT)

403 pts, St IB-IIA (≥ 5cm or + pelvic nodes), IIB, III & IVA, (-) PA nodes
Randomization: Pelvic RT + [CDDP + 5-FU] x 2-3 cycles vs EFRT
Acute tox. more significant in the CT+RT arm but no difference in late tox.
“Improvement in DFS, OS (IB-IIB), Distant relapse and LRR rate with pRT+CT”
RTOG 90-0. Updated Results
Eifel P et. al., JCO 22: 872, 2004

5y Overall survival
pRT+CT, 73% vs EFRT, 52%
p<0.0001

5y Overall survival
St IB-II: [70% pts]
pRT+CT, 79%; EFRT, 55%, (p<0.0001)
St III-IVA: [30% pts]
pRT+CT, 59%; EFRT, 45% - NS

Median FU time for 228 surviving pts 6.6 years

CT + RT resulted in:
- 52% reduction in the risk of death
- 58% reduction in the risk of LRR
- 52% reduction in the risk of distant metastasis
“Concurrent CDDP+RT vs RT alone for pts with locally advanced cervix cancer”

N=253 pts, cSt IB-IIA bulky and cSt IIB-IVA

- <10% IIIB Bilateral parametrium or IVA

Pelvic RT + CDDP 40 mg/m²/wk vs RT alone

- Median FU: 82 months
- Median duration of Tx
  - 50d (CT+RT), 51d (RT)
- % Late complications
  - 6% (CT+RT), 12% (RT)
- 3y Pelvic control rate
  - 83% (CT+RT), 78% (RT)
- No statistical difference between arms

5y survival
62% (CT+RT) vs 58% (RT)

Fig 3. Overall survival. Solid line, CDDP and RT; dotted line, RT alone.
# Pelvic Failures (First Site)

<table>
<thead>
<tr>
<th></th>
<th>CDDP-Based Chemotherapy</th>
<th>Non CDDP Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total # Pts</td>
<td>% LRR</td>
</tr>
<tr>
<td><strong>GOG 85</strong></td>
<td>177 (CF)</td>
<td>25%</td>
</tr>
<tr>
<td><strong>GOG 120</strong></td>
<td>176 (WC)</td>
<td>19%</td>
</tr>
<tr>
<td><strong>GOG 120</strong></td>
<td>173 (HFC)</td>
<td>20%</td>
</tr>
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<td><strong>RTOG 90-01</strong></td>
<td>193</td>
<td>19%</td>
</tr>
<tr>
<td><strong>NCI-C</strong></td>
<td>126</td>
<td>27%</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>1155</td>
<td>19%</td>
</tr>
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Why the discrepancy?

- **Potential explanations:**
  - Median overall Tx time
    - NCI-Canada: 45-50 days
    - RTOG trial: 58 days
    - GOG trials: 62-64 days
  - NCI Canada was the only study that mandated Hgb $\geq$ 11 g/dl
  - Shorter Tx time and higher Hgb levels may have provided less opportunity for improvement with CT
    - Tx prolongation of 8-10 days will potentially increase pelvic failure rate by 10-15% and CT may be partially compensating for this loss

- **Differences in PA nodes evaluation**
  - Surgical staging (GOG) and Lymphangiogram (RTOG) versus CT scan alone (NCI-Canada)
  - Potential inclusion of more pts with undetected PA-LN mets in the NCI-Canada $\Rightarrow$ Reduction in the benefit of locoregional Tx
## Meta-Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of trials</th>
<th>Number of patients</th>
<th>Improvement in PFS</th>
<th>Improvement in OS</th>
<th>Comments</th>
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<tr>
<td>Green, 2001</td>
<td>19</td>
<td>4580 pts randomized, 3656 evaluable</td>
<td>16% absolute benefit (47% to 63%) Benefit on both local control and distant failures</td>
<td>12% absolute survival benefit (40% to 52%) HR 0.71</td>
<td>Greater beneficial effect in trials that included a high proportion of St I and II pts (p=0.009)</td>
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<td>Meta-Analysis Collaboration, 2008</td>
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<td>1745</td>
<td>8% absolute benefit at 5 years (50% to 58%) Benefit on both local control and distant failures</td>
<td>6% absolute 5-year survival benefit (60% to 66%) HR 0.81</td>
<td>HRs translate to 5-year survival benefits of 10% for St IB- IIA 7% for St IIB 3% for St III-IVA</td>
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CT+RT vs RT alone in cervical cancer. RCT

CRT become the standard of care for treating almost all cervical carcinoma patients on the basis of the 1999 - NCI alert.

- The disease burden in developing countries is more advanced with poor general condition than in patients in the trials prompting the NCI alert.

RCT: RT vs CT+RT (weekly CDDP), St IB-IVA

- 305 patients: RT alone (150) and CRT (155)
- Median follow up was 34 months
- 2y LRFS: 55 and 54% for the RT and CRT group, respectively, with a median LRFS time of 27 and 30 months for the RT and CRT group, respectively, (P = 0.624)
- 2y OS: 58 and 60%, with a MST of 31 and 34 months for the RT and CRT group, respectively; (P = 0.9)
- The toxicity profile, both acute and late, were comparable in both groups;

CONCLUSION: the addition of cisplatin did not improve outcome. In the Indian subcontinent where patients present at late stages with poor general condition and limited access to good supportive care, RT alone still remains a valid option.
Concomitant CDDP+RT+HDR-ICB versus RT alone for Stage IIIB epidermoid cervical cancer: a RCT

- 147 pts with stage IIIB – SCC squamous cervical cancer randomized to
  - Cisplatin plus RT (72) or RT alone (75)
- The CRT group had significantly better DFI
- No improvement in survival with CRT
- Excluding hematological toxicity there was not significant difference between groups in acute toxicity
- No difference in late toxicity
- No difference in patterns of failure, including distant failures between the groups

**Conclusion:** In IIIB cervical cancer, the addition of cisplatin offers a small but significant benefit in DFI, with acceptable toxicity
Phase III, Open-Label, Randomized Study Comparing Concurrent Gemcitabine Plus Cisplatin and Radiation Followed by Adjuvant Gemcitabine and Cisplatin Versus Concurrent Cisplatin and Radiation in Patients With Stage IIB to IVA Carcinoma of the Cervix

Alfonso Dueñas-González, Juan J. Zarbo, Firdza Patel, Juan C. Alcedo, Semir Besiça, Luis Casanova, Pittayaporn Pattaranuaporn, Shahid Hameed, Julie M. Blair, Helen Barradough, and Mauro Orlando

- 515 pts, IIB-IVA
  - Weekly CDDP (40 MG/M2) + GEM (125 MG/M2) + RT followed by [CDDP+GEM] x 2 cycles
  - Weekly CDDP+RT
- ≈ 60% cSt IIB, ≈ 36% cSt IIIB
- Median FU 46.9 months
- Toxicity grade ≥ grade 3
  - 87% vs 46%
  - 2 Tx-related deaths in the GEM arm


Radiation and gemcitabine/cisplatin for patients with stage IIB to IVA cervical cancer are not cost-effective. The increased financial burden of radiation with gemcitabine/cisplatin and associated toxicities appears to outweigh the benefit of increased 3-year PFS and is primarily dependent on chemotherapy drug costs.
<table>
<thead>
<tr>
<th></th>
<th>Arm A</th>
<th>Arm B</th>
<th>P value</th>
<th>RTOG 90-01 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Objective</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS, 3 years</td>
<td>74%</td>
<td>65%</td>
<td>0.029</td>
<td>67% 5 years</td>
</tr>
<tr>
<td><strong>Secondary Objectives</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Survival</td>
<td>≈ 87%</td>
<td>69%</td>
<td>HR, 0.68</td>
<td>73% 5 years</td>
</tr>
<tr>
<td>Time to Progressive disease, TtPD</td>
<td></td>
<td></td>
<td>HR, 0.54</td>
<td></td>
</tr>
<tr>
<td>Tumor Response Rate, TRR</td>
<td>96%</td>
<td>93%</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Local Failure Rate, LFR</td>
<td>11%</td>
<td>16%</td>
<td>NS</td>
<td>19% 5 years</td>
</tr>
<tr>
<td>Distant Failure</td>
<td>8%</td>
<td>16%</td>
<td>0.005</td>
<td>14% 5 years</td>
</tr>
<tr>
<td>Grade ≥ 3 Acute Toxicity</td>
<td>87%</td>
<td>46%</td>
<td>0.001</td>
<td>45%</td>
</tr>
</tbody>
</table>
Cisplatin vs Gemcitabine

Whether Cisplatin in combination with an alternative agent to 5-FU would improve survival outcomes is not clear.

Phase III trial comparing CDDP alone with CDDP+GEM during RT [followed by 2 courses of CDDP+GEM]

- With a median FU=3 years, the use of CDDP+GEM resulted in:
  - Improved PFS (HR 0.68, 95% CI 0.49-0.95; 3-year PFS 74 versus 65%)
  - Improved overall survival (OS, HR for death 0.68, 95% CI 0.49-0.95)
  - Increased grade 3/4 toxicities (87 vs 46%) and rate of hospitalizations (30 versus 11)

It is not clear whether the benefits of the investigational treatment were due to the use of the CDDP+GEM during RT or following CT+RT.

Therefore, CDDP alone during CT+RT is still the standard of care.
Cisplatin-based Chemo-RT
Summary of Randomized trials

- 6 large randomized trials
  - 3 trials CT+RT vs RT alone
  - Diverse population: early-stage “high-risk” - locally advanced dis.
  - No impact in survival in the NCI-Canada Study
- More than 1800 pts randomized
- Increase in relative progression-free survival and relative survival by 30-50%
- 1999 NCI consensus statement: “Strong consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiation for women who require radiation therapy for the management of cervical cancer”
Role of CT after CT+RT in LACC

- It is not recommended the administration of CT after CT+RT in LACC
  - There is limited evidence of benefit to justify the additional toxicity risks
- However, some data suggest that there is a role for additional treatment
  - In the previously described trial, women who received two cycles of CDDP+GEM after CT+RT had significant improvements in both PFS and OS compared with women who received CDDP alone-based CT+RT and no further CT
    - However it is not clear if the survival benefit was due to combination chemotherapy delivered with RT, following RT, or both
    - In addition, the Gynecologic Oncology Group ran a similar trial of gemcitabine followed by cisplatin with concomitant RT but this trial was stopped due to excessive grade 3/4 toxicities
    - Given the concerns for toxicity and the unclear contribution of systemic treatment in this study, we await further results prior to administering further treatment after chemoradiation.
- The independent contribution of adjuvant CT to CT+RT is being addressed in an international randomized study (the OUTBACK trial) sponsored by the Gynecologic Cancer Intergroup
The OUTBACK Trial: Phase III

Primary endpoint: Overall Survival

Arm I
Weekly Cisplatin + EBRT + Brachytherapy

Arm II
Weekly Cisplatin + EBRT + Brachytherapy

Adjuvant Paclitaxel + Carboplatin (4 courses)

Adjuvant Chemotherapy Following CT+RT as Primary Treatment for LACC vs CT+RT Alone
Other systemic agents in Advanced Cervical Cancer
## Other RT + CT combinations

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>Agent</th>
<th>Study Phase</th>
<th># Pts</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GOG 98-03  DiSilvestro P. 2006</strong></td>
<td>Paclitaxel + CDDP</td>
<td>I</td>
<td>35 cSt IB-IVA</td>
<td>Well tolerated MTD: CDDP 40 mg/m2/wk + Taxol 40 mg/m2/wk</td>
<td>Completion of Tx in 8 wks in 52% and 9 wks in 79% of pts</td>
</tr>
<tr>
<td><strong>GOG 99-12  Rose P. 2007</strong></td>
<td>Gemcitabine + CDDP</td>
<td>I</td>
<td>13 cSt IB-IVA</td>
<td>MTD: Gemcitabine 50 mg/m2/wk + Cisplatin 40 mg/m2/wk</td>
<td>At this dose level severe chronic toxicity was observed</td>
</tr>
<tr>
<td><strong>RTOG C-0116  Small W. 2005</strong></td>
<td>CDDP+ EFRT Arm I</td>
<td>27 pts without Amifostine (+) common or PA nodes</td>
<td>Acute grade 3-4 toxicity: 81%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RTOG C-0116  Small W. 2011</strong></td>
<td>CDDP+ EFRT Arm II</td>
<td>18 pts treated with Amifostine (+) common or PA nodes</td>
<td>Acute grade 3-4 toxicity: 87%</td>
<td>Amifostine did not reduce acute toxicity</td>
<td></td>
</tr>
<tr>
<td><strong>GOG 191  Thomas G. 2008</strong></td>
<td>RT+ CDDP+/- Erythropoietin</td>
<td>Phase III 109 pts, FIGO IIB-IVA</td>
<td>Median FU 37 months PFS, 3 y: CT+RT, 65%; CT+RT+Epo, 58% OS, 3 y: CT+RT, 75%; CT+RT+Epo, 61% % of TEE: CT+RT, 8%; CT+RT+Epo, 19%</td>
<td>Trial stopped prematurely because of concerns regarding TEE with Epo</td>
<td></td>
</tr>
<tr>
<td><strong>GOG-219  DiSilvestro P. 2014</strong></td>
<td>RT+CDDP+/- Tirapazamine</td>
<td>Phase III 387 pts, FIGO IB2-IVA</td>
<td>Median follow-up 28.3 months, PFS, 3y: TPZ/CIS/RT and CIS/RT arms were 63.0% and 64.4%; NS OS, 3y: TPZ/CIS/RT and CIS/RT arms were 70.5% and 70.6%; NS</td>
<td>Trial stopped prematurely because of the lack of TPZ supply TPZ/CIS was not superior to CIS in either PFS or OS</td>
<td></td>
</tr>
</tbody>
</table>
RTOG 0128: A Phase I-II study of COX-2 inhibitor, Celebrex ® and CT+RT in patients with locally advanced cervical cancer

D. Gaffney D et al. IJROBP, 2007; 67: 104

- FIGO IIB-IVA and IB-IIA with (+) pelvic nodes or T ≥ 5cm
- Treatment Schema
  - Radiotherapy: EBRT+ICB
  - Chemotherapy, 3 cycles
    - CDDP (75 mg/m2/d), days 1, 22 and 43
    - 5-FU (1000 mg/m2/d x 4ds), days 2-5, 23-26 and 44-47
  - Celebrex®: day 1 of RT x 12 months, 400 mg bid
- Results
  - N= 84 pts, 77 evaluable for toxicity
  - Overall Grade 3-4 toxicity 48%
  - Non-hematological Toxicity: Grade 3, 53%; grade 4, 13%
- Conclusions: “Regimen excessively toxic not recommended for further evaluation”

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Acute GI toxicity Grade &gt; 3</th>
<th>Late GI toxicity Grade &gt; 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>5FU, CDDP, and Celecoxib</td>
<td>45.4%</td>
<td>2.7%</td>
</tr>
<tr>
<td>RTOG 9001</td>
<td>5FU and CDDP</td>
<td>8.7%</td>
<td>12.6%</td>
</tr>
<tr>
<td>GOG 85</td>
<td>5FU and CDDP</td>
<td>7.7%</td>
<td>NR</td>
</tr>
<tr>
<td>GOG 120</td>
<td>5FU, CDDP, and Hydroxyurea</td>
<td>18%</td>
<td>NR</td>
</tr>
<tr>
<td>GOG 120</td>
<td>CDDP weekly</td>
<td>12%</td>
<td>NR</td>
</tr>
<tr>
<td>GOG 123</td>
<td>CDDP weekly</td>
<td>14.2%</td>
<td>NR</td>
</tr>
<tr>
<td>NCIC</td>
<td>CDDP weekly</td>
<td>12.6%</td>
<td>4.8%</td>
</tr>
<tr>
<td>GOG 165</td>
<td>CDDP weekly</td>
<td>25%</td>
<td>NR</td>
</tr>
<tr>
<td>GOG 165</td>
<td>CI5FU</td>
<td>19%</td>
<td>NR</td>
</tr>
</tbody>
</table>
Molecular Targeted Agents in Advanced Cervical Cancer
A phase I trial of tailored radiation therapy with concomitant cetuximab and cisplatin in the treatment of patients with cervical cancer: A gynecologic oncology group study

Kathleen N. Moore a,*, Michael W. Sill b,c, David S. Miller d, Carolyn McCourt e, Koen De Geest f, Peter G. Rose g, Higinia R. Cardenes h, Robert S. Mannel a, John H. Farley i,2, Russell J. Schilder j,2, Paula M. Fracasso k

**GOG 9918: Gynecol Oncol, 2012; 127: 456-461**

- cSt IB-IVA cervical cancer with/without positive pelvic and/or PA nodes
  - **EBRT**
    - Negative PA nodes: WPRT 45 Gy
    - Positive PA nodes: EFRT 45 Gy
  - **ICB**
    - LDR, 40 Gy (1-2 ICI) or HDR, 30 Gy (6 Gy x 5 fx’s)
  - Dose escalation of CDDP and Cetuximab. Starting doses
    - CDDP: 30 mg/m²/wk x 6 wks
    - Cetuximab: 400 mg/m² loading dose wk 1, 250 mg/m²/wk x 5 wks
- **CONCLUSIONS:**
  - For patients receiving pelvic RT, CDDP+cetuximab was feasible
  - For patients receiving EFRT, CDDP+cetuximab was not feasible because of severe toxicity
Patients with bulky tumors IB-IIIB treated with weekly Cisplatin + Pelvic RT + ICB + Bevacizumab 10 mg/kg IV q 2 weeks x 3 cycles
- 60 pts enrolled (2006-2009), 49 evaluable
- Median FU 12.4 m (4.6-31.4 m)
- 63% pts FIGO stage IIB
- 80% SCC
- No tx-related SAEs
- 76% had chemotherapy + Avastin as per protocol
- 94% had RT as per protocol

Conclusions: the combination appears to be feasible and safe
Neoadjuvant Chemotherapy in Early Stage Cervical Cancer
Neoadjuvant Chemotherapy for Locally Advanced Cervical Cancer Meta-analysis Collaboration

*Eur J Cancer. 2003;39(17):2470*

**NACT followed by radical RT vs RT alone**
- 18 trials, 2074 patients
- No definitive conclusions could be made
- Substantial heterogeneity
  - Shorter cycle lengths and higher dose intensities of CDDP tended to show an advantage for NACT on survival

**NACT followed by surgery vs radical RT alone**
- 5 trials, 872 patients
- Significant reduction in the risk of death with NACT
- Significant heterogeneity between trials
  - Timing and dose intensity of cisplatin-based NACT appears to have an important impact on whether or not it benefits women with LACC
To assess the role NACT prior to Surgery in women with early or LACC
- Primary outcome: OS
- Secondary outcomes: PFS, local and distant recurrence, rates of resection and surgical morbidity

6 trials, 1078 women – NACT associated with:
- Improved OS and PFS
- Decreased risk of local recurrence
- No difference in distant recurrence and rates of resection
- Decreased adverse pathological findings: (+) LN, (+) parametrial
Neoadjuvant Chemotherapy

GOG 141

Primary Carcinoma of the Cervix
- Stage IB Bulky
- Squamous Carcinoma
- Adenosquamous Carcinoma
- Adenocarcinoma

Regimen II
Vincristine 1 mg/m^2
Cisplatin 50 mg/m^2 IV q 10 days x 3 courses

Clinical Assessment
No Progression
Progression during chemotherapy
GOG -141

Eddy, GL et al. Gynecol Oncol 2007; 106: 362

- 288 pts enrolled
- Closed after interim analysis showed study to be futile
- Median FU, 62 months
  - No difference between both groups in terms of need for adjuvant Tx: ~ 50%
  - No difference in terms of surgical pathological risk factors at the time of the RH
  - NACT did not increase operability rate: ~ 78%
  - No improvement in survival when compared with GOG 92 & GOG 109 data
  - Increased hematological, GI and neurological toxicity with NAcT

“Neoadjuvant CT should be considered unacceptable prior to Radical Hysterectomy” - B. Monk, MD
Phase III: EORTC-55994

Closed to Accrual. Primary Endpoint OS

St IB2-IIB cervical cancer Neoadjuvant Cisplatin followed by Radical Hysterectomy vs CDDP+RT

Arm I
Cisplatin based NACT - every 21 days

Type III-V Piver-Rutledge radical hysterectomy

Arm II
Standard therapy
Pelvic RT + weekly + ICBT

Adjuvant EBRT +/- ICB if:
Positive lymph nodes and/or Tumor invasion into the parametria and/or < 5 mm margins

Adjuvant hysterectomy allowed in case of histologically proven residual tumor
A Prospective Randomized Trial of NACT and Surgery Versus Concurrent CT+RT in Patients With Stage IB2-IIB SCC - Uterine Cervix

**ARM 1:**
NACT followed by Surgery
- NACT: Taxol + Carbo 3 cycles
- Radical Hysterectomy Class III + Bilateral PLND + Lower PA-LNS
- ICBT

**ARM 2:**
Concurrent CT+RT
- Pelvic RT + weekly Cisplatin
Potential Limitations of CT+RT

Serkies et al, IJROBP 2004; 60: 814-821

- Increased acute gastrointestinal and hematological toxicity, generally reversible
  - Hematological toxicity 49% (Grade 3-4, 5%)
  - GI toxicity 38% (Grade 3-4, 10%)

- Limitations in treatment delivery
  - Reduction in number of cycles of CDDP
    - Average of 4 cycles
    - Only 45% pts received 5 cycles
    - Full doses and timely planned CDDP in only 26% pts
    - 20% pts not compliant with CT schedule
  - Prolongation of RT treatment time
    - The intended total point A dose of 80 Gy was delivered in 34 patients (60%)
Effect of treatment time

- 113 with stage IB2 to IIIB cervical cancer
  - All patients received WPRT+CT+ICB
  - The effect of treatment time on outcome was examined with univariate and multivariate analyses
  - The median time to complete all RT was 68 days.

- The 3-year cumulative incidence of PF and DF were 18% and 23%

- On multivariate analysis, time to completion of BT >56 days was associated with increased PF (HR, 3.8; 95% CI, 1.2-16; P = .02)
  - The 3-year PF for >56 days versus ≤56 days was 26% versus 9% (P = .04)
  - Treatment time was not associated with DF

- Treatment prolongation was found to be associated with delay in starting BT and higher incidence of acute grade 3/4 toxicities

- In the setting of CT+RT, treatment time >56 days is detrimental to pelvic control but is not associated with an increase in DF
### 3D-EBRT vs IMRT

<table>
<thead>
<tr>
<th></th>
<th>3D</th>
<th>IMRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2 Acute GI toxicity</td>
<td>91%</td>
<td>60%</td>
</tr>
<tr>
<td>Chronic GI toxicity</td>
<td>50%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Grade 2+ WBC toxicity</td>
<td>60%</td>
<td>31.2</td>
</tr>
</tbody>
</table>

1. Mundt., et al. *IJROBP*; 52:1330-7; 2002
Conclusions – Early Stage disease

- Cervical cancer is a preventable disease, however, worldwide remains a significant problem
- Identification of population at risk, early screening and HPV vaccination
- Several Phase II-III trials of prophylactic HPV vaccines demonstrate high-level protection from HPV 6/11/16/18 infection and related precancerous cervical lesions
Conclusions – Early Stage disease

- Patients with early stage disease have favorable outcome
  - Identification of reliable factors to predict recurrence risk and death
  - Definition of risk-groups to adequately “tailor” therapy are imperative
  - Multidisciplinary approach
    - Integration of surgery, RT and CT
Conclusions

- Five out of six randomized Phase III trials demonstrated that cisplatin-based CT, when given concurrently with RT, prolongs survival in patients with locally advanced cervical cancer, FIGO stages IB-IVA, as well as in those women with “high risk” stages IB-IIA disease after radical hysterectomy.

- However, only 2 of 4 trials in advanced disease had a radiation alone arm and only 1 trial showed benefit for CT+RT over RT alone (RTOG 90-01).
Conclusions

- Concurrent cisplatin-based CT reduced the risk of recurrence by 30%-50% across a spectrum of treatment prescriptions.

- It is unclear whether these results are applicable to all stages of cervical cancer, since only 30% of the patients had stage III-IVA.

- Two Meta-analysis showed very minimal benefit for CT+RT in advanced cervical cancer.
Conclusions

- Currently available data do not allow conclusions to be drawn as to which drugs or regimens are optimal in the treatment of cervical cancer.

- Until further data become available, it is reasonable to suggest that weekly cisplatin should be the regimen of choice, concurrently with radiotherapy,
  - **PRIARILY** in patients with early stage disease,
  - **EXCELLENT** performance status with
  - **FULL ACCESS** to external beam RT and brachytherapy and
  - **ADEQUATE SUPPORTIVE CARE**

**In order to keep the overall treatment time limited to 8 weeks**
Current Investigations

- Education / Prevention / Vaccination
- Evaluation of new chemotherapy & radiosensitizer agents
- Evaluation of Molecular Targeted Therapy
- Implementation of 3-dimensional treatment planning and IMRT
- Imaged-guided Intracavitary Brachytherapy
  - CT/MRI and PET-based ICI