Gynecologic Cancer InterGroup (GCIG)

Cervix Cancer Committee

LIBERDADE I Room, DoubleTree Fontana Park, Lisbon
Friday, Oct.28, 2016, 7:30 am – 9:00 am

Chair: Bradley Monk                     Co-Chair: Antonio Casado
Harmonization Liaisons: Hiltz (Ops), Reuss (Stats)

1. EORTC
2. KGOG
3. RTOG
4. ANZGOG
5. MRC_NCI
6. CCTG (NCIC)
7. G-GOC
8. NRG (GOG)
9. GINECO
10. DGOG
**EORTC 55994**: Randomized phase III study of neoadjuvant chemotherapy followed by surgery vs. concomitant radiotherapy and chemotherapy in FIGO stage Ib2, IIa > 4 cm or IIb cervical cancer.

*PI’s: G. Kenter, S. Greggi, F. Landoni*

- **Primary endpoint:**
  - Overall survival at five years
- **Secondary endpoints:**
  - Overall survival
  - Progression free survival
  - Toxicity
  - Quality of life

- **Accrual (n = 626) completed June 2014**
  - Expected study completion = mid 2019
- **Protocol amendment (v4.0):**
  - New primary end-point: OS at 5 years instead of OS
  - Secondary end-point: OS
  - Change of total number of patients: 625 (instead of 686)
  - Revised TR chapter
**EORTC 55994**: Randomized phase III study of neoadjuvant chemotherapy followed by surgery vs. concomitant radiotherapy and chemotherapy in FIGO stage Ib2, IIA > 4 cm or IIB cervical

**SHORT TERM TOXICITY** and PRELIMINARY RESULTS FROM EORTC 55994 COMPARING NEOADJUVANT CHEMOTHERAPY FOLLOWED BY SURGERY TO CHEMORADIATION FOR LOCALLY ADVANCED (Stage IB2-IIB ) CERVICAL CANCER

IGCS, Lisbon 2016 (Saturday afternoon)
GOG 263/KGOG 1008
PI; Sang Young Ryu, MD

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

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
Cervical cancer
Locally advanced cervical cancer
Stage IB2, IIB-IVA

Control Arm; Weekly Cisplatin 40mg/m2 6 cycles

Study Arm; Tri-weekly Cisplatin 75mg/m2 3 cycles

TACO
(Tri-weekly Administration of Cisplatin in LOcally Advanced Cervical Cancer)

GCIG/KGOG1027/TGCS2012
A RANDOMIZED PHASE III STUDY (NRG Oncology’s RTOG 1203) OF STANDARD VS. IMRT PELVIC RADIATION FOR POST-OPERATIVE TREATMENT OF ENDOMETRIAL AND CERVICAL CANCER (TIME-C)

Ann H. Klopp MD, PhD
MD Anderson Cancer Center
IMRT for post-operative pelvic RT

IMRT reduces the dose delivered to small bowel in center of pelvis.

Retrospective studies show lower rates of acute and chronic GI toxicity with IMRT as compared to standard 4-field RT.

RTOG 0418 found IMRT to be feasible with a favorable rate of acute 2+ GI toxicity (25%).
Eligibility

Women with endometrial or cervical cancer requiring post-op pelvic RT or chemoRT

Stratification Factors

- **XRT Dose**: 45 Gy, 50.4 Gy
- **Chemo**: No chemo, 5 cycles of weekly cisplatin at 40mg/m²
- **Disease Site**: Endometrial, Cervix

DIAGRAM:
- IMRT pelvic radiation treatment
- 4-field pelvic radiation treatment
EPIC Bowel Score

<table>
<thead>
<tr>
<th></th>
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<th>Week 3 of RT</th>
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<th>4-6 weeks post-RT</th>
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<tr>
<td>4 Field</td>
<td>148</td>
<td>132</td>
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</table>

p-value = 0.048
Conclusions

Pelvic IMRT reduces acute patient reported GI and GU toxicity compared to standard pelvic RT.

Pelvic IMRT reduces need for anti-diarrheal medications as compared to standard pelvic RT.

Pelvic IMRT improves quality of life with regard to physical functioning and other treatment effects during treatment.

Longer term follow up will be needed to determine if these differences in acute toxicity result in lower rates of late toxicity.
A Phase III trial of adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone

Study Chair: A/Prof Linda Mileshkin
Patients with stage IB1 & positive nodes, IB2, IIA, IIB, 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 for a minimum of 3.5 years
Randomise

Carboplatin AUC2 & Paclitaxel 80mg/m²
Weeks 1-6

Standard CRT

Weeks 7 – 13
Standard CRT

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

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
Current status

Target recruitment – **770**

Accrual to date (UK and Mexico) – **172**

Number of sites open - **30**

- **GICOM (Mexico)** – 21 patients recruited since opening in Feb 2016

- **MaNGO (Italy)** – 5 sites in setup
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 CCTG

GCIG Trial Designation: The SHAPE Trial
CCTG Protocol Number: CX.5
Chair: Marie Plante
Trial Schema

Low-risk cervical cancer as defined by:
- squamous cell, adenocarcinoma, adenosquamous carcinoma
- Stage IA2 and modified IB1
- < 10mm SI on LEEP/cone
- < 50% stromal invasion on MRI
- max dimension of \( \leq 20 \text{ mm} \) on MRI
- Grade 1-3 or not assessable

* 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)
## Current Status

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<tr>
<th>Country</th>
<th># Sites Activated</th>
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<th># Patients Accrued</th>
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<td><strong>Total</strong></td>
<td><strong>96</strong></td>
<td><strong>Total</strong></td>
<td><strong>233 (33%)</strong></td>
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</tbody>
</table>
A Phase III Randomized Clinical Trial Comparing Laparoscopic or Robotic Radical Hysterectomy with Abdominal Radical Hysterectomy in Patients with Early Stage Cervical Cancer


N=740
International Collaboration
End points:
  DSF
  Recurrence rate
  Overall survival
  Treatment-related morbidity
  QOL
  Lymphatic mapping feasibility

Total Sites: 27
LACC Consort Statement as at 4th October 2016

Assessed for Eligibility
n = 985

- Pending
  n = 0

Randomised
n = 510

- Excluded n = 475
  - Not meeting eligibility criteria (n = 245)
  - Refused (n = 178)
  - Other (n = 42)
  - SHAPE Trial (n = 10)

- Allocated to TARH
  n = 254

- Allocated to TLRH/TRRH
  n = 256
ConCerv Trial

Kathleen M. Schmeler, MD
Associate Professor
Department of Gynecologic Oncology & Reproductive Medicine
ConCerv Trial

Inclusion Criteria

• Stage IA2 or IB1 cervical cancer
• Tumor diameter \( \leq 2 \) cm
• No LVSI
• \( \leq 10 \) mm stromal invasion
• Squamous cell histology (any grade) or adenocarcinoma (grade 1 or 2 only)
• Cone margins and ECC negative for malignancy or CIN/AIS (one repeat cone/ECC permitted)
• Imaging with PET scan, CT scan of the abdomen and pelvis, and/or MRI of the abdomen and pelvis must be performed and negative for metastatic disease within 12 weeks of enrollment
ConCerv – Preliminary Results

• 119 patients pre-enrolled
• 73 evaluable patients:
  – 31 simple hysterectomy + nodes (42.5%)
  – 25 cone and nodes (34.2%)
  – 17 cut-through hysterectomy (23.3%)

Not evaluable:
– 43 ineligible after MD Anderson review
– 1 cancelled due to + pregnancy test
– 1 declined surgery
– 1 patient did not have surgery on protocol due to study hold (amendment was submitted)
NRG Oncology (GOG/RTOG)

Current GCIG Studies in the NRG

1. GOG 278
2. GOG 263 (KGOG 0801)
3. GOG 0724 (RTOG)
4. GOG 0274 (ANZGOG OUTBACK)
5. AIM2CERV/GOG 3009
6. NRG GY006
7. TIME-C (RTOG)
8. GOG 270 (GROINSS-V II)
9. GOG 279
# NRG Oncology (GOG/RTOG)

## Current GCIG Studies in the NRG

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7. TIME-C (RTOG)
8. GOG 270 (GROINSS-V II)
9. GOG 279
PROTOCOL GOG-0278
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 (LVS1+) and IA2-IB1 (≤ 2CM) CERVICAL CANCER
NCI Version Date 09/20/2012

POINTS:
PER CAPITA - 20
MEMBERSHIP - 6

Study Chair: A Covens
AIM2CERV/GOG 3009

- High Risk, Locally Advanced Cervical Cancer
- FIGO Stage I-II with positive pelvic nodes
- FIGO Stage III-IVA
- Any Figo Stage with para-aortic nodes

Baseline tumor imaging must be performed within 28 days prior to the first study treatment infusion

Randomization 1:2 Reference and Treatment Groups

Primary Objective is Progression Free Survival

** 3 years of Lm surveillance from time of last dose to include 90 days of antibiotics **
NRG GY006

Newly diagnosed uterine cervix cancer
• Squamous
• Adenosquamous
• Adenocarcinoma

Clinical stage bulky (> 5 cm) IB2, or Clinical stage II, IIIB, or IVA followed by Negative para-aortic nodal staging by PET/CT

Stratify para-aortic node-negative patients by:
  a. Age (≤ 45 years or > 45 years)
  b. Performance status (0, 1, or 2)
  c. Intensity Modulated Radiation Therapy (yes or no)
  d. Stage (≤ clinical stage II, or ≥ clinical stage III)

RANDOMIZE

Arm 1:
• Radiation
• Cisplatin

Arm 2:
• Radiation
• Cisplatin
• Triapine

Radiation: 45 Gy / 25 fractions of 1.8 Gy + 5.4 Gy / 3 fraction parametrium boost + 40 Gy LDR or 30 Gy HDR brachytherapy

Cisplatin: X1 weekly cisplatin 40 mg/m² (maximum 70 mg) days 2, 9, 16, 23, 30 of radiation (5 total infusions; a sixth administration on day 36 is permissible at the treating physician’s discretion.)

Triapine: X3 weekly 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (Triapine) 25 mg/m² (maximum 50 mg) days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, 26, 29, 31, 33 of radiation (15 total infusions)
PROTOCOL GOG-0279
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

NCI Version Date: 11/02/2012
Includes Revision #1

POINTS:
PER CAPITA - 20
MEMBERSHIP – 3

Study Chair: NS Horowitz
Target 52 evaluable patients
NRG Enrollment to Cervical and Vulvar Cancer Studies October 2016

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Enrollment Goal</th>
<th>Current Total Enrollment</th>
<th>Current NRG (RTOG/GOG) Enrollment</th>
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</tbody>
</table>

*Includes 129 from KGOG and JGOG
Cervix cancer committee

SENTICOL III: International prospective validation trial of sentinel node biopsy in cervical cancer

A Gynecologic Cancer interGroup (GCIG) trial, lead by the GINECO

F Lecuru, M Leitao, P Mathevet, M Plante.
Schema

SCC/Adk
Stage ≤ IIa
<40mm
No pregnancy

SLN biopsy
Cormier algorithm
Neg Frozen section

pN0

SLN

Disease free survival
Quality of life

pN0

SLN + PLN

Randomized study
Surgical & pathological quality assurance
Statistics

1-DFS
- With a 3 years-disease free survival of 85% to demonstrate a non-inferiority of SLN biopsy vs SLN biopsy + lymphadenectomy with a non-inferiority margin of 5% (80 vs 85%, HR = 1.373). With a unilateral alpha error of 5%, and a power of 80%, 900 patients in 3 years, with 4 years of follow-up should be included to observe the required 219 DFS events. An interim analysis is planned when at least 110 events will be observed to reject H0 or H1 using O'Brien Fleming and alpha spending function.

2-HRQoL
- We target 3 HRQoL dimensions global health, pain and physical functioning of EORTC QLQC 30 compared at 3 years.
- To demonstrate a superiority of at least one of the 3 targeted dimensions without significant deterioration in at least one with a minimal important difference in mean score of at least 5 points (SD: 20), and a bilateral alpha type one error of 0.015 (Bonferroni adjustment it would be required to have 815 patients with available HRQoL scores to reach 85% statistical power.

950 patients have to be randomized
An international collaboration is requested
Participating & interested groups

- AGO
- NOGGO
- DGOG
- G-GOC
- MITO
- MANGO
- NCIC
- And….

- Patients association « 1000 femmes – 1000 vies »
Agenda

- GCIG June 2016
  - Final acceptation of the study and validation of the design

- June to sept 2016
  - Protocol writing

- Sept 2016
  - Full protocol submitted to INCa for funding

- Nov – dec 2016
  - Response of INCa

- 2017 KICK-OFF meeting?
GROINSS-V II

- Multicenter observational study

- Is radiotherapy a safe alternative for lymphadenectomy in patients with a positive SN?
  - SN negative: follow-up
  - SN positive: radiotherapy (50 Gy)
Update GROINSS-V II

1715 registrations

Inclusion every three months
GROINSS-V II

• On October 7, 2016 the study completed the accrual of 150 patients with micrometastases in the SN!

• GROINSS-V III: in preparation