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10.06.2014 Advanced Radiotherapy Techniques

Cervical cancer

- 650 – 700 new patients per year in The Netherland
  - About 300 advanced stages
  - 20-25 patients treated in UMCU
  - 2nd most frequent malignancy in women worldwide
  - 1st in India (200 000 new patients per year)

Traditional radiotherapy for advanced cervical cancer

Combination of EBRT and Brachytherapy

- 45-50 Gy external beam radiotherapy to the pelvic/PAO region
  - Conventional or conformal EBRT
- About 25 – 30 Gy brachytherapy to the central part of the pelvis
  - Point A based treatment planning
- Optional
  - External boost in case of parametrical invasion or affected lymph nodes
- Overall treatment time about seven weeks

Results of traditional RT not satisfying


- Loco-regional control for locally advanced cervical cancer 53%
- 5-year disease-free and overall survival less than 45%
- Grade 3 - 5 toxicity about 17%

WHO alert in 1999

- Improvement by combining radiotherapy with chemotherapy
  - 5 trials published, about 12% benefit in 5-year DSS
  - 2001 Meta-analysis; Green et al. Lancet
  - 16% benefit 5-year DSS
  - increased grade 3 and 4 haematological and gastro-intestinal toxicity

Outcome related to periods

<table>
<thead>
<tr>
<th>UMCU data</th>
<th>RT (± HT) ≤ 1999</th>
<th>RT ± CT 1999-2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>51</td>
<td>54</td>
</tr>
<tr>
<td>Median FU in months</td>
<td>49</td>
<td>46</td>
</tr>
<tr>
<td>FIGO stages</td>
<td>IB1 – IVa</td>
<td>IB1 – IVa</td>
</tr>
<tr>
<td>Planning aim EBRT Gy</td>
<td>41</td>
<td>45</td>
</tr>
<tr>
<td>Planning aim BT (BIP/MRI) Gy</td>
<td>24</td>
<td>35</td>
</tr>
<tr>
<td>Total planning aim dose Gy</td>
<td>70</td>
<td>81</td>
</tr>
<tr>
<td>Local control % at 3 years</td>
<td>62</td>
<td>81</td>
</tr>
<tr>
<td>NED % at 5 years</td>
<td>52</td>
<td>53</td>
</tr>
<tr>
<td>Overall survival % at 3 years</td>
<td>47</td>
<td>54</td>
</tr>
</tbody>
</table>

Conclusions

Concomitant chemo might not be enough

Can we improve the radiotherapy technique?

Might MRI guidance help?

Aim

- increase loco-regional control
- increase survival rates
- decrease toxicity
Challenges

- Combination of macroscopic tumor (primary and lymph node metastases) and a large elective area (uterus, parametria, vagina, lymphatics)
- Internal motion of primary tumor and organs at risk
- Tumor regression during treatment
- Large difference between tolerance dose to organs at risk (small bowel) and required dose to GTV

MRI guided UMCU Developments from 2004 on

Imaging
- From X-ray to MRI guidance

Radiotherapy technique
- EBRT: From conventional irradiation to IMRT and IGRT
- Brachy: From point A to GEC ESTRO recommendations
- From 2D to 4D adaptive treatment approach

Impact of MRI on EBRT

Impact of MRI on EBRT

EBRT imaging modalities

Clinical investigation at time of diagnosis
- Exophytic tumor in the whole cervix
- Infiltration of the middle part of the left parametrium
- No infiltration into the vagina
- Cystoscopy negative
- No hydronephrosis
- Rectum not involved

EBRT imaging modalities for nodes

Imaging to define tumor spread

EBRT imaging modalities for cervical tumor

Cervical tumor as depicted on CT or MRI
- FIGO IIb, cT2b

Match PET-MRI
EBRT

Imaging modalities

Cervical tumor as depicted on CT or MRI
• FIGO IB2, cT4a uterine corpus, rectum and bladder wall

Advantage of MRI to define primary GTV

MRI versus clinical investigation and CT
Overall staging accuracy of MRI is superior to clinical examination or CT with respect to
• parametrial infiltration
• infiltration into the uterus
• infiltration into bladder and rectum
Boss et al. 2000, Ozsarlik et al. 2003, Bipat et al. 2003

GTV = intermediate or high signal on T2 weighted MR images

Diagnostic imaging for cervix

Staging of uterine cervical cancer with MRI:
Consensus guidelines of the European Society of Urogenital Radiology
Eur Radiol. 2011, 21, 1102

Morphologic T2 weighted images
a) Hyperintense lesion invading cervical stroma
b) Low signal intensity excluding parametrial invasion
c) Enlarged lymphnode in para aortic space

Functional imaging
DWI images
ADC map (B 800)

Curr Opin Oncol. 2011 Sep;23(5):519-25.
“Particularly, functional MRI techniques have improved accuracy of disease staging…….”
“Once standardized and validated, the techniques should enable individualized patient treatment and optimization of outcome.”

Treatment volume definition

Impact of imaging modality on primary tumor depiction

Contouring guidelines

Consensus contouring guidelines for 3D treatment planning available for CT and MRI approaches
(Taylor 2005, Small 2008, Lim 2011)

• Bare chance on more conformity for target delineation and delineation of organs at risk
• Some discrepancies still exist
• At at this moment not clinically proved

Delineation of the targets and OAR

Consensus guidelines
Lim et al. 2011
Consensus guidelines “Small” versus “Taylor”

Impact of MRI on EBRT treatment techniques

- Conventional
  - Based on bony anatomy
  - AP/PA fields
  - 3-4 treatment fields

- Image based
  - 3DC-RT or IMRT
  - 3-4 treatment fields
  - IMRT: 5 or more fields

MRI based treatment planning

- 3DC-RT
  - 4-field box

- IMRT
  - 7 beam IMRT

VMAT with SIB to pathological nodes

But!!

- Higher conformity gives higher chance on geographical miss

Impact on treatment margins

Patient related:
- Motion and deformation of tumor and OAR
- Tumor regression

Externally:
- Contouring uncertainties
- Position verification method
- Set-up uncertainties
**Inter-fraction motion of primary GTV**

- 5 consecutive MRI's during EBRT
- Impact of changes in bladder and bowel filling on position changes of uterus
- Not only one organ is responsible

**High impact of bladder and bowel**

**Low impact**

**GTV**

**CTV**

**PTV**

Van de Bunt et al 2008

**Inter-fraction motion of primary GTV**

- Extreme difference in bladder filling
- Extreme difference in position of the uterus
- 6 – 40 mm in different publications

**Pre-treatment MRI**

**MRI in first week of EBRT**

**CTV**

**PTV**

**Intra-and inter-fraction motion**

- 4 consecutive sagittal images taken within 30 minutes of MR imaging
- Impact of patient’s movement en pelvic rotation
- Impact of bowel filling

**weak1**

**week4**

Kerkhof et al 2009

**Intra-and inter fraction motion**

- Impact of changes in bladder and bowel filling, pelvic rotation
- Impact of volume changes of uterus

**Pre-treatment**

**week1**

**week2**

**week4**

Kerkhof 2008

**Inter-fraction motion of node GTV**

- Affected nodes change their position (< 8 mm)
- Position shifts less extensive than for primary GTV

**Position shifts of primary tumor and nodes**

- 48 nodes, 15 patients
- Position shifts in 6 directions

**Margin (ml)**

- med
- lat
- ant
- post
- sup
- inf

Maximal margins (computer)
Motion depicted on repetitive MRI

- Organ motion and deformation contribute essentially to the treatment margin concept!
- Order of magnitude between position shifts of primary tumor and affected nodes is different!

MRI to monitor primary tumor regression

- Primary tumors individually shrink during EBRT
- Impact on elective CTV and PTV is low

Average decrease in volume after 30 Gy EBRT

<table>
<thead>
<tr>
<th>Volume in cc</th>
<th>GTV</th>
<th>CTV</th>
<th>PTV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment</td>
<td>800</td>
<td>700</td>
<td>600</td>
</tr>
<tr>
<td>Intra-treatment</td>
<td>500</td>
<td>400</td>
<td>300</td>
</tr>
</tbody>
</table>

GTV 49.2%  CTV 13.4%  PTV 9.7%

MRI to monitor nodal tumor regression

Node > 10 mm on MRI, PET positive, boost given

At diagnosis
- Enlarged (15 mm)
- Irregular shape
- Inhomogeneous

4th week of EBRT
- Partial response in week 4
- EBRT total dose = 55 Gy (45 + 10)

Recommended CTV-PTV margins for elective EBRT

- For primary CTV 15 – 20 mm
- For nodal regions 10 mm
- Position verification on bony landmarks, off-line protocol
- Under investigation for soft tissue contrast, on-line protocols, replanning

Impact of treatment margins on coverage

Planning aim dose: 50 Gy

Comparison:
- Four Field Box
- Large margin IMRT 10-20 mm
- Small margin IMRT 5 mm

For GTV en CTV not that much difference between planning aim and delivered dose

Ongoing

Image based margin concept for highly conformal adaptive EBRT

- Currently subject of investigation (repetitive CT/MRI)
- Promising developments
  - Image-based adaptive “plan of the day” strategies
  - Several treatment plans based on repetitive CT with variable bladder filling (Rotterdam group)
- Margin choice depends on position verification method
  - Bone anatomy, soft tissue, internal markers
  - On-line, off-line
Ongoing research

Adaptive RT: variable bladder filling scans
- Separate movers/non-movers: large/smaller margins → direct clinical gain
- CBCT based introduction and monitoring
- Repeat MR

Possible gain of an MRI accelerator

Online MRI guidance
Reduction CTV-PTV margin to 4 mm
Clear reduction of in-field amount of OAR

Position verification

Integration of Cone-beam CT and accelerator

Integration of MRI and accelerator

MRI in postoperative situation

Endometrium en cervical cancer after hysterectomy
5 consecutive MRI’s during EBRT

Regions of interest for Brachytherapy
- macroscopic tumor after EBRT
- suspected microscopic tumor extension
- pre-treatment tumor extension
- most exposed volume of rectum, sigmoid and bladder

Impact of MRI on Brachytherapy
From ICRU rules to GEC ESTRO recommendations

According to Manchester System/ICRU 38
- X-ray guided (2D)
- Point A
- ICRU rectum point
- ICRU bladder point
- Point B
- 60 Gy volume
- Total

According to GEC ESTRO and ABS recommendations
- MRI/CT guided adaptive
- GTV (macroscopic tumor)
- HR-CTV (GTV + suspected microscopic tumor)
- IR-CTV (pre-treatment extension)
- 2cc rectum
- 2cc sigmoid
- 2cc bladder
- TRAK

Pötter et al., Radiotherapy and Oncology, 2006, 78, 67
ICRU 38, 1985

X-ray guided brachytherapy

Standard type Fletcher application for LDR, PDR or HDR treatments

Standard pear shaped isodose distributions

MRI guided brachytherapy

MRI guided delineation

MRI with applicator in situ
Regions of interest delineated

GTV
HR-CTV
IR-CTV
bladder
rectum
bowel

X-ray guided versus MRI guided intracavitary brachy planning

Aimed tumor dose EBRT+ BT > 84 Gy (64 Gy per PDR pulse)

OAR constraints D2cc
- < 90 to Bladder (cc < 1 cc)
- < 75 to rectum, sigmoid, bowel (cc < 1 cc)

<table>
<thead>
<tr>
<th>Case</th>
<th>A1</th>
<th>A2</th>
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<tbody>
<tr>
<td>75%</td>
<td>75%</td>
<td>75%</td>
</tr>
<tr>
<td>90%</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td>95%</td>
<td>95%</td>
<td>95%</td>
</tr>
</tbody>
</table>

Improved dose volume parameters!

Locations with inadequate coverage by intracavitary applications

Results of planning study with 20 applications

75% of the case
A1
20% of the case
A2
95% of the case

Adaptation of a the applicator

Applicator produced by Nucletron

Start clinical introduction July ’07

Two BT applications
- First one without needles
- Second with needles, if necessary
  - Pre-planning for 2nd application based on dose distribution and DVH analysis of first application:
    - Needles necessary?
    - Where? How deep?

Example

2 needles left side

Improved coverage by combining intracavitary and interstitial approach

Aimed tumor dose
EBRT + BT > 84 Gy
(60 cGy per PDR pulse)

OAR constraints D2cc
- < 90 to Bladder (35 cGy pp)
- < 75 to rectum, sigmoid, bowel (53 cGy pp)

Dosimetric gain for one application

Effect of IC/IS applicator on HR-CTV dose during learning curve

Effect of IC/IS applicator on HR-CTV dose during learning curve

Optimized IC

Optimized IC/IS
3 needles used

Effect of IC/IS applicator

Dosimetric gain for one application

Total dose EBRT + BT

<table>
<thead>
<tr>
<th></th>
<th>Average</th>
<th>SD</th>
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<tbody>
<tr>
<td>HR-CTV</td>
<td>88</td>
<td>7</td>
</tr>
<tr>
<td>Bladder</td>
<td>83</td>
<td>6</td>
</tr>
<tr>
<td>Rectum</td>
<td>67</td>
<td>6</td>
</tr>
<tr>
<td>Sigmoid</td>
<td>61</td>
<td>5</td>
</tr>
<tr>
<td>Bowel</td>
<td>64</td>
<td>9</td>
</tr>
</tbody>
</table>

From 3D to 4D
MRI guided optimization and additional interstitial component allow to cover larger HR-CTV volumes adequately, has dosimetric benefit

Work in progress

Repeated and interventional imaging easier to realize when MR machine is part of brachytherapy
- Application, imaging and irradiation in the same room
- Offer possibility to adapt when necessary
- Less time consuming
- Offer possibility to work with new tools

Difference PDR / HDR

Impact of MRI guidance on outcome

<table>
<thead>
<tr>
<th>UMCU</th>
<th>RT (s, HT) x 1999</th>
<th>RT p, CT 1999-2004</th>
<th>RT p, CT 2005-2006 (Retro-EMBRACE)</th>
<th>RT p, CT 2006-2008 (EMBRACE)</th>
<th>RT p, CT 2008-2015 (EMBRACE II)</th>
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<tbody>
<tr>
<td></td>
<td>Number of patients</td>
<td>50</td>
<td>34</td>
<td>46</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Median FU in months</td>
<td>49</td>
<td>46</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FGGO stages</td>
<td>7-1 / 7</td>
<td>8-1 / 8</td>
<td>8-1 / 8</td>
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<tr>
<td></td>
<td>Planning aim</td>
<td>&gt; 70</td>
<td>&gt; 80</td>
<td>&gt; 84</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Local control %</td>
<td>62</td>
<td>81</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PFS % (3 years)</td>
<td>52</td>
<td>53</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OS % (3 years)</td>
<td>47</td>
<td>54</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Late ≥ G3 morbidity %</td>
<td>80 (RT16G)</td>
<td>80 (CTCAE 3.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Ongoing and future UMCU effort

IGART for primary and post-op treatments
- Treatment margin reduction
- SIB techniques (vulva, vagina, pelvic and PAO nodes)
- MRI based daily position verification
- Deformable registration tools
- Adaptive re-planning strategies

Affected nodes/Nodal recurrence
- Detection of small nodes possible on anatomical MRI
- Impact of PET-CT, contrast enhanced or functional MRI
- More precise dose calculation from EBRT and BT
- Better understanding of dose response relation

Patterns of regional recurrence after standard chemo-radiation therapy

> 1800 cervical cancer patients, definitive radiotherapy
- Pelvic control about 82 %
- Local control about 86 %

UMCU MRI guided treatment 2006-2011

<table>
<thead>
<tr>
<th>Node status</th>
<th>All</th>
<th>Node positive</th>
<th>Node negative</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Overall survival</td>
<td>65</td>
<td>50</td>
<td>17</td>
<td>0.008</td>
</tr>
<tr>
<td>Cancer specific survival</td>
<td>76</td>
<td>60</td>
<td>94</td>
<td>0.088</td>
</tr>
<tr>
<td>Local control</td>
<td>96</td>
<td>93</td>
<td>99</td>
<td>0.790</td>
</tr>
<tr>
<td>Nodal control</td>
<td>81</td>
<td>78</td>
<td>98</td>
<td>0.370</td>
</tr>
<tr>
<td>Distant metastases free survival</td>
<td>77</td>
<td>68</td>
<td>95</td>
<td>0.188</td>
</tr>
<tr>
<td>Progression free survival</td>
<td>58</td>
<td>54</td>
<td>95</td>
<td>0.058</td>
</tr>
</tbody>
</table>

Node example on MRI

Node 8 mm, PET negative, no boost

Inside the field = dosimetric problem
Outside and marginal = geographical miss

Summary

MRI guided treatment for cervical cancer
- Supports better defining the disease at time of diagnosis
- Supports monitoring motion and deformation during treatment
- Supports adaptive treatment approaches
- Supports development of advanced EBRT and BT techniques
- Results in improved local control and survival
- Will hopefully help to improve nodal control
- Will hopefully help to reduce morbidity and improve QoL (also important for intensifying chemo)

UMCU Team

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