Where are we at with organ preservation for rectal cancer?

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Queen Elizabeth Hospital Birmingham
ACPGBI Edinburgh 2016
Disclosures

• Consultant for Johnson and Johnson (Ethicon Inc)
Encompasses treatment of polar opposites
Local surgery for small lesions

• Technically straightforward
• Minimal morbidity
• Local recurrence rates 15-30%
Histopathological stratification
Local recurrence rates following TEMS

<table>
<thead>
<tr>
<th>Depth of Invasion</th>
<th>LyV</th>
<th>Maximum Tumour Diameter (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤1</td>
<td>1.1 - 2</td>
</tr>
<tr>
<td>pT1 sm1</td>
<td>-</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>5.2</td>
</tr>
<tr>
<td>pT1 sm2/3</td>
<td>-</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>17.8</td>
</tr>
<tr>
<td>pT2</td>
<td>-</td>
<td>9.8</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>16.7</td>
</tr>
</tbody>
</table>

Bach SP, Hill J, Monson JR, Simson JN, Lane L, Merrie A, Warren B, Mortensen NJ. BJS 2009
Early rectal cancer: the European Association for Endoscopic Surgery (EAES) clinical consensus conference
CRT for advanced disease
Habr Gamma IJROBP 2014

CRT n=183

12 WEEKS
- cCR n=90
- EARLY REGROWTH n=17
  - FTLE n=5
  - TME n=9
  - Unresect n=3

1 YEAR
- cCR n=73
- LATE REGROWTH n=11
  - FTLE n=2
    - Brach n=1
  - TME n=5
  - Unresect n=3

SUSTAINED
- cCR n=62
  - ORGAN PRESERVATION n=70
  - UNRESECTABLE n=6

34% 38% 3%
# UK Cohort cCR following CRT (OnCoRe)

Renehan et al Lancet Oncol 2015

<table>
<thead>
<tr>
<th>CRT n=259</th>
<th>cCR n=31</th>
<th>PROSPECTIVE &gt;12 WEEKS</th>
<th>EARLY REGROWTH</th>
<th>LOCAL</th>
<th>TME</th>
<th>No resect</th>
</tr>
</thead>
<tbody>
<tr>
<td>12%</td>
<td>12%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>CRT n=???</th>
<th>cCR 129</th>
<th>ENRICHED 98 cCR</th>
<th>LATE REGROWTH n=44</th>
<th>Papillon n=5</th>
<th>TME n=31</th>
<th>No resect n=8</th>
</tr>
</thead>
<tbody>
<tr>
<td>38%</td>
<td>38%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
CRT for advanced disease

- High response rates have not been replicated
- Low relapse rates have not been replicated
# Pooled analysis pCR after CRT

Maas et al Lancet Oncol 2010

<table>
<thead>
<tr>
<th>Clinical T stage</th>
<th>All</th>
<th>pCR</th>
<th>No pCR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>0% (12/2785)</td>
<td>2% (7/462)</td>
<td>58% (5/2323)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>T2</td>
<td>5% (145/2785)</td>
<td>9% (41/462)</td>
<td>28% (104/2323)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>83% (2301/2785)</td>
<td>81% (374/462)</td>
<td>16% (1927/2323)</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>12% (327/2785)</td>
<td>9% (40/462)</td>
<td>12% (287/2323)</td>
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</tr>
<tr>
<td>Missing</td>
<td>10% (320/3105)</td>
<td>5% (22/484)</td>
<td>11% (298/2621)</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical N stage</th>
<th>All</th>
<th>pCR</th>
<th>No pCR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N+</td>
<td>59% (1699/2858)</td>
<td>59% (277/466)</td>
<td>59% (1422/2392)</td>
<td>0.10</td>
</tr>
<tr>
<td>Missing</td>
<td>8% (247/3105)</td>
<td>4% (18/484)</td>
<td>9% (229/2621)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Adjuvant chemotherapy</th>
<th>All</th>
<th>pCR</th>
<th>No pCR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant chemotherapy</td>
<td>53% (1398/2642)</td>
<td>39% (155/402)</td>
<td>55% (1243/2240)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Missing</td>
<td>15% (463/3105)</td>
<td>17% (82/484)</td>
<td>15% (381/2621)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Median follow-up time (months)</th>
<th>All</th>
<th>pCR</th>
<th>No pCR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up time (months)</td>
<td>48 (0-277)</td>
<td>46 (0-187)</td>
<td>48 (0-277)</td>
<td>0.058</td>
</tr>
<tr>
<td>Missing</td>
<td>3% (96/3105)</td>
<td>4% (17/484)</td>
<td>3% (79/2621)</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean (SD), % (n/N), or median (range). pCR=pathological complete response. LAR=low anterior resection. APR=abdominoperineal resection.

Table 3: Baseline characteristics of all patients, and of those with or without pathological complete response.
Stage shift in rectal cancer

“Bowel screening saved my life”
High dose CRT and watchful waiting for rectal cancer
Appelt et al Lancet Oncology 2015

• Eligibility
  • T2-T3N0 (protocol amended to allow N1)

• Phase II single arm study

• CRT with IMRT
  • 60Gy in 30F to tumour
  • 50Gy in 30F to nodal regions
  • 5Gy enorectal brachytherapy boost (final week)
  • Oral tegafur – uracil 300mg/m2 weekdays

• Complete response at 11-12 weeks
High dose CRT and watchful waiting for rectal cancer
Appelt et al Lancet Oncol 2015

CRT n=51

12 WEEKS

cCR n=40

EARLY REGROWTH
n=9

TME
n=9

Unresect
n=0

78%

10%

• Rectal bleeding
• Faecal incontinence
• Difficult salvage surgery
CRT and Local Excision Early Stage Disease

- **CARTS** – CRT, Capecitabine + TEMS
- **ACOSOG Z6041** – CRT, Capox + local excision

- Rectal sparing treatment is feasible – 55-65% success
- Local recurrence rare (3/79 ACOSOG)
- Rectal sparing treatments have own toxicities

- No direct comparison with ‘gold standard’ TME
CRT with either boost or local excision

- Toxicities still prohibit treatment
- Purpose of organ preservation is to reduce treatment toxicity
  - Modify organ preserving treatments
  - Investigate molecular stratifiers
SCRT and TEM for early disease

RECTAL CANCER
mri T1-2 N0

Too frail for radical surgery

SCPRT

8-10 WEEKS

TEMS
Short Course Radiotherapy (5x5Gy)

10 week assessment

Flat mucosa

No residual tumour evident

Shallow ulceration
At 2 years

- Flat white scar
- Telangectasia
SCPRT and TEMS cohort study
Manchester, Chichester, Bradford and Birmingham

<table>
<thead>
<tr>
<th></th>
<th>pCR</th>
<th>ypT1</th>
<th>ypT2</th>
<th>ypT3</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>23</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>%</td>
<td>32%</td>
<td>36%</td>
<td>30%</td>
<td>2%</td>
</tr>
<tr>
<td>R1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Local recurrence</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0</td>
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<tr>
<td>Distant recurrence</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Mean follow up m (range)</td>
<td>18 (12-30)</td>
<td>12 (6-30)</td>
<td>15 (3-36)</td>
<td>12</td>
</tr>
</tbody>
</table>

A multicentre study of SCRT and TEMS for early rectal cancer. Smart et al. BJS 2016
Clinical Investigation

Results of Neoadjuvant Short-Course Radiation Therapy Followed by Transanal Endoscopic Microsurgery for T1-T2 N0 Extraperitoneal Rectal Cancer

Alberto Arezzo,* Simone Arolfo, MD,* Marco Ettore Allaix, MD, PhD,* Fernando Munoz, MD,† Paola Cassoni, Chiara Monagheddu, MD,‡ Umberto Ricardi, Giovanni Ciccone, MD,§ and Mario Morino *

*General Surgery 1, Department of Surgical Sciences, University of Turin, Turin, Italy; †Radiation Oncology, Department of Oncology, University of Turin, Turin, Italy; ‡Pathology Unit, Department of Medical Sciences, University of Turin, Turin, Italy; and §Clinical Epidemiology Unit, Piedmont Reference Centre for Epidemiology and Cancer Prevention, City of Health and Science Hospital of Turin, Turin, Italy

Received Jul 1, 2014, and in revised form Jan 7, 2015. Accepted for publication Jan 20, 2015.
TREC
Randomised phase II

• Can we randomise 46 patients in 2 years?

• Secondary endpoints
  • Safety
    • Morbidity
    • Mortality
  • Efficacy
    • Downstaging
    • Conversion
    • QoL
### TREC Recruitment
Randomised and Registered

<table>
<thead>
<tr>
<th>Centre</th>
<th>Surgeon</th>
<th>Rand</th>
<th>Reg</th>
<th>Centre</th>
<th>Surgeon</th>
<th>Rand</th>
<th>Reg</th>
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</thead>
<tbody>
<tr>
<td>QE B’ham</td>
<td>Bach</td>
<td>6</td>
<td>6</td>
<td>Glan Clwyd</td>
<td>Mao</td>
<td>0</td>
<td>3</td>
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<tr>
<td>Good Hope</td>
<td>Korsgen</td>
<td>6</td>
<td>9</td>
<td>St Mary’s</td>
<td>Ziprin</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Chichester</td>
<td>Levy</td>
<td>2</td>
<td>3</td>
<td>Aintree</td>
<td>Slawick</td>
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<tr>
<td>Colchester</td>
<td>Tutton</td>
<td>2</td>
<td>9</td>
<td>Newcastle</td>
<td>Hainsworth</td>
<td>7</td>
<td>0</td>
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<tr>
<td>Oxford</td>
<td>Cunningham</td>
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<td>1</td>
<td>Sandwell</td>
<td>Cruikshank</td>
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<tr>
<td>Bradford</td>
<td>Stewart</td>
<td>3</td>
<td>4</td>
<td>Portsmouth</td>
<td>Khan</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Clatterbridge</td>
<td>Sun Myint</td>
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<td>1</td>
<td>St Peters</td>
<td>Nisav</td>
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<tr>
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<td>Hill</td>
<td>5</td>
<td>12</td>
<td>Bristol</td>
<td>Thomas</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>North Tees</td>
<td>Gill</td>
<td>9</td>
<td>1</td>
<td>Cardiff</td>
<td>Davies</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Preston</td>
<td>Beveridge</td>
<td>2</td>
<td>0</td>
<td>Poole</td>
<td>Flubacher</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Randomisation is feasible

Patient selection
- T stage – not selecting very early
- N stage – low incidence node positive in patients randomised to TME

SCPRT and TEM appears safe in short term
- n=120
- no stomas
- no perineal fistulae
- 25% conversion rate to TME
- Too early to comment on recurrence
Unique opportunity

• To boldly go......

• And provide the highest level of evidence that compares the standard of care (radical surgery) with organ preservation strategies.
Saving the rectum by watchful waiting or TransAnal surgery after (chemo)Radiotherapy versus Total mesorectal excision for early REctal Cancer

STAR TREC

Simon Bach
Queen Elizabeth Hospital Birmingham
On behalf of the Netherlands, Denmark and UK groups
New concepts for STAR-TREC

• Smaller radiotherapy fields to reduce toxicity

• Opportunities for watch and wait

• Moved away from mandatory TEMS for rectal sparing treatment
Inclusion Criteria

• Biopsy proven adenocarcinoma

• mrT1-T3b (<= 5mm extramural spread) V0 N0 CRM-ve

• Endorectal ultrasound defined rectal cancer uT1-T3 (optional: in centres where high quality ERUS is available)

• The multidisciplinary team considers that TME, CRT, SCPRT and TEMS are all reasonable and feasible treatments
Exclusion Criteria

- Maximum tumour diameter >4cm
- MRI evidence of EMVI
- MRI evidence of Node +ve
- Mesorectal fascia threatened (<=1mm clearance)
- Definite evidence of metastatic disease (patients with indeterminate lesions agreed by the MDT are eligible)
- Anterior tumour above peritoneal reflection on MRI
STARTREC – Study design
Phase II/III clinical trial

cT1-T3b N0

Radical Surgery
- TME (week 1-5)

Organ preservation
- 5x5 Gy
- CRT
- evaluation
  - Good response
  - Not CCR
    - CCR
    - Not CCR
      - W&W
      - TEM
      - high risk conversion TME

Organ preservation
- CRT

Week 11-13 – central review

Week 16-20 – central review

Poor response
- TME
Conclusions

• We can boldly go!

• TREC has shown that randomisation is possible

• Both TREC and CARTS have provided the platform

• We need to show that we can recruit enough patients

• Great opportunity for the practice changing trial!