Image guided response assessment to neoadjuvant chemoradiation in esophageal cancer patients

Where are we today?

Gert Meijer

480,000 new diagnoses annually
400,000 deaths annually
8th most common cancer type worldwide

traditionally surgery cornerstone of curative treatment, but…


n=1851
CROSS trial

368 patients

23 × 1.8 Gy
5 × (carboplatin + paclitaxel)

surgery


R0 resections: 92%
R0 resections: 69%


Pathologic outcome

Can we identify response during or after nCRT?

Can we identify response during or after nCRT?

Pathologic outcome


Aim of response prediction is two-fold

1. Predict pathologic complete response
   - Why: omission of surgery
   - When: before surgery
   - How: test(s) with high NPV

2. Predict pathologic poor response
   - Why: modification or discontinuation of nCRT
   - When: (before or) early during nCRT
   - How: test(s) with high PPV
Can we accurately predict pathologic response using:

1. Endoscopic biopsy or EUS?
2. FDG-PET?
3. DW-MRI / DCE-MRI?
4. A combination of modalities?

Results – Endoscopic biopsy
Results – EUS ~ ypT+ versus ypT0

Implications of findings in CROSS-setting
Cohort of 1000 patients

<table>
<thead>
<tr>
<th>Test</th>
<th>Endoscopic biopsy</th>
<th>EUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>True positive</td>
<td>210 per 1000</td>
</tr>
<tr>
<td></td>
<td>Justified surgery</td>
<td></td>
</tr>
<tr>
<td></td>
<td>False positive</td>
<td>35 per 1000</td>
</tr>
<tr>
<td></td>
<td>Unnecessary surgery</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>True negative</td>
<td>355 per 1000</td>
</tr>
<tr>
<td></td>
<td>Justified omission of surgery</td>
<td></td>
</tr>
<tr>
<td></td>
<td>False negative</td>
<td>400 per 1000</td>
</tr>
<tr>
<td></td>
<td>Unjustified omission of surgery</td>
<td></td>
</tr>
</tbody>
</table>

Can we accurately predict pathologic response using:

1. Endoscopic biopsy or EUS? **NO**
2. FDG-PET?
3. DW-MRI / DCE-MRI?
4. A combination of modalities?
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What can FDG-PET really add to prediction of pathCR?

Retrospective diagnostic (prediction) study, MD Anderson

n=217
Results – Clinical characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PathCR (n=59)</th>
<th>No pathCR (n=158)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>54 (91.5)</td>
<td>148 (93.7)</td>
<td>0.585</td>
</tr>
<tr>
<td>Age (y)</td>
<td>58.8 ± 12.3</td>
<td>60.1 ± 9.9</td>
<td>0.445</td>
</tr>
<tr>
<td>Tumor location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle third of esophagus</td>
<td>2 (3.4)</td>
<td>13 (8.3)</td>
<td>0.324</td>
</tr>
<tr>
<td>Distal third of esophagus</td>
<td>9 (15.3)</td>
<td>138 (87.1)</td>
<td></td>
</tr>
<tr>
<td>Gastro-esophageal junction</td>
<td>5 (8.5)</td>
<td>14 (9.6)</td>
<td></td>
</tr>
<tr>
<td>EUS-based tumor length (cm)</td>
<td>5.0 ± 2.4</td>
<td>5.9 ± 2.7</td>
<td>0.034*</td>
</tr>
<tr>
<td>Histologic differentiation grade</td>
<td></td>
<td></td>
<td>0.034*</td>
</tr>
<tr>
<td>Moderate</td>
<td>9 (57.6)</td>
<td>68 (43.0)</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>15 (42.4)</td>
<td>86 (57.0)</td>
<td></td>
</tr>
<tr>
<td>Signet ring cell adenocarcinoma</td>
<td>5 (8.5)</td>
<td>20 (13.0)</td>
<td>0.061</td>
</tr>
<tr>
<td>Clinical T-stage</td>
<td></td>
<td></td>
<td>0.001*</td>
</tr>
<tr>
<td>cT2</td>
<td>14 (23.7)</td>
<td>15 (9.5)</td>
<td></td>
</tr>
<tr>
<td>cT3</td>
<td>45 (76.3)</td>
<td>143 (90.5)</td>
<td></td>
</tr>
<tr>
<td>Clinical N-stage</td>
<td></td>
<td></td>
<td>0.458</td>
</tr>
<tr>
<td>cN0</td>
<td>18 (30.5)</td>
<td>58 (36.7)</td>
<td></td>
</tr>
<tr>
<td>cN+</td>
<td>36 (60.1)</td>
<td>86 (54.2)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>5 (8.5)</td>
<td>13 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Induction chemotherapy</td>
<td></td>
<td></td>
<td>0.031*</td>
</tr>
<tr>
<td>Post-chemoradiation endoscopic biopsy</td>
<td>56 (93.2)</td>
<td>126 (79.7)</td>
<td>0.023*</td>
</tr>
<tr>
<td>No residual cancer</td>
<td>4 (6.8)</td>
<td>32 (20.3)</td>
<td></td>
</tr>
<tr>
<td>Days from completion CRT to surgery</td>
<td>61.5 ± 20.4</td>
<td>58.3 ± 19.3</td>
<td>0.285</td>
</tr>
</tbody>
</table>

Model 1: Clinical predictors only

AUC: 0.67

Predictors:
- EUS-based tumor length
- Clinical T-stage
- Induction chemotherapy
- Post-chemoradiation endoscopic biopsy

Model 2: Clinical predictors + subjective PET

AUC: 0.73

Predictors:
- EUS-based tumor length
- Clinical T-stage
- Induction chemotherapy
- Post-chemoradiation endoscopic biopsy
- Subjective assessment nuclear medicine specialist
Model 3: Model 2 + quantitative PET

- AUC: 0.67
- AUC: 0.73
- AUC: 0.74

Predictors:
- EUS-based tumor length
- Clinical T-stage
- Induction chemotherapy
- Post-nCRT endoscopic biopsy
- Subjective assessment nuclear medicine specialist
- Total lesion glycolysis

Model 4: Model 3 + PET texture/geometry features

- AUC: 0.67
- AUC: 0.73
- AUC: 0.74
- AUC: 0.77

Predictors:
- EUS-based tumor length
- Clinical T-stage
- Induction chemotherapy
- Post-nCRT endoscopic biopsy
- Subjective assessment nuclear medicine specialist
- Total lesion glycolysis
- PET texture/geometry features

Conclusions FDG-PET

- FDG-PET provides statistical benefit in terms of discrimination.

- However, clinical relevance of this benefit is limited.
Overview

Can we accurately predict pathologic response using:

1. Endoscopic biopsy or EUS?  NO
2. FDG-PET?  NO
3. DW-MRI / DCE-MRI?
4. A combination of modalities?

MRI in esophageal cancer
challenging because of:

- motion
- magnetic field inhomogenities
Optimization study

no triggering free breathing

cardiac triggering breath hold

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DW-MRI: diffusion weighted MRI

- Microscopic mobility of water
- Brownian motion:
  - viscosity
  - cellular environment

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DW-MRI: diffusion weighted MRI

- Microscopic mobility of water
- Brownian motion:
  - viscosity
  - cellular environment
Pulse Sequence: Spin-Echo

Excitation
RF
Gx
Gy
Gz

Image Acquisition

180°

90°

G

Pulse Sequence: Spin-Echo Diffusion Weighting

Excitation
RF
Gx
Gy
Gz

Image Acquisition

180°

90°

G

Pulse Sequence: Spin-Echo Diffusion Weighting

Excitation
RF
Gx
Gy
Gz

Image Acquisition

180°

90°

G

G
diffusion gradient

Ex vivo 3T MRI

b0

b200

b800

Ex vivo 3T MRI

tumor

Courtesy David Norris
Quantitative ADC Measurement of Esophageal Cancer Before and After Chemoradiation

Methods – DWI response assessment study

<table>
<thead>
<tr>
<th>nCRT</th>
<th>2-3 weeks</th>
<th>2-3 weeks</th>
<th>3-9 weeks</th>
<th>0-4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>T2w</td>
<td>DWI</td>
<td>MRI</td>
<td>T2w</td>
</tr>
</tbody>
</table>

N=20

van Rossum, et al. Radiother Oncol. 2015
Before

During

After

Results – ΔADC measurements vs. response

- AUC: 0.90
- NPV: 100%
**Dynamic Contrast Enhanced MRI**

- Area under the curve (AUC)
- Start after inflow of contrast in artery
- Integral of 60 seconds on concentration time-curve

**DCE-MRI for predicting response**

- $AUC_{per-pre}$
- Threshold: 15.9%
- $AUC_{ROC}$: 0.78
- Specificity: 77%
- Sensitivity
- PPV
- NPV

**Overview**

Can we accurately predict pathologic response using:

1. Endoscopic biopsy or EUS? **NO**
2. FDG-PET? **NO**
3. DW-MRI / DCE-MRI? **MAYBE**
4. A combination of modalities?
Overview

Can we accurately predict pathologic response using:

1. Endoscopic biopsy or EUS? **NO**
2. FDG-PET? **NO**
3. DW-MRI / DCE-MRI? **MAYBE**
4. A combination of modalities? **HOPEFULLY**

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Hot off the press

- Multi center response assessment trial at MDACC, AvL and UMCU:
  - n=90 patients, so far n≈50

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Ongoing research collaboration
Personalized adaptive treatment approach?

- **Good responders**: Assess response after 10 fractions.
  - Active surveillance approach
  - Surgery

- **Poor responders**: CRT for esophageal cancer
  - PET

**ADC vs. AUC per voxel**

- TRG 1 (pCR)
- TRG 2 (0-10% tumor)
- TRG 3 (10-50% tumor)
- TRG 4 (>50% tumor)