Assessing Complete Response after CRT

Memorial Sloan Kettering Cancer Center
New York

Complete Tumor Response after Neoadjuvant Therapy

Long-term Outcomes in Rectal Cancer Patients with or without a pCR after CRT: a Pooled Analysis

Do rectal cancer patients with a complete response to CRT benefit from TME?

Maas et al, The Lancet Oncology 2010; 11(9): 835-844
Clinical Response ≠ Pathologic Response

Assessment of Clinical Response

- Clinical Exam
  - Digital rectal exam
  - Endoscopy
- Imaging
  - ERUS
  - PET
  - MRI
- Biopsy?

Clinical Response does not Predict Pathological Response

  - Retrospective review
  - 488 stage T2 rectal cancer
  - Stage by ERUS/DRE
  - CRT followed by TME 4-6 weeks later
  - Pathologic complete response in 50 patients (10%)
  - Clinical complete response in 93 patients (19%)
  - Only 23 of 93 (25%) clinical complete responders had a pathologic complete response
  - ¾ of patients with clinical complete response have residual cancer cells!!

Clinical Response does not Predict Pathological Response Prospective Data

- Prospective study, 2000-03
- Adenocarcinoma, stage T3, T4, N+
- CRT (Bolus or CI 5-FU)
- Interval between CRT and Surgery 48 days
- Clinical response assessed at the time of surgery
  - Scale from 1 (progression) to 5 (near or complete response)
- Pathologic staging according to standard

Guillem et al, JCO 2005
Clinical Response does not Predict Pathological Response
Prospective Data

- 14 (15%) of patients achieved a pCR
- Digital rectal exam identified only 3 of 14 (21%) patients with pCR
- Correlation between clinical and pathologic complete response:
  - Sensitivity 24%
  - Specificity 56%
  - PPV 19%
  - NPV 61%
- No difference between observers

Guillem et al, JCO 2005

Definition of Clinical Response

- Features of cCR
  - Whitening of the mucosa
  - Association of any telangiectasia
  - Loss of pliability on insufflation
  - No palpable mass or induration
- Features of residual disease
  - Ulceration
  - Palpable nodule
  - Stricture

Habr-Gama et al, DCR 2010

How Reliable is the Clinical Definition of cCR?

- 220 rectal cancer patients treated with CRT and TME
- 31 patients had a ypT0 tumors
- 19 of them didn’t meet criteria for complete clinical response
- Almost 2/3 of patients with a pCR will be excluded from NOM

Smith et al, BJS 2012
Can a biopsy help identify responders?

“Discontinuous response” to CRT

- Evidence of scattered nests of tumor cells deep in the bowel wall

Cancer Cells in the Different Layers of the Bowel Wall by ypT Stage

Positive Nodes By pT in Rectal Wall after Chemoradiation in Clinical Stage II or III Rectal Cancer

<table>
<thead>
<tr>
<th>Series</th>
<th>pT0</th>
<th>pT1</th>
<th>pT2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read</td>
<td>2%</td>
<td>4%</td>
<td>47%</td>
</tr>
<tr>
<td>Pucciarelli</td>
<td>2%</td>
<td>15%</td>
<td>17%</td>
</tr>
<tr>
<td>Tulchinsky</td>
<td>6%</td>
<td>0</td>
<td>19%</td>
</tr>
<tr>
<td>Bujko</td>
<td>5%</td>
<td>8%</td>
<td>26%</td>
</tr>
<tr>
<td>Coco</td>
<td>2%</td>
<td>6%</td>
<td>18%</td>
</tr>
<tr>
<td>Bedrosian</td>
<td>9%</td>
<td>18%</td>
<td>7%</td>
</tr>
<tr>
<td>Guillem</td>
<td>3%</td>
<td>7%</td>
<td>20%</td>
</tr>
<tr>
<td>Smith</td>
<td>3%</td>
<td>0</td>
<td>30%</td>
</tr>
</tbody>
</table>
Nodal Status by ypT Stage

TIMING Results

<table>
<thead>
<tr>
<th></th>
<th>ypT0</th>
<th>ypTis</th>
<th>ypT1</th>
<th>ypT2</th>
<th>ypT3</th>
<th>ypT4</th>
</tr>
</thead>
<tbody>
<tr>
<td>SG1 (7 w)</td>
<td>ypN0</td>
<td>11</td>
<td>2</td>
<td>3</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>ypN1-2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>SG2 (11 w)</td>
<td>ypN0</td>
<td>20</td>
<td>1</td>
<td>3</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>ypN1-2</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>SG3 (16 w)</td>
<td>ypN0</td>
<td>20</td>
<td>1</td>
<td>5</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>ypN1-2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>SG4 (20 w)</td>
<td>ypN0</td>
<td>25</td>
<td>1</td>
<td>3</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>ypN1-2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>11</td>
</tr>
</tbody>
</table>

Tumor Biopsy after CRT

- A full-thickness biopsy may compromise TME
- Endoscopic biopsies only informative if positive
- Risk of nodes positive in ypT0 may be lower in patients treated with “total” neoadjuvant therapy

Imaging in Assessing Tumor Response after CRT

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Sensitivity</th>
</tr>
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<tbody>
<tr>
<td>Endorectal Ultrasound</td>
<td>48-72%</td>
</tr>
<tr>
<td>CT</td>
<td>&lt; 50%</td>
</tr>
<tr>
<td>PET Scan</td>
<td>60%</td>
</tr>
<tr>
<td>MRI</td>
<td>&lt; 60%</td>
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</tbody>
</table>

FDG-PET and CT

MRI parameters used to assess response to neoadjuvant therapy

- Morphologic changes based on standard sequences
- mrTRG (tumor regression grade) based on T2w-images
- Volume measurements
- Diffusion weighted (DW) MRI

Re-staging after CRT using MRI: A meta-Analysis

- Re-staging is challenging
- Difficult to differentiate fibrosis from residual tumor
- Poor mean sensitivity for tumor staging (40%), but sensitivity was higher (57%) when comparing ypT0 vs. yp T1-4, sensitivity was 19%, but the specificity was 95%
- MRI is not reliable for evaluation of nodal status after CRT
- Results seems to be better with DW imaging

MRI-detected tumor regression grade (mrTRG)

- mrTRG based on same principles as histological TRG
- Degree of tumor replaced by fibrosis
- mrTRG correlates with clinical outcomes

Comparison of ROC curves displaying the diagnostic performance for pre- and post-CRT volumes and ∆volume (Delta) on T2- and DW MR images and ADC in the assessment of a CR.

(Numbers = AUC values for each sequence, numbers in parentheses = 95% confidence interval)

MRI Volume Measurements in Predicting Response
Tumor volume measurements on T2-w MRI and DFG-PET for assessment of response to neoadjuvant chemotherapy

MRI volume change most accurate predictor of tumor response (AUC:0.853)
The addition of FDG-PET do not improve performance

Aiba et al, Ann Surg Oncol, published online Feb 2014

Diffusion-Weighted Magnetic Resonance Imaging
Prediction and Early Assessment of Response to CRT


DW-MRI: false-positive for pCR


DW-MRI: False-Negative for PCR

Strategies to increase the probability of identification of non-responders

- Increase the response rate
- Delay the time to assess response

Pathological Tumor Characteristics in the Z6041 Trial

<table>
<thead>
<tr>
<th>Tumor T stage</th>
<th>Overall n = 77</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>34 (44%)</td>
</tr>
<tr>
<td>Tis</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>T1</td>
<td>10 (13%)</td>
</tr>
<tr>
<td>T2</td>
<td>23 (30%)</td>
</tr>
<tr>
<td>T3</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Tx</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

| Pathologic tumor size, cm | 0.9 ± 1.1 |

| Resection with negative margins | 76 (99%) |

<table>
<thead>
<tr>
<th>Clinical Diagnosis of PCR in the Z6041 Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR</td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>cCR</td>
</tr>
<tr>
<td>Non</td>
</tr>
</tbody>
</table>

Sensitivity: 86%
Specificity: 70%
Positive predictive value: 69%
Negative predictive value: 86%
Time to response

Princess Margaret Hosp series of radiotherapy alone for medically unfit: 10 yr survival of 17% for pts with mobile rectal cancers.¹

For patients who achieved a cCR, 60% did so by 4 months after the start of radiation and nearly all by 8 months.²


52 y/o female very distal rectal tumor

Baseline 8 cycles Folfox CRT

Folfox x 4 10/16/2013
Folfox x 8 12/18/2013
2/19/2014

61 y/o, healthy otherwise, cT3N1

Baseline 4 cycles of mFOLFOX6 8 cycles of mFOLFOX6

August 2013 October 2013 December 2013
Summary

- Assessment of tumor response to neoadjuvant therapy is challenging
- Clinical exam – endoscopy and digital rectal exam – probably most accurate tools
- MRI imaging promising
- Increasing response rate and delaying time of assessment may increase accuracy