GCIG Cervix Committee:
Chicago 2012

William Small Jr.
Satoru Sagae
Bradley Monk
Conflict of Interest Disclosures
Closed Trials – GOG 240 and Active Trials
GOG Protocol 240

• 2 x 2 Factorial Design
  – First randomization: Winner of GOG 204 (Cisplatin + Paclitaxel) vs Topotecan + Paclitaxel
  – Second Randomization: Bevacizumab vs No Bevacizumab

• Primary Endpoint = survival, superiority trial (30% reduction in HR)
• Accrual Goal = 450 patients
• Activated = April 6, 2009
• Closed = January 3, 2012

KS Tewari Study Chair
“Dear Investigator Letter” and “Dear Patient Letter”  
– April 10, 2012

GOG Data Safety and Monitoring Board scheduled interim analysis showed:

“topotecan is not a superior substitute for cisplatin with paclitaxel chemotherapy by overall survival in this group of patients”

“Importantly, the study was not designed to determine whether topotecan was equivalent”
A PHASE II TRIAL EVALUATING CISPLATIN (NSC #119875) AND GEMCITABINE (NSC # 613327) CONCURRENT WITH INTENSITY-MODULATED RADIATION THERAPY (IMRT) IN THE TREATMENT OF LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE VULVA

N Horowitz Study Chair
GOG 279 Background

- Management of advanced stage disease remains a challenge
- Historically required exenterative procedures but now typically treated with multimodality therapy
  - Chemotherapy + radiation followed by surgery
- GOG 205 most recently completed trial
  - AP-PA radiation (5670 Gy) + weekly cisplatin 40 mg/m²
  - 20% dose escalation and elimination of treatment break compared GOG 101
  - 37 of 58 (64%) complete clinical response
  - 29 of 58 (50%) complete pathologic response
GOG 279 vs GOG 205

• IMRT rather than AP-PA external beam radiation
  – 6400 Gy to vulva vs 5670 Gy

• Cisplatin + Gemcitabine vs weekly Cisplatin
  – Phase 1: GOG 9912 Rose PG Gynecol Oncol 2007;107:274-9
GOG 279 Objectives

• Primary
  – To determine the efficacy of cisplatin, gemcitabine, and IMRT in achieving a complete pathologic response (increase from 50 to 70%)

• Secondary
  – To determine the efficacy of cisplatin, gemcitabine, and IMRT in achieving a complete clinical response (historically 64%)
  – To determine the vulvar progression-free survival and groin progression-free survival (historically 70% at 1 year).
  – To determine the toxicity and surgical morbidity of the combined modality approach of cisplatin, gemcitabine and IMRT followed by reduced-scope surgery
Locally advanced squamous cell carcinoma of the vulva, T2 or T3 primary tumors (N0-3, M0) not amenable to surgical resection by standard radical vulvectomy

**Resectable Lymph Nodes**
Patients will undergo a pre-treatment inguinal-femoral lymph node dissection or sentinel lymph node biopsy

- **LN (-)**
  - No radiation vs. 45 Gy to groin(s) and low pelvis; 64 Gy to vulva
  - Gemcitabine 50 mg/m² + Cisplatin 40mg/m² administered weekly throughout radiation therapy

- **LN (+)**
  - 50 Gy to groin(s) and low pelvis with groin boost to 60 Gy to involved sides if:
    - 3 LN (+) or
    - extra capsular extension or
    - close/positive margin
  - 64 Gy to vulva
  - Gemcitabine 50 mg/m² + Cisplatin 40mg/m² administered weekly throughout radiation therapy

**Unresectable Lymph Nodes**

- Radiation 64 Gy to vulva and unresectable groin(s) and 50 Gy to non-malignant groin and low pelvis
- Gemcitabine 50 mg/m² + Cisplatin 40mg/m² administered weekly throughout radiation therapy

Clinical/Radiographic assessment 6-8 weeks after chemoradiation with core biopsy or local excision of residual disease or (+) LN
GOG 279 Anticipated Accrual

- Target 52 evaluable patients
- 1-2 patients per month
- Duration 30-48 months
- Post accrual follow up 6 months
EVALUATION OF PHYSICAL FUNCTION AND QUALITY OF LIFE (QOL) BEFORE AND AFTER NON-RADICAL SURGICAL THERAPY (EXTRA FASCIAL HYSTERECTOMY OR CONE BIOPSY WITH PELVIC LYMPHADENECTOMY) FOR STAGE IA1 (LVSI+) and IA2-IB1 (≤ 2CM) CERVICAL CANCER
GOG 278 Background

- Risk of isolated parametrial metastases rare in early cervical cancer
- Morbidity high after radical surgery
  - Bladder
  - Sexual
  - GI
- GOG peer reviewers noted fertility sparing surgery as high unmet scientific and clinical need
GOG 278 Objectives

• **Primary**
  - To examine the changes before and after non-radical surgery in bladder, bowel and sexual function
  - To evaluate incidence and severity of lymphedema after non-radical surgery

• **Secondary**
  - Toxicity
  - QOL (FACT-Cx), cancer worries and sexual/reproductive concerns
  - Conception & fertility rates
  - Recurrence rates
Women with IA1 – IB1 ($\leq 2$cm) carcinoma of the cervix who have been consented for surgery will be approached for study participation and entered on study.

**Medical Information/Physician Checklist:**
Medical extraction form CTCAE v. 4.0 criteria

**Preoperative Study Survey (15 min to complete):**
Bladder and Bowel Function Items
Female Functioning Index & 2 PROMIS items
GCLQ – Gyn Cancer Lymphedema Questionnaire
Functional Assessment Cancer Therapy – FACT-Cx
Impact of Events Scale (IES)
Conization Group only Reproductive Items (ICF & RCS)

**Post-Operative**
(Patients requiring adjuvant therapy will be removed from the study)

**Assessments Schedule Post-op**
- 4-6 weeks post-op
- and every 6 months (6, 12, 18, 24, 30, 36) for three years

**Medical Information/Physician Checklist:**
Medical extraction form CTCAE v. 4.0 criteria

**Preoperative Study Survey (15 min to complete):**
Bladder and Bowel Function Items
Female Functioning Index & 2 PROMIS items
GCLQ – Gyn Cancer Lymphedema Questionnaire
Functional Assessment Cancer Therapy – FACT-Cx
Impact of Events Scale (IES)
GOG 278 Anticipated Accrual

- The minimum sample size = 200
  - Three stages
- At least 60 patients per annum
- At least 1.5 years for post accrual follow-up
Locoregionally advanced cervical cancer (Stages IB2, IIA ≥4 cm, IIB-IVA) or High risk endometrial cancer, i.e. grade 3 endometrioid, clear-cell, serous papillary, carcinosarcoma or grade 1 or 2 endometrioid carcinoma with cervical stromal involvement

Fusion PET-CT scan of the chest, abdomen and pelvis. CT to be performed with oral and intravenous contrast

No disease outside of the abdominopelvic nodes

Evidence of disease outside of the abdominopelvic nodes

Advanced lymphadenopathy not amenable to surgery

Pelvic & para-aortic lymphadenectomy

Biopsy distant disease

Negative bx
Patient-Scanner Disconnect

Scanners
★ >10million
★ >5/million

Global incidence of cervical cancer, projections for 2005

ACRIN™
GOG233-ACRIN6671

- Michael Gold (GOG), Mosta Atri (ACRIN)
- Activated for invasive cervix September 2007
- Amended to expand to endometrial January 2010
- US, Korea, Canada & Japan
- 24/27 open sites actively accruing

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<td>Accrued so far</td>
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<td>95</td>
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<td>Projected accrual</td>
<td>October 2013</td>
<td>June 2014</td>
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## Open Non-US Sites

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<td>Seoul National University</td>
<td>Korea</td>
<td>9/2/10</td>
<td>9</td>
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<td>3</td>
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<td>CHUQ L’Hotel-Dieu de Quebec</td>
<td>Canada</td>
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<td>8</td>
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<tr>
<td>Asan Medical Center</td>
<td>Korea</td>
<td>5/20/11</td>
<td>0</td>
</tr>
<tr>
<td>KIRAMS</td>
<td>Korea</td>
<td>12/22/10</td>
<td>0</td>
</tr>
</tbody>
</table>
Projected Growth in Imaging
Main eligibility criteria:

- Cervical carcinoma of one of the following histological types:
  - squamous cell carcinoma
  - adenosquamous cell or adenocarcinoma
- FIGO stage Ib2, IIa > 4 cm or IIb.
- WHO performance status 0-2.
- Age 18-75.
- No prior irradiation or chemotherapy.

PIs: G. Kenter, S. Greggi, F. Landoni
Cervix Cancer. Treatment Scheme

Eligibility Check

Randomization

N=680

EORTC 55994

Arm 1: Neoadjuvant QT

Cisplatin based chemotherapy:
- min. cumulative cisplatin dose of 225 mg/m²
- 25 mg/m² per week,
- final dose no later than D64

Followed by surgery (radical hysterectomy)

Arm 2: concomitantly QT/RDT

Cumulative cisplatin dose 200-240 mg/m².
- Max 6 administrations.
- Dose 40 mg/m², max 80 mg

External radiotherapy (45-50 Gy) in fractions of 1.8 Gy to 2 Gy + external boost or brachytherapy
- min. 75 Gy EQD2 to point A (80 Gy to High Risk PTV) is mandatory
- overall treatment time ≤ 50 days

Pls: G. Kenter, S. Greggi, F. Landoni
Randomized Phase III Clinical Trial of Adjuvant Radiation vs Chemoradiation In Intermediate Risk, Stage I/IIA Cervical Cancer Treated With Initial Radical Hysterectomy and Pelvic Lymphadenectomy

Sang Young Ryu, M.D.
Korea Cancer Center Hospital
Seoul, Korea
GOG 263

Cervical cancer
Stage I-IIA
Radical hysterectomy+BPLND
>2 of intermediate risk factors

Randomization

Control Arm; Radiation therapy

CRT Arm; Weekly CDDP
40mg/m² concurrent to radiation
RTOG–0724 (GOG): ChemoRT with and without adjuvant chemotherapy in high risk cervix cancer after hysterectomy
A Phase III trial of adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone
- multi-centre GCIG study
- women to participate = 780
STUDY SCHEMA

Patients with stage IB1 & positive nodes, IB2, II, IIIB or IVA cervical cancer who have given informed consent

Eligible patients

RANDOMISE

Max 6 weeks

Arm A – Control Arm
Concurrent chemoradiation

Arm B – Intervention Arm
Concurrent chemoradiation followed by adjuvant chemotherapy

Follow up 3 monthly for 2 years, and then 6 monthly for 3 years (5 years follow up in total)
Primary objective: To determine if adding adjuvant chemo to standard chemo-XRT improves overall survival

• A sample size of 780 (390 per arm) will have 80% power with 95% confidence for detecting a reduction in the hazard of death of at least 30% (HR 0.68) from the control regimen (approx 10% improvement in OS at 5 years from 63% to 73%)

• Based on 3 year accrual rate and median time to recurrence of 12 months
INCLUSION CRITERIA

• Stage IB1 & positive nodes, IB2, II, IIIB or IVA cervical cancer suitable for primary treatment with chemoradiation with curative intent in addition to:
  • ECOG performance status 0-2
  • Histological diagnosis of squamous cell carcinoma, adenocarcinoma or adenosquamous cell carcinoma
  • Adequate haemopoietic, renal and hepatic function
  • No contraindication to the use of cisplatin, carboplatin or paclitaxel chemotherapy
  • Written informed consent
INTERVENTION

• Standard chemo-radiation with Cisplatin 40mg/m² weekly
• Overall treatment time for the chemoXRT component should not exceed 8 weeks.
• Within 4 weeks of completion of XRT and following recovery from toxicities: 4 cycles of 3 weekly adjuvant chemotherapy using Carboplatin AUC 5 and Paclitaxel 155 mg/m²
INTERNATIONAL PARTICIPATION

• Australia/New Zealand - 13 sites open
• USA GOG – 27 sites open, 40 in start-up
• USA RTOG – 4 sites in start-up
• India – 1 site in start-up
• Saudi Arabia – expressed interest
• Ghana – expressed interest
• Brazil – expressed interest
• Romania – expressed interest
RECRUITMENT

- 43 patients: 27 ANZ, 16 GOG (at 24 May)
ONGOING PROGRESS / WORK

• Finish activating all US sites
• Get other countries started including RTOG sites in Canada
• Membership of IDSMC finalized and TOR drafted – interim analysis for toxicity after 60 patients completed intervention
• Administrative protocol amendment to clarify minor inconsistencies detected
• Get QA for RT happening
• Work on plan for translational studies
Developing Concepts – Discussions
A RANDOMIZED TRIAL COMPARING RADICAL HYSTERECTOMY AND PELVIC NODE DISSECTION VS SIMPLE HYSTERECTOMY AND PELVIC NODE DISSECTION IN PATIENTS WITH LOW RISK EARLY STAGE CERVICAL CANCER

A Gynecologic Cancer Intergroup (GCIG) Trial led by the NCIC CTG

GCIG Trial Designation: The SHAPE Trial
NCIC CTG Protocol Number: CX.5

Chair: Marie Plante
Background

 лечение модалитети за стадион IA2/IB1

- 75% хирургия въобще
  - 1/3: конус въобще
  - 1/3: проста хистадексия с / без ноди
  - 1/3: радиохистадексия с / без ноди

- 25% някакъв вид на радиация терапия
Background

- Considerable variation exists in international practices.
- Lack of high-quality evidence upon which clinicians can base their decisions and advice women.
- Need to standardize treatments and a need to identify the patient and disease for which a less radical surgery can safely be offered.
- In the context of “survivorship” issues related to long-term surgical effects:
  - Compromised sexual, bowel and bladder function.
  - Infertility.
Background

Retrospective studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Low-risk criteria</th>
<th>N</th>
<th>Parametial involvement in low-risk group (%)</th>
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<tr>
<td>Kinney [13]</td>
<td>1995</td>
<td>Squamous histology only, tumor &lt;2 cm, no LVSI*</td>
<td>83</td>
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<tr>
<td>Covens [14]</td>
<td>2002</td>
<td>All histologies, tumor &lt;2 cm, DOI** &lt; 10 mm, negative pelvic lymph nodes</td>
<td>536</td>
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<tr>
<td>Stegeman [15]</td>
<td>2007</td>
<td>Squamous, adenocarcinoma, adenosquamous or clear cell histology, tumor &lt;2 cm, DOI** &lt; 10 mm, negative pelvic lymph nodes</td>
<td>103</td>
<td>0.0%</td>
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<tr>
<td>Wright [16]</td>
<td>2008</td>
<td>All histologies, tumor &lt;2 cm, no LVSI*, negative pelvic lymph nodes</td>
<td>270</td>
<td>0.4%</td>
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<tr>
<td>Frumovitz [19]</td>
<td>2009</td>
<td>Squamous, adenocarcinoma or adenosquamous histology, tumor &lt;2 cm, no LVSI*</td>
<td>125</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

N=1117 < 1%

Schmeler K et al. Gynecol Oncol 120:321, 2011
Background

Concept of the trial

- To demonstrate that simple hyst and nodes is not inferior to radical hyst and nodes in terms of pelvic relapse rate and is associated with better quality of life/sexual health
Background

Definition

- «Low-risk» early-stage cervical cancer
  - IA2
  - IB1 < 2 cm
  - Limited stromal invasion
    - < 10 mm SI on LEEP/cone
    - < 50 % SI on pelvic MRI
**Patient Population**
- Stage IA2-IB1
- Squamous and Adenocarcinoma
- < 2cm and < 50% SI or <10mm DOI
- Grade 1, 2 & 3

**Randomization**

**Control Arm**
Radical Hysterectomy & PLND +/- SLN Mapping*
- Positive Nodes
- Extrauterine Disease

**Experimental Arm**
Simple Hysterectomy with PLND +/- SLN Mapping*
- Positive Nodes
- Extrauterine Disease

- Yes
  - Treatment According to Local Protocol
    - Abandon Hysterectomy vs. Completion Hysterectomy
    - +/- Para-aortic LND
- No
  - Treatment According to Randomization

*Sentinel lymph node mapping optional, laparoscopic approach preferred

**SI:** Stromal Invasion; **DOI:** Depth Of Invasion

**LVSI allowed**
Exclusion criteria

- High risk histology
  - clear cell, small cell
- Stage IA1
- Evidence of lymph node metastasis or extrauterine disease *(pelvic MRI)*
- Neoadjuvant chemotherapy
- Pregnancy
- Desire to preserve fertility
SHAPE

Stratification

- Cooperative group
- Surgical approach (Abd vs MIS)
- Stage (IA2 vs IB1)
- Histology (squamous vs adeno)
- Grade (1,2 vs 3)
- SN mapping (yes vs no)

Note: LVSI will not be included as a stratification factor but will be evaluated separately in the final data analysis.
Trial schema

Low-risk cervical cancer as defined by:
- Stage IA2-IB1 squamous cell, adenocarcinoma/adenosquamous carcinoma
- < 2cm, at least 3mm of intact cervical stroma and < 50% stromal invasion
- Grade 1-3

* Regardless of treatment assignment, surgery will include pelvic lymph node dissection with optional sentinel lymph node (SN) mapping. If SN mapping is to be done, the mode is optional, but the laparoscopic approach is preferred.

Planned sample size: 700 (non-inferiority at 0.05 level with 80% power)
Objectives

.primary trial objective:

- To show that simple hysterectomy in low risk cervix cancer patients is safe and is associated with less morbidity than radical surgery
- To show that overall survival will not be significantly different between rad hyst and simple hyst
Trial Endpoints

Primary endpoint
• Pelvic relapse-free survival (PRFS)

Secondary endpoints
• Treatment-related toxicity
• Extrapelvic relapse-free survival
• Overall survival
• Rate of sentinel node detection
• Rate of + parametria, margins, and pelvic node
• Patient Reported Outcome (PRO)
  • Quality of life (including measures of sexual health)
  • Cost effectiveness and cost utility
NCIC-CTG  early cervix trial

Trial Design
- 1:1 multicenter prospective randomized trial
- Non-inferiority trial design at 0.05 level with 80% power
- Sample size: 700 patients

Duration of the study
- 3.5 years for accrual (200 ptes/year)
- 3.5 years of follow-up
- Total duration: 7.0 years
Treatment plan

- **Radical Hysterectomy - Type II**
  The uterus, cervix, medial 1/3 of parametria, 2 cm of the uterosacral ligaments and upper 2 cm of the vagina are to be removed *en bloc*

- **Simple Hysterectomy**
  The uterus with cervix but without adjacent parametria and a max of 0.5 cm of vaginal cuff

*Procedure can be done abdominally, laparoscopically, robotically or vaginally*
Treatment plan

- Lymphadenectomy
  - Pelvic (mandatory)
  - Para-aortic (as required)
  - Sentinel Node Mapping (based upon previous credentialing)
Adjuvant treatment

- **Adjuvant Therapy**
  - Most patients will not require adjuvant Tx
  - If there is evidence of intermediate or high risk features on final pathology, then patients will have adjuvant therapy
SHAPE

纪律 NCIC has received **CIHR grant** (2.2 millions)
  * In effect, April 1st 2012, for a total of 8 years

纪律 Will cover
  * **Central office cost** to conduct the trial
    * Regulatory, data management, IT support, statistics, etc
  * **Canadian per case funding**

纪律 Each cooperative group is responsible for securing its own funding
INduction ChemoThERapy in Locally Advanced Cervical Cancer

INTERLACE

Mary McCormack
for the NCRI Gynaecological Clinical Studies Group
Chicago, 2012
Carboplatin AUC2 & Paclitaxel 80mg/m²
Weeks 1-6

Standard CRT

Standard CRT: 40—50.4Gy in 20-28 fractions plus Intracavitary brachytherapy to give total EQD2 dose of 78-86Gy to point A/volume.
Weekly cisplatin 40mg/m² x 5 weeks

Follow-up
3 monthly for 2 years; 6 monthly for 3 years
Eligibility - inclusion

- Histologically confirmed FIGO stage Ib2-IVa squamous, adeno or adenosquamous ca of cervix, fit to receive radical CRT
- +ve nodes (either histologically/PET +ve/radiologically enlarged) at or below the level of aortic bifurcation
- HIV –ve (from high risk countries); no active TB
- ECOG 0/1; Age 18 and over; normal ECG
- Adequate renal/liver/bone marrow function
- Contraception precautions if appropriate
- Written / witnessed informed consent
Eligibility - exclusion

- Previous diagnosis of cancer unless 10 yrs disease free (except BCC skin)
- Any previous pelvic cancer regardless of interval since diagnosis
- Positive lymph nodes above aortic bifurcation
- Involvement of lower 1/3 vagina (FIGO IIIA)
- Evidence of distant metastasis
- Previous pelvic RT
- Crohn’s or ulcerative colitis
- Uncontrolled cardiac disease
- Pregnant/lactating
Induction Chemotherapy

Paclitaxel and carboplatin - weekly treatment for six weeks

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## Chemoradiation

### Cisplatin weekly treatment for five weeks

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<td>40-50.4Gy in 20-28 fractions</td>
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<tr>
<td>Cisplatin 40mg/m² Mon, Tues or Wed</td>
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Radiation

- Conformal 3D planning mandatory for all participating centres UK/Eire
- External beam RT: 40-50.4 Gy/20-28 fractions
- Plus Intracavitary brachytherapy to give a total EQD2 dose to point A / volume of 78-86 Gy
- Overall treatment time ≤ within 50 days
Quality Assurance - Radiotherapy

1. Site Survey - team members
2. Baseline questionnaire - equipment/planning system etc
3. Outlining exercise for nodes/GTV
4. Planning exercise for all
5. Verification protocols
6. Brachytherapy technique
Stratification

- FIGO stage
- Node status – positive / negative
- Tumour Volume
- Squamous vs. non-squamous
- IMRT vs. no IMRT
- Age
- Recruiting site
Outcome measures

Primary endpoint:
  OS at 5 years

Secondary endpoints:
  PFS
  Toxicity
  QOL (UK & Eire only)
  Pattern relapse of (local and/or systemic)
Statistics

Sample size of 730 provide 80% power to detect a 10% increase in 5 year OS (60 to 70%) (HR 0.70, 2 sided test at 5% sig level)

To allow for 5% loss to FU – recruit 770

Assumes accrual over 4 years with 3 years FU
Current Status

- Funding from Cancer Research UK
- Ethical/regulatory approvals – January 2012
- Anticipated 1st site (UK) activated – June 2012
- No. interest sites in UK – 37
- No. currently in set-up in the UK – 23
- International sites in set-up – 2 in Mexico
- Interested international Sites: Eire, Romania, Belarus
- Potential interest: France, Italy, Hong Kong, Ghana + others
- UK Trial Launch October 5th 2012, London

Contact: Mandy Feeney – a.feeney@ucl.ac.uk
Cancer Research UK and UCL Cancer Trials Centre
TAKO Trial

RCT of Weekly vs Tri-weekly Cisplatin based CRT in Cervical Cancer

Sang Young Ryu, MD
Korea Cancer Center Hospital
Seoul, Korea
Cervical cancer
Locally advanced cervical cancer
Stage IIB-IVA

Randomization

Control Arm; Weekly Cisplatin 40mg/m^2 6 cycles

Study Arm; Tri-weekly Cisplatin 75mg/m^2 3 cycles
Cervix Cancer Research (CCRN) Report
GCIG Symptom Benefit Working Group Report
A RANDOMIZED PHASE III STUDY OF STANDARD VS. IMRT PELVIC RADIATION FOR POST-OPERATIVE TREATMENT OF ENDOMETRIAL AND CERVICAL CANCER (TIME-C)
TIME-C: Objectives

Primary Objective:
- To determine if acute gastrointestinal toxicity is reduced with IMRT using patient reported measure of toxicity

Secondary Objective:
- To determine if acute grade 2 gastrointestinal toxicity (CTCAE v. 3.0) is reduced with IMRT compared to conventional WPRT.
- To determine if acute grade 3+ hematologic toxicity (CTCAE v. 3.0) is reduced with IMRT compared to conventional WPRT.
- To determine if acute urinary toxicity is reduced with IMRT using a patient reported measure of toxicity.
- To assess the impact of pelvic IMRT on quality of life using patient reported outcomes.
Eligibility
Women with endometrial or cervical cancer requiring post-operative pelvic radiation or chemoradiation

Stratification factors
- XRT dose
  - 45 Gy
  - 50.4 Gy
- Chemotherapy
  - No Chemotherapy
  - 5 cycles of weekly cisplatin at 40mg/m²
- Disease Site
  - Endometrial
  - Cervix

Randomize
IMRT pelvic radiation treatment
4-field pelvic radiation treatment
Time points for toxicity evaluation

- Toxicity assessment at each time point
  - CTCAE v 3.0 toxicity
  - GI PRO: bowel domain sections of EPIC
  - Urinary PRO: urinary domain sections of EPIC
  - QOL assessment: FACT-G
  - Cervix subscale of FACT

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<th>Time Point</th>
<th>Purpose</th>
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<tr>
<td>Before RT</td>
<td>Baseline</td>
</tr>
<tr>
<td>3 weeks after RT start</td>
<td>Compare early acute toxicity</td>
</tr>
<tr>
<td>End of RT</td>
<td>Maximum difference in acute toxicity</td>
</tr>
<tr>
<td>4-6 weeks after RT</td>
<td>Compare resolution of acute toxicity</td>
</tr>
<tr>
<td>1 year from the start of RT</td>
<td>Early chronic toxicity</td>
</tr>
<tr>
<td>3 years from the start of RT</td>
<td>Long term toxicity</td>
</tr>
</tbody>
</table>
Additional Secondary Endpoints

- PRO-CTCAE for GI toxicity
- Local-regional control, disease free survival and overall survival
- Cost analysis with cost utility
- Identify molecular predictors of radiation toxicity
- Validation of the EPIC bowel and urinary domains
- QOL, assessed by the FACT-Cx
TIME-C: Methods

• Sample size calculation
  ○ Primary endpoint is acute GI toxicity, as measured by the EPIC bowel domain, at week 5 of radiation treatment.
  ○ Estimated sample size of 284
    ✷ Based on a two-sample t-test and two-sided alpha=0.05, a sample size of 225 is needed to achieve 85% statistical power.
    ✷ Assuming an attrition rate of 10%, 250 patients will be required to ensure there are at least 225 evaluable patients.
    ✷ Since a patient-reported outcome is the primary endpoint for this study and thus compliance is an added concern, the sample size will be increased by an additional 10%, requiring a maximum of 284 patients in order to ensure 227 evaluable patients for the primary endpoint analysis.

• Feasibility
  ○ Extrapolations from RTOG 0418 enrollment (similar entrance criteria) predict it would take 2.6 years to enroll these 119 patients.
  ○ Intergroup and international collaborations are anticipated to double the enrollment rate.