Rectal cancer: optimizing radiotherapy

Karin Haustermans

ESMO Vienna 2012
Patient 1

- 52 year old man, good general condition
- No relevant medical history
- Presents with anal blood loss, no other symptoms
Patient 1

- PPA: palpable lesion, ulcerated, distance to anal verge 1-2 cm (IAS/EAS invasion?)
- Colonoscopy: semicircular rectal tumor of 6 cm length, centrally ulcerated, not obstructive
- Biopsy: well to moderately differentiated adenocarcinoma
- Normal CEA (1.6 µg/L)
- No evidence of distant metastases
Patient 1

- Endoscopic ultrasound: uT3N1, distance to IAS 10 mm, EAS 18 mm and external anal verge 49 mm
Patient 1

- MRI pretreatment
  - Tumor in posterolateral wall of distal rectum, transmural growth, possibly invading the internal anal sphincter and possible focal microinvasion of the left levator muscle (bad T3, rather than T4).
  - Several suspect mesorectal lymph nodes (N2)
Treatment options?

1. Surgery

2. Preoperative radiotherapy short schedule

3. Preoperative chemoradiotherapy

4. Other
Treatment

• Preoperative chemoradiation (45 Gy in 1.8 Gy fractions combined with capecitabine)

• Patient was willing to participate in
  – PETACC-6 study
  – Functional imaging study
Patient 1

- MRI presurgery (5.5 weeks after CRT)
  - Very limited down sizing of the tumor in the posterolateral wall of the distal rectum, transserosal growth is less obvious as well as the impression of focal microinvasion of the left levator muscle
  - Central necrotic mesorectal lymph node anterolaterally on the left side
  - Other lymph nodes are comparable in size
  - cT3N2
Treatment

• Restorative TME after 8 weeks
  – ypT2N1a
  – Tumor of 2.5 cm, invading muscularis propria
  – CRM at 8 mm
  – 1/25 affected LN (macroM+)
Functional imaging study

PET-CT  MRI  DW-MRI

Before CRT

During CRT

Pre-surgery
Functional imaging study

Before CRT

During CRT

Pre-surgery
# PET analyses

<table>
<thead>
<tr>
<th></th>
<th>Before RCT</th>
<th>During RCT</th>
<th>Before surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SUVmax</strong></td>
<td>SUVmax1</td>
<td>SUVmax2</td>
<td>SUVmax 3</td>
</tr>
<tr>
<td><strong>Threshold</strong></td>
<td>Treshold 1</td>
<td>Treshold 2</td>
<td>Treshold 3</td>
</tr>
<tr>
<td><strong>SUV mean</strong></td>
<td>SUV mean1</td>
<td>SUV mean 2</td>
<td>SUVmean3</td>
</tr>
<tr>
<td><strong>SUVmin</strong></td>
<td>SUVmin 1</td>
<td>SUVmin 2</td>
<td>SUVmin3</td>
</tr>
<tr>
<td><strong>SUV median</strong></td>
<td>SUVmedian 1</td>
<td>SUVmedian 2</td>
<td>SUVmedian 3</td>
</tr>
<tr>
<td><strong>SUV peak</strong></td>
<td>SUVpeak1</td>
<td>SUVpeak2</td>
<td>SUVpeak3</td>
</tr>
<tr>
<td><strong>Diameter</strong></td>
<td>Diameter 1</td>
<td>Diameter 2</td>
<td>Diameter 3</td>
</tr>
<tr>
<td><strong>Volume</strong></td>
<td>Volume 1</td>
<td>Volume 2</td>
<td>Volume 3</td>
</tr>
<tr>
<td><strong>TLG</strong></td>
<td>TLG1</td>
<td>TLG2</td>
<td>TLG 3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
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<th>During RCT</th>
<th>Before surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>patient 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUVmax1</td>
<td>15,92</td>
<td>9,37</td>
<td>10,28</td>
</tr>
<tr>
<td>Treshold 1</td>
<td>40</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>SUV mean1</td>
<td>9,17</td>
<td>5,38</td>
<td>6,55</td>
</tr>
<tr>
<td>SUVmin 1</td>
<td>5,36</td>
<td>3,74</td>
<td>5,8</td>
</tr>
<tr>
<td>SUVmedian 1</td>
<td>8,97</td>
<td>5,2</td>
<td>6,32</td>
</tr>
<tr>
<td>SUVpeak1</td>
<td>10,81</td>
<td>6,46</td>
<td>7,31</td>
</tr>
<tr>
<td>Diameter 1</td>
<td>38</td>
<td>45</td>
<td>31</td>
</tr>
<tr>
<td>Volume 1</td>
<td>11,65</td>
<td>16,38</td>
<td>4,98</td>
</tr>
<tr>
<td>TLG1</td>
<td>106,8305</td>
<td>88,1244</td>
<td>32,619</td>
</tr>
</tbody>
</table>
Patient 2

- 60 year old female, good general condition
- No relevant medical history
- Presentation with altered bowel habits and tenesmus, no other symptoms
Patient 2

- PPA: no palpable lesion
- Colonoscopy: circular tumor between 9 and 18 cm, easily bleeding, not obstructive
Patient 2

- Biopsy: adenocarcinoma
- Normal CEA (0.5 µg/L)
- No evidence of distant metastases
- Endoscopic ultrasound: tumor between 9 and 14 cm with muscular invasion (uT3), no invasion of the internal anal sphincter. Visualisation of 2 small lymph nodes
Patient 2

- MRI pretreatment
  - Tumor in proximal rectum over a 7 cm distance, transmural growth. Distance between tumor and mesorectal fascia 1-2 mm (CRM <2mm)
  - Several (>3) suspect lymph nodes in mesorectal fat (N2)
Treatment options?

1. Surgery
2. Preoperative radiotherapy short schedule
3. Preoperative chemoradiotherapy
4. Other
Treatment

- Preoperatieve chemoradiation treatment (45 Gy in 1.8 Gy fractions combined with capecitabine)
- Patient was willing to participate in
  - PETACC-6 study
  - Functional imaging study
Patient 2

- MRI presurgery (4.5 weeks after CRT)
  - Obvious volume reduction of the tumor in proximal rectum
  - Clear regression of the signal in the tumor on DW-MRI
  - Clear volume reduction of suspect lymph nodes in mesorectal fat
  - cT3N0, distance to CRM 2.5 mm
Treatment

• Restorative TME after 6 weeks
  – ypT0N0
Functional imaging study

PET-CT  MRI  DW-MRI

Before CRT

During CRT

Pre-surgery
Functional imaging study

Before CRT

During CRT

Pre-surgery
## PET analyses

### Before RCT

<table>
<thead>
<tr>
<th>Patient 2</th>
<th>SUVmax1</th>
<th>Threshold 1</th>
<th>SUV mean1</th>
<th>SUVmin 1</th>
<th>SUV median 1</th>
<th>SUV peak1</th>
<th>Diameter 1</th>
<th>Volume 1</th>
<th>TLG1</th>
</tr>
</thead>
<tbody>
<tr>
<td>patient 2</td>
<td>17.87</td>
<td>35</td>
<td>9.11</td>
<td>5.55</td>
<td>8.7</td>
<td>11.01</td>
<td>45</td>
<td>17.77</td>
<td>161.8847</td>
</tr>
</tbody>
</table>

### During RCT

<table>
<thead>
<tr>
<th>Patient 2</th>
<th>SUVmax2</th>
<th>Threshold 2</th>
<th>SUV mean2</th>
<th>SUVmin 2</th>
<th>SUV median 2</th>
<th>SUV peak2</th>
<th>Diameter 2</th>
<th>Volume 2</th>
<th>TLG2</th>
</tr>
</thead>
</table>

### Before surgery

<table>
<thead>
<tr>
<th>Patient 2</th>
<th>SUVmax 3</th>
<th>Threshold 3</th>
<th>SUV mean3</th>
<th>SUVmin3</th>
<th>SUV median 3</th>
<th>SUV peak3</th>
<th>Diameter 3</th>
<th>Volume 3</th>
<th>TLG 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>patient 2</td>
<td>5.33</td>
<td>70</td>
<td>4.31</td>
<td>3.73</td>
<td>4.22</td>
<td>4.46</td>
<td>25</td>
<td>2.97</td>
<td>12.8007</td>
</tr>
</tbody>
</table>
Progress has been made

• In treatment **planning** and radiation **delivery**

- Conventional radiotherapy
- 3D-Conformal radiotherapy
- Intensity modulated radiotherapy

• Thanks to advances in **anatomical** and **structural imaging**
Imaging in the RTO process

- Work-up (Chemo-) Radiotherapy
  - Target definition
  - Target delineation

- Follow-up
  - Response prediction
  - Response assessment

- Adaptive radiotherapy
  - Response prediction

- Detection of recurrent disease
Response to pre-op CRT

**Good responders**

- Can we use functional imaging to distinguish responders and non-responders?
- ~30% pCR after CRT
- Organ preservation?

**Poor responders**

- Standard CRT insufficient
- Treatment-intensification
- FDG-PET
- DW-MRI
Maas et al, JCO 2011
FDG-PET: response prediction

\[ \Delta \text{SUV}_{\text{max}} \] during

\[ \Delta \text{SUV}_{\text{max}} \] post

\[ P = 0.0036 \]

AUC = 0.92 at threshold of 40%

Lambrecht et al. Acta Oncol 2010
DW-MRI: response prediction

(a) Volume Reduction (%)

(b) ΔADC (%)

Response to pre-op CRT

Good responders

~50% pCR after CRT

Organ preservation?

Poor responders

Standard CRT insufficient

Treatment-intensification

Is there a role for radiation dose escalation in rectal cancer?
RAPIDO trial

- Rectal Cancer And Pre-operative Induction Therapy Followed by Dedicated Operation trial
- Randomized multicentre Phase III study

Arm A = control
- Long course chemo-RT (5 weeks)
- Surgery
- (adjuvant chemo)

Pts with primary high risk rectal cancer
N = 885

Arm B = exp
- 5 x 5Gy
- 6 cycles of capecitabine + oxaliplatin
- Surgery
Dose escalation

- Meta-analysis

Radiotherapy dose of >45Gy leads to significantly higher pCR rates

<table>
<thead>
<tr>
<th>Dose Range (Gy)</th>
<th>Weighting (number of patients)</th>
<th>Adjusted pCR means with 95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;45</td>
<td>458</td>
<td>0.09 (0.05, 0.13)</td>
</tr>
<tr>
<td>45–&lt;50</td>
<td>1914</td>
<td>0.14 (0.11, 0.19)</td>
</tr>
<tr>
<td>50–&lt;55</td>
<td>2236</td>
<td>0.16 (0.12, 0.20)</td>
</tr>
<tr>
<td>55+</td>
<td>124</td>
<td>0.20 (0.10, 0.31)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Estimated biological equivalent dose</th>
<th>Weighting (number of patients)</th>
<th>Adjusted pCR means with 95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>481</td>
<td>0.09 (0.05, 0.14)</td>
</tr>
<tr>
<td>50–&lt;55</td>
<td>1631</td>
<td>0.14 (0.10, 0.19)</td>
</tr>
<tr>
<td>55–&lt;60</td>
<td>1726</td>
<td>0.15 (0.11, 0.19)</td>
</tr>
<tr>
<td>60+</td>
<td>894</td>
<td>0.17 (0.13, 0.22)</td>
</tr>
</tbody>
</table>
Higher radiation dose increases the rate of major response by 50% in T3 tumors.

Endorectal boost is feasible, with no significant increase in toxicity or surgical complications.
Dose-response relationship

Appelt et al. Radiother Oncol 2012 (S185; ESTRO 31)
Challenges for dose escalation

1. Accurate GTV delineation
   – Histopathological validation
   – Multi-modality imaging: registration

2. Motion
### Validation

FDG-PET TVs delineated with WCA matched closer with the pathological TV than MR-based TV

<table>
<thead>
<tr>
<th></th>
<th>MR</th>
<th>FDG-PET</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAT1</td>
<td>7,76</td>
<td>3,54</td>
<td>1,37</td>
</tr>
<tr>
<td>PAT2</td>
<td>5,77</td>
<td>0,53</td>
<td>0,05</td>
</tr>
<tr>
<td>PAT3</td>
<td>20,36</td>
<td>12,95</td>
<td>11,19</td>
</tr>
<tr>
<td>PAT4</td>
<td>8,79</td>
<td>1,02</td>
<td>0,77</td>
</tr>
<tr>
<td>PAT5</td>
<td>7,15</td>
<td>3,61</td>
<td>pCR</td>
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<tr>
<td>PAT6</td>
<td>3,59</td>
<td>0</td>
<td>0,55</td>
</tr>
<tr>
<td>PAT7</td>
<td>6,99</td>
<td>2,92</td>
<td>0,43</td>
</tr>
<tr>
<td>PAT8</td>
<td>3,2</td>
<td>0</td>
<td>pCR</td>
</tr>
<tr>
<td>PAT9</td>
<td>18,29</td>
<td>3,18</td>
<td>2,25</td>
</tr>
<tr>
<td>PAT10</td>
<td>3,45</td>
<td>2,05</td>
<td>pCR</td>
</tr>
<tr>
<td>PAT11</td>
<td>2</td>
<td>7,09</td>
<td>0,32</td>
</tr>
<tr>
<td>PAT12</td>
<td>4,08</td>
<td>0</td>
<td>pCR</td>
</tr>
<tr>
<td>PAT13</td>
<td>0,48</td>
<td>0,35</td>
<td>pCR</td>
</tr>
<tr>
<td>PAT14</td>
<td>1,32</td>
<td>0</td>
<td>pCR</td>
</tr>
<tr>
<td>PAT15</td>
<td>8</td>
<td>5,4</td>
<td>0,13</td>
</tr>
</tbody>
</table>
### Mismatches

<table>
<thead>
<tr>
<th></th>
<th>FDG volume</th>
<th>Mismatch FDG</th>
<th>MR volume</th>
<th>Mismatch MR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td>Before RT</td>
<td>16</td>
<td>28</td>
<td>69%</td>
</tr>
<tr>
<td></td>
<td>During RT</td>
<td>6</td>
<td>14</td>
<td>79%</td>
</tr>
<tr>
<td><strong>Stdev</strong></td>
<td>Before RT</td>
<td>13</td>
<td>17</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>During RT</td>
<td>6</td>
<td>10</td>
<td>13%</td>
</tr>
</tbody>
</table>

- **MGK** volume mismatch:
  - Before RT: 16 ± 47%
  - During RT: 6 ± 53%
  - Before CRT: 13 ± 30%
  - During CRT: 6 ± 26%

- **Max of shortest distances (mm)**:
  - Before CRT: 22 ± 9
  - During CRT: 22 ± 7
  - Before CRT: 8 ± 5
  - During CRT: 8 ± 3

- **Mean of shortest distances (mm)**:
  - Before CRT: 12 ± 6
  - During CRT: 12 ± 8
  - Before CRT: 5 ± 4
  - During CRT: 5 ± 4

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Tumor motion

- Attempt to better visualize the tumor = placement of fiducial markers (Olympus HK-610-090)

2 clips cranial from tumor

2 clips caudal from tumor
Inter-fraction tumor motion
Adaptive Radiotherapy

• The “Nearby” Future
  – Optimize integration of anatomical and functional imaging in the treatment process

• The “Long term” Future
  – Integration of biology in the radiation treatment process
  – Personalised treatment
Biomarker studies

Work-up | (Chemo-)Radiotherapy | Surgery | Follow-up

Prognostic / predictive modelling

Body fluids

Tissue

Imaging

Early integration

Intermediate integration

Late integration

Patient features

Dataset I

Features

Outcome

LS-SVM