Complications of Pelvic Radiotherapy
Clinical Overview from
Gynae Oncology Perspective

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Complications of Pelvic Radiotherapy

• How do we Justify the Complications
• How do we Minimise the Complications
• How do we Manage the Complications
Pelvic Radiotherapy for Gynae Malignancies

- Radical (Primary Treatment)
- Adjuvant
- Palliative
- External Beam Radiotherapy
- Brachytherapy
- Chemotherapy
Locally advanced Cervical Cancer

Pre – Chemo radiotherapy

During brachytherapy
Pelvic Radiotherapy – Organs at Risk

- Small Bowel and Rectum – Radiation enteritis / proctitis
- Bladder – Radiation cystitis
- Ovaries – Infertility, Early menopause,
- Vagina - Stenosis
- Sacrum – Insufficiency fractures/myelopathy
- Lymph nodes – Lymphoedema
- 2nd Cancer at 15-20 years
How Do we Justify Complications – Locally Advanced Cervical Cancer

- Concurrent ChemoRadiotherapy and Brachytherapy
- Randomised Trials and 2 Meta- analyses
- Improved pelvic control rates and survival benefit (16% OS, 12% PFS)
- Aim to 75- 80 Gy to tumour

- **Morris et al, NEJM Apr 1999**, Pelvic radiation with Concurrent Chemotherapy compared with pelvic and para aortic radiation for high risk cervical cancer
- **Rose et al, NEJM Apr 1999**, Concurrent cisplatin **Keys et al, NEJM Apr 1999**, Cisplatin, Radiation and Adjuvant hysterectomy compared with Radiation and adjuvant Hysterectomy for bulky stage 1B Cervical Carcinoma
- **Whitney et al, JCO May 1999**, 5FU plus Cisplatin vs Hydroxyurea as an adjunct to radiation therapy in Stage2B-4A Carcinoma cervix
- **Peters et al, JCO Apr 2000**, Concurrent Chemotherapy and Pelvic Radiotherapy compared with Pelvic radiation therapy alone after radical surgery in high risk early stage carcinoma cervix.

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RCR Audit Cervix Cancer: Results – Total Dose HDR

Standard: EQD2 should be at least 75Gy = 27%
Median 72.1 (Inter-quartile Range 69.4 - 75.8)

![EQD2 for HDR chart]

- Median = 72.1
- Interquartile range = 69.4-75.8
- 41/151 EQD2 > 75 Gy
NICC Audit Cervical Cancer 2008/2012

• First 138 Patients from Oct 2008
• Median Follow up 18.3 months
• DFS 76%, OS 79% at 3 years
• 6.5% Grade 3 late GI toxicity
### RCR UK AUDIT

<table>
<thead>
<tr>
<th>Main sites of complications</th>
<th>Radical radiotherapy (355 patients)</th>
<th>Radical chemoradiation (471 patients)</th>
<th>Surgery + postoperative radiotherapy (249 patients)</th>
<th>Non-radical treatment (168 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vagina</td>
<td>11 (4%)</td>
<td>17 (5%)</td>
<td>2 (1%)</td>
<td>1 (1%)</td>
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<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rectum</td>
<td>6 (2%)</td>
<td>10 (3%)</td>
<td>2 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Colon</td>
<td>3 (&lt;1%)</td>
<td>7 (1.5%)</td>
<td>1 (&lt;1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>2 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>2 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Small bowel</td>
<td>1 (&lt;1%)</td>
<td>3 (1%)</td>
<td>3 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>2 (&lt;1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bladder</td>
<td>5 (2%)</td>
<td>9 (2%)</td>
<td>1 (&lt;1%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</table>
How Do we Minimise Risk of Complications?

- External Beam Planning
- Brachytherapy Planning

Organs at Risk

- Small Bowel – radiation enteritis
- Large bowel, rectum – proctitis, Fistula, stricture
- Bladder – radiation cystitis, Fistula
- Ovaries- Infertility, premature Menopause
- Bone, bone Marrow – insufficiency fractures
- Lymphoedema
- 2nd Cancer – 1% risk at 10 years
Minimising Risk of Complications
The Future of Pelvic Radiotherapy
IMRT Planning
Organ Motion of Intact Cervix
IGRT Delivery

CLINICAL INVESTIGATION

CONSENSUS GUIDELINES FOR DELINEATION OF CLINICAL TARGET VOLUME FOR INTENSITY-MODULATED PELVIC RADIOTHERAPY FOR THE DEFINITIVE TREATMENT OF CERVIX CANCER

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Purpose: Accurate target delineation is vitally important for definitive treatment of cervix cancer with intensity-modulated radiotherapy (IMRT), yet a definition of clinical target volume (CTV) remains variable within the literature. The aim of this study was to develop a consensus CTV definition in preparation for a Phase 2 clinical trial being planned by the Radiation Therapy Oncology Group.

Methods and Materials: A guidelines consensus working group meeting was convened in June 2008 for the purpose of developing target definition guidelines for IMRT for the intact cervix. A draft document of recommendations was circulated to all participants prior to the meeting. A consensus was reached among the participants either by consensus or by a majority vote. A 2 × 2 table was used to analyze for consistency and clarity of target delineation using an expectation maximization algorithm for simultaneous truth and performance level estimation (STAPLE), with kappa statistics as a measure of agreement between participants.

Results: Nineteen experts in gynecologic radiation oncology generated on average 31 axial magnetic resonance images of the pelvis. Substantial STAPLE agreement sensitivity and specificity values were seen for gross tumor volume (GTV) delineation (84% and 99.6%, respectively) with a kappa statistic of 0.48 (p < 0.0001). Agreement for delineation of cervix, uterus, vagina, and parametria was moderate.

Conclusions: This report provides guidelines for CTV definition in the definitive cervix cancer setting for the purposes of IMRT, building on previously published guidelines for IMRT in the postoperative setting. © 2011 Elsevier Inc.
1.2 Trial Schema
Multicentre phase III randomised controlled trial

**Induction Chemotherapy in Locally Advanced Cervical Cancer**

- **Randomise**
  - Carboplatin AUC2 & Paclitaxel 80mg/m² Weeks 1–6
  - Standard CRT: 40–50.4Gy in 20–28 fractions plus intracavitary brachytherapy to give a total EQD2 dose of 78–86Gy to point Al volumen. Weekly cisplatin 40mg/m² x 5 wks

- **Weeks 7–13 Standard CRT**

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

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### Table 9
Clinical Target Volume and Planning Target Volume Margins

<table>
<thead>
<tr>
<th>Clinical Target Volume 1 (CTV1)</th>
<th>CTV1 should include the whole cervical tumour and its local extension (GTV). Also, the cervix and uterus.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Target Volume 2 (CTV2)</td>
<td>Proximal half of the uterosacral ligament, bilateral parametria and upper half of the vagina, or 2 cm below known vaginal disease. If there is uterosacral involvement, the entire ligament needs to be encompassed. The external iliac, obturator, internal iliac and common iliac nodes are also included in this volume. The superior extent is at the aortic bifurcation. The nodal areas are defined by using a 7mm around blood vessels. It should be extended to include visible disease and lymphoceles. It should be modified to exclude bone, psoas muscle, bladder and bowel. The subaortic prosacral nodes can be covered by connecting the nodal areas either side of S1 and S2 with a 10mm strip volume.</td>
</tr>
<tr>
<td>Clinical Target Volume 3 (CTV3) (Extended field)</td>
<td>Where nodes at the aortic bifurcation or at the level of the common iliac vessels are positive (histology/CT/PET &gt; 15mm on imaging) the most superior extent of CTV3 will be at the renal hilum. In general, a margin of at least 2cm should be added above the highest involved lymph node region.</td>
</tr>
<tr>
<td>Planning Target Volume 1 (PTV1)</td>
<td>Add 15 to 20mm to CTV1 anteroin/posterior/superior and inferior, 7 to 10mm in the lateral extension.</td>
</tr>
<tr>
<td>Planning Target Volume 2 (PTV2)</td>
<td>Add 7 to 8mm to CTV2.</td>
</tr>
<tr>
<td>Planning Target Volume 3 (PTV3)</td>
<td>Add 5mm to CTV3.</td>
</tr>
</tbody>
</table>
Carcinoma Cervix

Optimising Local Control –HDR Brachytherapy
HDR Brachytherapy

- Spinal or GA
- Insertion Intrauterine Tube and vaginal ovoids
- Xrays
- CT
- Treatment planning
- Treatment
Cannulation under USS Control

Minimises risk of Uterine Perforation
GEC –ESTRO /RCR 3-D planning Guidelines

- 3 Fractions
- CT or MRI scan with applicators in situ
- Safe dose per fraction to Limit bladder / bowel toxicity
- MRI allows safe dose escalation to improve pelvic control rates
GEC- ESTRO 2cc volume
Organs at Risk

Rectum - 70 Gy
Bowel 75 Gy
Bladder 90 Gy
RCR Audit Cervix Cancer: Results - IGBT

- 58 % centres had implemented 3-D Planning
- Only 20 % Centres had access to MRI Based planning
- NI does not have access to routine MR Based Planning despite RCR, European and American standard of care
Endometrial Cancer – How do we Minimise Toxicity – Patient Selection

- Surgery – Stage 1a G1/2
- Surgery / vault Brachytherapy – Stage 1a G3, 1b G2
- Surgery / external beam radiotherapy / vault brachytherapy - Stage 1b G3 Stage 2 and 3
- Platinum based Chemotherapy in addition to radiotherapy for high grade tumours
EXTERNAL PELVIC AND VAGINAL IRRADIATION VERSUS VAGINAL IRRADIATION ALONE AS POSTOPERATIVE THERAPY IN MEDIUM-RISK ENDOMETRIAL CARCINOMA—A PROSPECTIVE RANDOMIZED STUDY

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*Department of Gynaecological Oncology, Örebro University Hospital, Örebro, Sweden; †Department of Gynaecological Oncology, Sahlgrenska University Hospital, Gothenburg, Sweden; ‡Department of Gynaecological Oncology, Umeå University Hospital, Umeå, Sweden; †Department of Gynaecological Oncology, Karolinska University Hospital, Stockholm, Sweden; and ‡Medical Products Agency, Uppsala, Sweden

Purpose: To evaluate the value of adjuvant external beam pelvic radiotherapy as adjuvant to vaginal brachytherapy (VBT) in medium-risk endometrial carcinoma, with regard to local-regional tumor control, recurrences, survival, and toxicity.

Methods and Materials: Consecutive series of 527 evaluable patients were included in this randomized trial. Median follow-up for patients alive was 62 months. The primary study endpoints were local-regional recurrences and overall survival. Secondary endpoints were recurrence-free survival, recurrence-free interval, cancer-specific survival, and toxicity.

Results: Five-year locoregional relapse rates were 1.5% after external beam radiotherapy (EBRT) plus VBT and 5% after vaginal irradiation alone (p = 0.013), and 5-year overall survival rates were 89% and 99%, respectively (p = 0.548). Endometrial cancer-related death rates were 3.8% after EBRT plus VBT and 6.8% after VBT (p = 0.118). Pelvic recurrences (exclusively vaginal recurrence) were reduced by 93% by the addition of EBRT to VBT. Deep myometrial infiltration was a significant prognostic factor in this medium-risk group of endometrioid carcinomas but not International Federation of Gynecology and Obstetrics grade or DNA ploidy. Combined radiotherapy was well tolerated, with serious (Grade 3) late side effects of less than 2%. However, there was a significant difference in favor of VBT alone.

Conclusions: Despite a significant locoregional control benefit with combined radiotherapy, no survival improvement was recorded, but increased late toxicity was noted in the intestine, bladder, and vagina. Combined RT should probably be reserved for high-risk cases with two or more high-risk factors. VBT alone should be the adjuvant treatment option for purely medium-risk cases. © 2012 Elsevier Inc.

Endometrial cancer, Locoregional tumor control, Medium-risk group, Postoperative radiotherapy, Prognostic factors, Randomized trial.

Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial


Summary

Background. After surgery for intermediate-risk endometrial carcinoma, the vagina is the most frequent site of recurrence. This study established whether vaginal brachytherapy (VBT) is as effective as pelvic external beam radiotherapy (EBRT) in prevention of vaginal recurrence, with fewer adverse effects and improved quality of life.
Minimising Bowel Toxicity -

External Beam Radiotherapy vs Vault Brachytherapy Alone

**Vault Brachytherapy**

- 6-8 weeks post surgery
- 4 treatments as outpatient
- No sedation necessary
- Localised high dose region, reduced risk of bowel and bladder toxicity
- Each treatment lasts 10-15 minutes each, over 2-2.5 weeks
- Vaginal Dilators to minimise vaginal stenosis
Post Operative Ca Uterus IMRT – Optimise locoregional control, minimise bowel, bladder and bone side effects
IMRT Bowel Sparing vs 3-D
IMRT Bowel Sparing vs 3-D
IMRT Bowel Sparing vs 3-D
How Do we Manage Complications?

Organs at Risk

- Small Bowel – radiation enteritis
- Large bowel, rectum – proctitis, Fistula, stricture
- Bladder – radiation cystitis, Fistula
- Ovaries – Infertility, premature Menopause
- Bone, bone Marrow – insufficiency fractures
- Lymphoedema
- 2nd Cancer – 1% risk at 10 years
How Do We Manage Unavoidable Side Effects - Infertility

- Counselling by Regional Fertility Centre pre surgery or pre chemoradiotherapy
- Category 1 Patients should start within 31 days of diagnosis, rapidly dividing tumour, often life threatening bleeding requires urgent radiotherapy

- Uterine Preservation Radical Trachellectomy +/- Primary Chemotherapy in stage 1 disease
- Embryo Harvesting and Surrogacy
- Egg or ovarian harvesting less successful
How Do We Manage Unavoidable Side effects – Early Menopause

- Reassure – young patients minimal risk of breast cancer
- Specialist advice re oestrogen, progestagen and testosterone replacement
- Psychosexual counselling

- Hot Flushes,
- Poor sleep pattern,
- Mood disturbance,
- Loss of Libido
- Vaginal dryness and Dyspareunia
- Osteoporosis,
- Cardiovascular risks
Pelvic Insufficiency Fractures

- Low BMI
- Check DEXA and consider bisphosphonates
- Mobilisation and analgesia
- MR to confirm and exclude pelvic relapse
- Reassure patient NOT metastatic
Radiation Cystitis – Frequency, urgency, dysuria, haematuria, sphincter disturbance, reduced bladder capacity

**Acute** -
- During – 3 months post radiotherapy
- Mucosal damage, rapidly dividing cells
- Inflammatory response
- Tissue oedema
- Usually self-limiting

**Late** -
- At least 3 months to 2-3 years post XRT
- Vascular and connective tissues of submucosa
- Fibrosis, ulceration, Fistula
- Telangiectasia – haematuria
- Fibrosis, reduced bladder capacity
Vesico-vaginal Fistula post treatment
Vesico Vaginal Fistula
Ureteric Diversion, Ileal Conduit

- All patients and their medical teams are warned essential to avoid bladder biopsy post radiotherapy
- Close liaison with urology, interventional radiology and urogynaecology services
Radiation Proctitis

- Sucralfate Enemas
- APC with Caution
- Hyperbaric O2
- Formalin
- Metronidazole
- Avoid Steroids
- Post Brachy 2%

Risk of ant rectal wall fistula with biopsy
Management of Pelvic Complications – Palliative Care Team Input

- Dr B Corcoran, Dr J Regan, Dr Pauline Wilkinson and Macmillan Team
- Physical Symptom Control
- Patient Advocate
- Psychosocial Support
- Involvement of Palliative Care Team where patients have been cured from cancer but quality of life grossly impaired by severe consequences of successful treatment
Complex Pelvic MDT

- CNS/ Specialist Radiographer
- Symptom Control / Palliative Care Physicians
- GI Physicians
- Upper and Lower GI Surgeons
- Urologist
- Uro gynaecologist
- Gynae Oncological Surgeon
- Clinical Oncologist
- Radiologist – Gynae / GI/ Interventional
Questions?