Advances in diagnosis and imaging technology: MRI

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Advances in Imaging Technology
Rectal Cancer

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The promised future of imaging....

- Perfusion and tumour permeability
- Diffusion and tumour cellularity
- PET-CT and tumour metabolism
- Textural analysis
- Hypoxia imaging

- Tumour microenvironment
- Biology of tumour
- Angiogenesis in tumours
- Tumour cellularity and proliferation
- Likely response to treatment?
- Biomarker for treatments?
Quantitative Biomarkers in Imaging

- Predicting prognosis – stage assessment
- Predicting response
- Assessing response
- Independent prognostic / predictive imaging biomarkers to determine treatment
Quantitative DCE

Quantitative estimates
- \( K_{\text{trans}} \) (efflux constant)
- \( V_e \) (interstitial space)
- \( T1AUC \)

\[
C(t) = D.K_{\text{trans}} \sum_{i=1}^{2} \frac{a_i}{m_i} \left( e^{(K_{\text{trans}} / EES)(t - t_0)} - e^{m_i(t - t_0)} \right)
\]

Tofts and Kermode
Pre-treatment tumour Permeability, Perfusion and Diffusion predict response to chemoradiotherapy

George M, Dzik-Jurasz ASK et al, BJS 2001
Dzik-Jurasz ASK et al, Lancet 2002
“the mean is significantly higher for responders....”

What does data such as this mean for an individual patient?

How can this be translated to clinical practice?
Table 2: Results of $K^{true}$, $k_{app}$, AUC 90 and AUC 180 (ROI, decile and quartile) versus quantitative variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>$K^{true}$</th>
<th>$k_{app}$</th>
<th>AUC 90</th>
<th>AUC 180</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ROI</td>
<td>Decile</td>
<td>Quartile</td>
<td>ROI</td>
</tr>
<tr>
<td>Pre Rx</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Res</td>
<td>-0.20</td>
<td>0.37</td>
<td>-0.16</td>
<td>0.50</td>
</tr>
<tr>
<td>Size US</td>
<td>0.001</td>
<td>0.99</td>
<td>0.07</td>
<td>0.78</td>
</tr>
<tr>
<td>Size PATH</td>
<td>0.22</td>
<td>0.38</td>
<td>0.18</td>
<td>0.47</td>
</tr>
<tr>
<td>Change</td>
<td>-0.30</td>
<td>0.27</td>
<td>-0.45</td>
<td>0.09</td>
</tr>
<tr>
<td>Post Rx</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Res</td>
<td>-0.46</td>
<td>0.04</td>
<td>-0.43</td>
<td>0.04</td>
</tr>
<tr>
<td>Size US</td>
<td>0.41</td>
<td>0.10</td>
<td>0.26</td>
<td>0.29</td>
</tr>
<tr>
<td>Size PATH</td>
<td>0.47</td>
<td>0.05</td>
<td>0.55</td>
<td>0.01</td>
</tr>
<tr>
<td>Change</td>
<td>-0.20</td>
<td>0.47</td>
<td>-0.31</td>
<td>0.22</td>
</tr>
<tr>
<td>% Change</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Res</td>
<td>-0.29</td>
<td>0.20</td>
<td>-0.36</td>
<td>0.10</td>
</tr>
<tr>
<td>Size US</td>
<td>0.38</td>
<td>0.13</td>
<td>0.25</td>
<td>0.34</td>
</tr>
<tr>
<td>Size PATH</td>
<td>0.21</td>
<td>0.40</td>
<td>0.45</td>
<td>0.06</td>
</tr>
<tr>
<td>Change</td>
<td>0.15</td>
<td>0.59</td>
<td>-0.08</td>
<td>0.78</td>
</tr>
</tbody>
</table>

ROI = Region of Interest, RR = treatment, US = endorectal ultrasound, PATH = final pathological specimen, S = Spearman, P = P-value, % Res = % response.
Conclusions drawn for post hoc data analysis

ROC analysis for K trans post-treatment, revealed that K trans has an AUC of 0.7941 (0.5764, 1.0119) in predicting pCR.

A K trans of 0.3 emerged as the best cut-off for distinguishing pCR from non-pCR.

Was this validated in a prospective dataset? – we’re still waiting for the prospective data breakthrough....
Another post hoc analysis

Figure 2. Relative Volume change (ΔVolume, a) and relative Ktrans change (ΔKtrans, b) for the pathological complete responders (pCR) and non-pCR group and for the good responders (GR) and non-GR group. The median (p50) Ktrans values are shown. The dashed line represents the optimal cutoff value to distinguish response groups. −70% for the ΔVolume and −32% for the ΔKtrans.
Using ROC analysis to derive a cut-off.

“We used the ad-hoc analysis because when starting the study no earlier data was available to set the cutoff value.”

Before clinical implementation of the DCE-MR for response assessment a larger prospective multicenter study with a predefined cutoff value will need to be performed…..
Examples from PET-CT publications

Fig. 3. (A) ROC curves of the $SUV_{\text{max}}$ RI on day 15 of the RCT relative to the TRG stage before (solid line indicates AUC of 0.87) and after (dashed line indicates AUC of 0.97) exclusion of the patients with a reported peritumoral inflammatory response. (B) RIs of the $SUV_{\text{max}}$ on day 15 relative to the TRG stage. The gray horizontal line indicates the ROC curve analysis based on the cutoff value of 43%, differentiating pathological responders from nonresponders. The grey dots highlight the four patients with a reported peritumoral inflammatory response.
PET SUV validation did not work as well

- ROC curve cut-off of 48% for pathological responders vs nonresponders

Janssen et al
2011
FDG-PET assessment of SUV max at 2 weeks

Metabolic response

Post Radiotherapy
Acute inflammatory changes
DIFFUSION WEIGHTED MRI IN ASSESSING RECTAL CANCER
## Assessing response: the role of new technologies?

<table>
<thead>
<tr>
<th>Method</th>
<th>Prospectively validated against DFS outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI DWI</td>
<td>No – many retrospective quantitative cut-offs and qualitative assessments – none prospectively validated</td>
</tr>
<tr>
<td>DCE-MRI</td>
<td>No – many retrospective values proposed – none validated</td>
</tr>
<tr>
<td>PET-CT</td>
<td>No – but retrospective SUV cut-offs proposed – unverified prospectively</td>
</tr>
</tbody>
</table>
Checklist of Biomarker Recommendations

1. Has the proposal laid out proof of a clinical need i.e. proof of outcomes/consequence.

2. What is the true degree of error/deficiency and consequence in current non-quantitative imaging or non imaging test?
Checklist of Biomarker Recommendations

3. Does the biomarker being tested have a predefined threshold/criteria or range for positive vs negative test or is it exploratory – if exploratory (ie shown a correlation)

4. Have the authors then completed the study by defining and then validating thresholds in an independent dataset
Checklist of Biomarker Recommendations

5. Has the biomarker been tested against other clinical variables and other imaging methods of assessment and found to be an independent predictor compared with the current best standards of care?
6. Has the imaging measure been tested against PFS/DFS/survival outcomes and shown to be independent of existing clinical and imaging non quantitative tests?
Developments in MRI based management of Rectal Cancer

• The unimportance of nodal status
• The importance of extramural depth of spread as a biomarker
• Recognition and effective preoperative treatment of mrCRM involvement
• Recognition and effective preoperative treatment of mrEMVI – impact on survival
• Staging and assessment of low rectal cancer
• Staging and assessment of Early Rectal Cancer
• Using the post treatment MRI TRG assessment as a biomarker for further preoperative treatment stratification
Are lymph nodes still a biomarker for local recurrence?

The Dukes era 1932 - 1990s

The TME era 2000 - present
Randomised trial evidence unimportance of nodal status on local recurrence

- For a **good quality** total mesorectal excision that is circumferential resection margin negative – there is no difference – CR07 5-6% LR (Quirke et al Lancet Oncology) rates irrespective of node status, Lancet 2009
- OCUM trial (Germany) and Quicksilver trial (Canada)

<table>
<thead>
<tr>
<th>TNM stage</th>
<th>Muscularis propria</th>
<th>Intramesorectal HR (95% CI)*</th>
<th>Mesorectal HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>8%</td>
<td>2%, 0.33 (0.07-1.59)</td>
<td>0%, 0.01 (0.00-0.10)</td>
</tr>
<tr>
<td>II</td>
<td>6%</td>
<td>2%, 0.11 (0.01-0.94)</td>
<td>5%, 0.78 (0.20-3.08)</td>
</tr>
<tr>
<td>III</td>
<td><strong>20%</strong></td>
<td>14%, 0.72 (0.33-1.56)</td>
<td>6%, 0.37 (0.15-0.89)</td>
</tr>
</tbody>
</table>

LR and stage III disease, is linked to poor quality surgery. Where surgical quality is good and CRM is clear, lymph nodes are not associated with LR. Lymph Nodes are not the cause of CRM involvement.
Limitations of the TNM – T3 category forms 80% of rectal cancers

- Jass (St Marks, UK): independent prognostic significance
- Harrison (Tennessee, USA): prognostic score depth of spread in mm
- Cawthorne (Guildford, UK): depth of spread significance
- Merkel and Hermanek (Erlangen, Germany):
  - T3 subclassification
    - T3a <1mm
    - T3b>1-5mm
    - T3c>5-15mm
    - T3d>15mm (TNM staging system 1993 supplement)

Erlangen: >800 patients
pT3<5mm N any same survival as T2 85%
pT3>5mm N any, 54% survival
“measuring extramural depth is the least subjective and most reliable of all the observations by radiologists”

295/311 (95 %) patients who underwent primary surgery. The mean difference between MRI and histopathology assessment of tumor EMD was -0.046 mm, SD = 3.85 mm, the 95 % CI was -0.487 to 0.395 mm.

MRI and histopathology assessment of tumor spread are considered equivalent to within 0.5 mm (θR). *Radiology 2007*
MERCURY trial

• 2002-2003
• 11 international centres (30 radiologists)
• 295 patients undergoing primary surgery
• Policy to avoid pre and post operative radiotherapy for mrCRM clear, mrEMVI negative, T3b or less rectal cancers, regardless of N stage
Outcomes for MRI good prognosis rectal cancers: regardless of N stage

**MERCURY—MRI-predicted Good Prognosis Patients**

<table>
<thead>
<tr>
<th>Disease-free survival</th>
<th>Local Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients (n = 122)</td>
<td>3.3%</td>
</tr>
<tr>
<td>T3a/b N0, N1, and N2 (n = 58)</td>
<td>1.7%</td>
</tr>
<tr>
<td>T1,2, or, 3b. N positive disease (n = 22)</td>
<td>0%</td>
</tr>
</tbody>
</table>

**5-Year Disease-free Survival**

- 84.7% (95% CI, 76.0%–90.4%)
- 81% (95% CI, 66.1%–89.8%)
- 95% (95% CI, 69.5%–99.3%)

Taylor et al, MERCURY
Annals of Surgery 2011
mrCRM involvement defined as tumour spread (continuous or discontinuous) within 1mm of the TME plane (bounded by mesorectal fascia and intersphincteric plane). Independent risk factor for local recurrence (Hazard Ratio 3.5)

mrCRM clear local recurrence 7% versus 20% if mrCRM involved
pCRM clear local recurrence 6.5% versus 26% if pCRM involved
Measuring size of nodes **worsens** results – overstaging and overtreatment of low risk patients

- node positive if either irregular border or mixed signal intensity.
- Metastases demonstrated in 51/56 nodes (91%, 95% CI 81% to 96%) with either an irregular border or a mixed intensity signal.
- only 9/225 nodes (4%, CI 2.1% to 7.4%) with smooth borders and a uniform signal contained metastases irrespective of size.
- **Size of node bears no relationship to malignant risk**

*Brown et al Radiology 2003*
MRI detected **Lymph Nodes** close to the mesorectal fascia are not associated with pCRM involvement (Shihab et al, BJS 2010)

- Involvement of CRM by lymph node metastases alone is **uncommon** (1.3% of all patients in MERCURY series).
- Caution when recommending neoadjuvant therapy based solely on an MRI-detected lymph node close to the mesorectal fascia.
1. **MRI Low Rectal Stage 1**: tumour on MRI images appears confined to bowel wall (intact muscularis propria of the internal sphincter).

2. **MRI Low Rectal Stage 2**: tumour on MRI partially replaces the muscle coat but there is >1mm distance to TME/intersphincteric plane. Above sphincter it is confined to the mesorectum.

3. **MRI Low Rectal Stage 3**: invading into the intersphincteric plane or lying within 1mm of levator muscle above the level of the sphincter complex.

4. **MRI Low Rectal Stage 4**: invading the external anal sphincter and infiltrating/ extending beyond the levators +/- invading adjacent organ.

Primary Surgery for Low Rectal Cancers

- Almost half (44.4%, 124/279) of study participants had a ‘safe’ mrLRP and no adverse MRI features. The recommended management was to proceed straight to surgery with an intersphincteric resection, adhering to this guidance (50%) led to a clear 16 pCRM in 98% of cases.
- When MRI low-risk patients were offered CRT or an ELAPE - this resulted in a numerically higher pCRM involvement. Additional treatment and more radical surgery did not result in a benefit to the patient and may represent overtreatment.

# Results from 19 sites recruiting to MERCURY

## All Cause pCRM in all patients
(Surgery with or without pre-operative therapy, n=279)

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mrLRP††</td>
<td></td>
<td></td>
</tr>
<tr>
<td>‘Safe’</td>
<td>5.48 (2.7 – 13.2)</td>
<td>0.0002</td>
</tr>
<tr>
<td>‘Unsafe’</td>
<td>3.49 (1.3 – 9.0)</td>
<td>0.010</td>
</tr>
<tr>
<td>MRI Quadrant of tumour invasion²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2.53 (1.1 – 5.8)</td>
<td>0.029</td>
</tr>
<tr>
<td>Anterior</td>
<td>2.80 (1.1-6.8)</td>
<td>0.027</td>
</tr>
<tr>
<td>MRI Height (from the anal verge)³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 4cm</td>
<td>4.00 (1.7-9.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>&lt; 4cm</td>
<td>3.39 (1.3-8.8)</td>
<td>0.012</td>
</tr>
<tr>
<td>mrT stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤mrT3b</td>
<td>4.42 (1.9 – 10.3)</td>
<td>0.0006</td>
</tr>
<tr>
<td>&gt;mrT3b</td>
<td>2.86 (1.2 – 6.6)</td>
<td>0.014</td>
</tr>
<tr>
<td>mr Node status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>2.86 (1.2 – 6.6)</td>
<td>0.014</td>
</tr>
<tr>
<td>Positive</td>
<td>3.76 (1.5 – 9.6)</td>
<td>0.006</td>
</tr>
<tr>
<td>mr EMVI status†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>4.66 (2.0 – 10.9)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Positive</td>
<td>3.76 (1.5 – 9.6)</td>
<td>0.006</td>
</tr>
</tbody>
</table>
MRI Tool for predicting risk of pCRM involvement

- MRI 'Unsafe' plane: 15% (5% of which are considered no risk factors, 2% pCRM risk)
- MRI Height <4cm: 12%
- MRI invading edge: 4%
- mrEMVI: 5%

Venn Diagram:
- Overlap between MRI Height <4cm and MRI invading edge: 9%
- Overlap between MRI invading edge and mrEMVI: 12%
- Overlap between MRI 'Unsafe' plane and mrEMVI: 53%
- Overlap between MRI 'Unsafe' plane, MRI Height <4cm, and MRI invading edge: 31 %
TME Mesorectal plane
For coloanal anastomosis/intersphincteric
>1mm of intersphincteric plane clear
Beyond TME ELAPE plane
<1mm intersphincteric plane clear
Beyond TME exenterative planes
When is a node not a node?
Developments in the assessment of venous invasion in colorectal cancer: implications for future practice and patient outcome

David E. Messenger MBChB\textsuperscript{a}, David K. Driman MBChB\textsuperscript{b,\ast}, Richard Kirsch MBChB, PhD\textsuperscript{c}

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\textsuperscript{b}Department of Pathology, London Health Sciences Centre and University of Western Ontario, London, Ontario, Canada N6A 5A5
\textsuperscript{c}Departments of Pathology and Laboratory Medicine, Mount Sinai Hospital and University of Toronto, Toronto, Ontario, Canada M5G 1X5

- Poor interobserver agreement for EMVI
- Large variations in reporting rates 10\% - 50\% - underreporting widespread
- Lack of agreement of definitions
• pEMVI detection rates should be >30%
• For units with <30%, should use elastin staining
• MRI is reliable as method of detecting EMVI and can be used to audit pathology
• Lone arteriole sign, to improve detection of discontinuous vascular deposits
Characteristic features of mrEMVI

- Expansion of extramural vessels by tumour
- Serpiginous / tubular extension of tumour signal

MRI for detection of extramural vascular invasion in rectal cancer.

mrEMVI is associated with pelvic sidewall tumour deposits
Magnetic Resonance Imaging (MRI) detected Extramural Vascular Invasion (EMVI) score & Outcome

n=135. Median follow-up=3.12 (0.9-5.7) years.


MRI-EMVI score= 0-2
MRI-EMVI score= 3-4

% Relapse-free
71%
32%

Time since operation (Years)

p = 0.0015
MRI detected more persistent EMVI post CRT than pathology

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group</th>
<th>Patient Numbers</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>Patient characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>67</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>121</td>
<td>1.093</td>
<td>0.625–1.912</td>
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<tr>
<td>Height</td>
<td>Upper/mid</td>
<td>119</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>69</td>
<td>1.369</td>
<td>0.815–2.298</td>
</tr>
<tr>
<td><strong>Baseline MR staging</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>mrt stage</td>
<td>Good</td>
<td>51</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>137</td>
<td>1.187</td>
<td>0.638–2.206</td>
</tr>
<tr>
<td>mnR stage</td>
<td>Negative</td>
<td>65</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>123</td>
<td>1.196</td>
<td>0.691–2.071</td>
</tr>
<tr>
<td>mrEMVI</td>
<td>Negative</td>
<td>188</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>107</td>
<td>0.902</td>
<td>0.527–1.544</td>
</tr>
<tr>
<td>mrCRM</td>
<td>Negative</td>
<td>81</td>
<td>0.846</td>
<td>0.497–1.441</td>
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<td></td>
<td>Positive</td>
<td>116</td>
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<td><strong>Post-CRT preoperative MR staging</strong></td>
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<tr>
<td>ymrT stage</td>
<td>Good</td>
<td>116</td>
<td>Ref</td>
<td></td>
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<tr>
<td></td>
<td>Poor</td>
<td>72</td>
<td>1.218</td>
<td>0.723–2.052</td>
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<td>ymrN stage</td>
<td>Negative</td>
<td>104</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>84</td>
<td>1.179</td>
<td>0.701–1.982</td>
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<td>ymrEMVI</td>
<td>Negative</td>
<td>89</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>99</td>
<td>1.987</td>
<td>1.237–4.323</td>
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<tr>
<td>ymrCRM</td>
<td>Clear</td>
<td>148</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Involved/threatened</td>
<td>40</td>
<td>1.26</td>
<td>0.674–2.354</td>
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<tr>
<td><strong>Final pathology staging</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ypT</td>
<td>Good</td>
<td>64</td>
<td>Ref</td>
<td></td>
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<td></td>
<td>Poor</td>
<td>124</td>
<td>1.125</td>
<td>0.695–1.279</td>
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<tr>
<td>ypN</td>
<td>Negative</td>
<td>118</td>
<td>Ref</td>
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<td></td>
<td>Positive</td>
<td>70</td>
<td>2.912</td>
<td>1.724–4.878</td>
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<tr>
<td>ypEMVI</td>
<td>Negative</td>
<td>142</td>
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<td></td>
<td>Positive</td>
<td>46</td>
<td>3.889</td>
<td>2.088–6.281</td>
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<tr>
<td>ypCRM</td>
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<td>178</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>10</td>
<td>3.352</td>
<td>1.421–7.907</td>
</tr>
</tbody>
</table>
A good prognosis tumour?

Looks like a T1sm3
Discontinuous EMVI in ERC
And a pelvic sidewall tumour deposit
mrEMVI

- mrEMVI seen in 40% of rectal cancers
- Detected more readily than by pathology
- Independent risk factor for CRM involvement, local and distant recurrence
Lymph nodes versus extranodal deposits
These tumours have entirely different prognostic outcomes

Stage II (T3N0):
- mrT3dN0EMVI pos
- CRM+:CRT+chemo + beyond TME surgery

Stage III (T3N1):
- mrT3aN1CRM-ve
- Primary TME surgery

Stage I (T1N0):
- mrT1 EMVI deposit,
  CRM+ve, Preoperative CRT and ELAPE
## Assessing response

<table>
<thead>
<tr>
<th>Method</th>
<th>Prospectively validated against DFS outcomes</th>
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<tbody>
<tr>
<td>MRI DWI</td>
<td>No – many retrospective quantitative cut-offs and qualitative assessments – none prospectively validated</td>
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<tr>
<td>DCE-MRI</td>
<td>No – many retrospective values proposed – none validated</td>
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<tr>
<td>PET-CT</td>
<td>No – but retrospective SUV cut-offs proposed – unverified prospectively</td>
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<tr>
<td>mrVolume assessment</td>
<td>Yes: &gt;80% volume reduction</td>
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<tr>
<td>mrTRG</td>
<td>Yes : TRG1-5 validated prospectively and against outcomes</td>
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<tr>
<td>mrT and mrN stage</td>
<td>validated prospectively and against outcomes</td>
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Timing after CRT? When is maximum response reached?

Baseline: mrT4
6 weeks: ymrT3b
12 weeks: ymrT2
Final Pathology: ypT2N0
TRG and Survival (Patel et al JCO 2011)

72% at 5 yrs
27% at 5 yrs

p=0.001
HR 3.28 (95%CI; 1.22 – 8.80).

MRI TRG 1-3
MRI TRG 4-5
Royal Marsden n=208 patients

Yu et al, ESMO World GI Congress, Barcelona 2015
EXPERT C trial for patients at high risk of local and distant failure

- Tumors within 1 mm of mesorectal fascia (i.e., potential circumferential resection margin involvement)
- T3 c (extramural spread 5-15 mm) and T3 d (extramural spread >15 mm), regardless of N stage
- MRI T4a or T4b disease regardless of N stage
- Low rectal cancer with tumor bordering the intersphincteric/distal TME plane on MRI
- Tumors with MRI extramural venous invasion (mrEMVI)
Overall Survival by TRG (1-2 v 3 v 4-5) after Chemo-Radiotherapy in EXPERT-C trial (both arms)

mrTRG1-2, 89.8%
mrTRG3, 29%
mrTRG4-5, 31%
mrTRG is a prognostic (and predictive) biomarker

- Shows good interobserver radiology agreement and reproducibility
  - MERCURY trial (JCO 2011 – multiple radiologists)
  - EXPERT-C trial
  - GEMCAD study (17 radiologists)
  - CORE study (interobserver agreement)

- Identified 40% of patients with mrTRG1/2 – 89.8% overall survival. Compared with only 8.8% patients with pathologic CR.

- Therefore mrTRG could be justified as a more clinically relevant endpoint
mrTRG is a prognostic (and predictive) biomarker

- Shows good interobserver radiology agreement and reproducibility
  - MERCURY trial (JCO 2011 – multiple radiologists)
  - EXPERT-C trial
  - GEMCAD study (17 radiologists)
  - CORE study (interobserver agreement)
  - MERCURY 2 trial – risk factor for CRM involvement
- In EXPERT C trial identified 40% of patients with mrTRG1/2 – 89.8% overall survival. Compared with only 15% pathologic CR rate (90% survival).
- Therefore mrTRG could be justified as a more clinically relevant endpoint
TRIGGER: randomised phase III trial patients will be randomised to an mrTRG based treatment strategy. Training of Radiologists to undertake mrTRG
MRI Trials and the Colorectal Patient Pathway

Colorectal Cancer Imaging Clinical Trials – Using MRI to Stratify Treatment

Patient Pathway

- mrT1c/mrT1d Nx
- mrEMVI (Extramural Venous Invasion) +ve & mrCRM safe
- mrT3c/mrT3d Nx

MRI Staging

Management

- Local Excision
- Avoidance of Radiotherapy & Sphincter Conservation

Diagnosis

- mrT1c/mrT1d Nx
- Low Rectal Stage 1/2

Trials

- MINSTREL (Staging Polyps 2 & 3): with MRI
- MERCURY II (Low Rectal Cancer & Quality of Life)
- MARVEL (Studies the biology of Extramural Venous Invasion in Rectal Cancer)
- SERENADE (Screening for synchronous metastases in colorectal cancer with PET-MRI)
- cT DNA (The relationship between Extramural Venous Invasion and cT DNA)
- TRIGGER (mrCRM stratified management of rectal cancer patients)

- Chemoradiotherapy and Chemoradiotherapy
- Chemoradiotherapy and MRI Re-Stage

- Potential mrCRM unsafe
- MRI Advanced Rectal Cancer
- mTRG 1 & 2
- Poor mTRG

- TRIGGER (‘Good Responders’ omit deferral of surgery & neoadjuvant chemotheraphy)
- Beyond TME (Recalibration deferral for patients undergoing neoadjuvant chemotheraphy)
- Soprano (Biology of Good and Poor Response)
DISCOVERY CONSISTS NOT IN SEEKING NEW LANDS BUT IN SEEING WITH NEW EYES.

— Marcel Proust —
www.slideshare.net/ginabrown3

- MRI reporting templates
- MRI high resolution technique
- How to identify mrEMVI
- Details of workshops for surgeons and radiologists
Baseline assessment of Rectal cancer MRI report

**Primary tumour**
The primary tumour is demonstrated as an [Annular | Semi-annular | Ulcerating | Polypoidal | Mucinous] mass with a [nodular / smooth] infiltrating border.

The distal edge of the luminal tumour arises at a height of [ ] mm from anal verge:
The distal edge of the tumour lies [ ] mm [Above, at, below] the top of the puborectalis sling
The tumour extends craniocaudally over a distance of [ ] mm
The proximal edge of tumour lies [above at below] the peritoneal reflection
Invading edge of tumour extends from [ ] to [ ] O’clock
Tumour is [confined to] [extends through] the muscularis propria:
Extramural spread is [ ] mm

mrT stage: [T1] [ T2 ] [ T3a ] [ T3b ] [ T3c ] [ T3d ] [ T4visceral ] [ T4 peritoneal ]

Tumour is [present] [not present] the level of the puborectalis sling at this level:
[Tumour is confined to the submucosal layer/part thickness of muscularis propria indicating that the intesphincteric plane/mesorectal plane is safe and intersphincteric APE or ultra low TME is possible]
[Tumour extends through the full thickness of the muscularis propria: intesphincteric plane/mesorectal plane is unsafe, Extralevator APE. is indicated for radial clearance]
[Tumour extends into the intersphincteric plane: intesphincteric plane/mesorectal plane is unsafe, therefore an extralevator APE. is indicated for radial clearance]
[Tumour extends into the external sphincter: intesphincteric plane/mesorectal plane is unsafe.] [ Tumour extends into adjacent [prostate/vagina/bladder/sacrum] : exenterative procedure will be required]

Lymph node assessment
Only benign reactive and no suspicious nodes shown [N0]
[ ] mixed signal/irregular border nodes [N1/N2]

Extramural venous invasion: [ No evidence ] [ Evidence]
[ ] Small [ ] Medium [ ] Large vein invasion is present

CRM
The closest circumferential resection margin is at o’clock
The closest CRM is from [Direct spread of tumour] [Extramural venous invasion] [Tumour deposit]
Minimum tumour distance to mesorectal fascia: mm [CRM clear ] [CRM involved]

Peritoneal deposits: [ No evidence ] [ Evidence]

Pelvic side wall lymph nodes:
[ None ] [ Benign ] [ Malignant mixed signal/irreg border]
Location: [Obturator fossa • R •L] . [External Iliac Nodes • R •L]. [Internal iliac • R •L]

Summary: MRI Overall stage: T N M [CRM clear] , [ CRM involved ] , [ EMVI positive] [EMVI negative],[PSW positive ] [PSW negative]
No adverse features eligible for primary surgery
High risk safe margins for preoperative therapy : eligible for Serenade, Marvel
Poor prognosis unsafe margins eligible for preoperative chemoradiotherapy: eligible for 6 vs 12 trial
Low Rectal <6cm – eligible for the Low Rectal Study.

Additional comments:
Post Treatment Assessment MRI Rectal Cancer

Comparison is made with the previous examination of:

• The treated tumour: shows no fibrosis, TRG5
• Less than <25% fibrosis, predominant tumour signal, TRG4
• 50% tumour/fibrosis, TRG 3
• >75% fibrosis, minimal tumour signal intensity, TRG2
• low signal fibrosis only no intermediate tumour signal TRG1

The distal edge of the luminal tumour arises at a height of [    ] mm from anal verge:

The distal edge of the tumour lies [     ] mm [Above, at, below] the top of the puborectalis sling compared with [   ] mm previously

The tumour extends craniocaudally over a distance of [     ] mm compared with [  ] mm previously

The proximal edge of tumour lies [above at below] the peritoneal reflection

The invading edge of treated tumour extends from [ ] to [ ] O'clock

Tumour signal is [Confined to / Extends through the muscularis propria.]

Fibrotic signal is [Confined to / Extends through muscularis propria.]

Extramural spread: [   ] mm for tumour signal [   ] for fibrotic stroma

yMR T stage: • T1 • T2 • T3a • T3b • T3c • T3d • T4 visceral • T4 peritoneal

Treated tumour [is/is not] present at or below the puborectalis sling

• tumour signal/fibrosis extends into the submucosal layer/part thickness of muscularis propria:
  • intersphincteric plane/mesorectal plane is safe intersphincteric APE or ultra low TME possible, CRM is safe
  • tumour signal/fibrosis extends through the full thickness of muscularis propria: intersphincteric plane/mesorectal plane is unsafe, for extralevator APE.
  • tumour signal/fibrosis extends into external sphincter: intersphincteric plane/mesorectal plane is unsafe: for extralevator APE
  • tumour signal/fibrosis extends into beyond external sphincter into [prostate/vagina]: intersphincteric plane/mesorectal plane is unsafe, for extralevator APE.

Lymph nodes:

• None / Only benign reactive [N0]
• Present number mixed signal/irregular border [N1/N2]

Extramural venous invasion:

• No evidence
• Evidence

• Small
• Medium
• Large

CRM Closest circumferential resection margin: [  ] O'clock

Closest CRM is from [  ] Direct spread of tumour • Extramural venous invasion • Tumour deposit

Minim tumour distance to mesorectal fascia: [   ] mm

• CRM clear
• CRM involved

Peritoneal deposits:

• No evidence
• Evidence

Pelvic side wall lymph nodes:

• None
• Benign
• Malignant

Location: Obturator fossa • R • L. External Iliac Nodes • R • L. Inf Hypogastric • R • L

Summary:

y MRI Overall stage ymrT ymr N M, TRG

• Low/intermediate risk, CRM clear, TRG 1-2, EMVI negative
• High prognosis, CRM pos or TRG4/5 or EMVI positive