In what stages can radiation be avoided in the management of rectal cancer?

Dr Rob Glynne-Jones
Mount Vernon Cancer Centre
Rectal Cancer

- I want to improve survival
- with good function
- And best possible Quality of Life
“With a blanket approach to SCPRT and good surgery we can virtually eliminate local recurrence in rectal cancer”

David Sebag-Montefiore 2009
Rectal Cancer: Accepted wisdom (Minsky 2013)

Preoperative chemoradiation (CRT) + Surgery standard of care in the USA/Europe for all patients with clinical stage II and III rectal cancer

- Low rates of local recurrence
- Potential for sphincter preservation
- Allows integration of systemic chemotherapy
- Acceptable acute and late toxicity
Evidence Base: Sphincter sparing

- Meta-analysis Bujko 2006
  No evidence preop RT/CTRT achieves sphincter sparing surgery

- Cochrane Review Wong 2007
  No evidence preop RT/CTRT achieves sphincter sparing surgery

- Polish and TROG 01.04 phase III trials
  No evidence preop CTRT achieves sphincter sparing surgery
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- Allows integration of systemic chemotherapy
- Acceptable acute and late toxicity
Individualized Medicine in 2013
Individualized Medicine in 2013

The ultimate goal of individualized medicine is to identify/define groups of patients

- most likely
- and least likely

to benefit from a particular intervention
Individualized Medicine in 2013

The ultimate goal of individualized medicine is to identify/define groups of patients

- Targetted biological drugs
Individualized Medicine in 2013

The ultimate goal of individualized medicine is to identify/define groups of patients

- Targetted biological drugs
- Cytotoxic agents
Individualized Medicine in 2013

The ultimate goal of individualized medicine is to identify/define groups of patients

- Targetted biological drugs
- Cytotoxic agents
- Preoperative Radiotherapy /Chemoradiotherapy
Individualized Medicine in 2013

- Can we identify patients with a particularly low risk of local recurrence who do not require RT?

- Can we identify patients with a particularly high risk of metastatic disease for whom pelvic RT is probably irrelevant?
For individualized therapy we need:

- Clinical staging (TNM) - precise risks for local recurrence and metastases.
- The associated clinical characteristics which also define risks and different subpopulations
- The molecular pathways which underpin the disease
- Likely outcomes for the above
- The input from all members of the MDT
MDT - in rectal cancer

- knowledge of the individual skills
- and available technical hardware of the MDT
  radiologists,
  radiation oncologists,
  surgeons,
  pathologists
Evolution

- It is not the strongest of the species that survives, nor the most intelligent that survives. It is the one that is the most **adaptable** to change.

Charles Darwin
4 major advances

- Improvements in surgical technique
4 major advances

- Improvements in surgical technique
- High quality MRI
4 major advances

- Improvements in surgical technique
- High quality MRI
- Improvements in pathology
4 major advances

- Improvements in surgical technique
- High quality MRI
- Improvements in pathology
- More information related effects and 2nd cancers

We need to adapt to these developments
And remember

The phase III trials only partly used these advances
So what is low risk?
CR07 Study: local recurrence per TNM stage and treatment arm

<table>
<thead>
<tr>
<th>TNM stage</th>
<th>Number</th>
<th>RT + TME (%)</th>
<th>TME alone (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>335</td>
<td>1.9%</td>
<td>2.8%</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>395</td>
<td>1.9%</td>
<td>6.4%</td>
<td>0.004</td>
</tr>
<tr>
<td>Stage III</td>
<td>542</td>
<td>7.4%</td>
<td>15.4%</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Management of local disease – patients with rectal cancer

Patient with rectal cancer

MRI to assess local recurrence determined by anticipated resection margin, tumour and lymph node staging, unless contraindicated

Risk of local recurrence

Low risk

Moderate risk

High risk (locally advanced)

Consider

Consider

Chemoradiotherapy

SCPRT

Interval before surgery to allow shrinkage and response

Proceed immediately to

Surgery

See algorithm on “Post-operative care”
Preoperative Adjuvant Radiotherapy

- Reduces Local recurrence
- No impact on Disease free Survival
- No impact on Overall Survival
- Acute Toxicity
- Compliance
- Surgical morbidity
- Late Toxicity/second malignancy
- Impacts on function
In decisions re SCPRT/CRT

So does the risk of local recurrence trump everything else?
So why have we such a limited vocabulary?
MRI defined rationale acc to CRM

Diagram adapted from Shihab et al Lancet Oncology 2009
What if the mesorectal fascia is not threatened?

- cT3
- cN+
- Extramural vascular invasion (EMVI)
Nagtegaal 2002 – unirradiated group (n= 656)

<table>
<thead>
<tr>
<th>Dutch TME study</th>
<th>3 year Local recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>+CRM &lt; or = 2 mm</td>
<td>16%</td>
</tr>
<tr>
<td>-CRM &gt;2 mm</td>
<td>5.8%</td>
</tr>
</tbody>
</table>

p=0.0001
Overall CR07 data (both arms)

<table>
<thead>
<tr>
<th>CR07</th>
<th>3 year Local recurrence</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>+CRM (1mm)</td>
<td>17%</td>
<td>0.0011</td>
</tr>
<tr>
<td>-CRM</td>
<td>6%</td>
<td></td>
</tr>
</tbody>
</table>
Question?

- Is it really worthwhile reducing local recurrence from 6% to 2% with RT?
Patient and Oncologist preferences are different Pieterse et al., 2007
Patient and Oncologist preferences are different Pieterse et al., 2007
Break-down of Recurrence Location by Treatment Arm: Crude % at 5 Years

<table>
<thead>
<tr>
<th>Location</th>
<th>1805 Total Pts</th>
<th>RT+TME</th>
<th>TME alone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># of LR (total)</td>
<td>% total</td>
<td>crude % LR</td>
</tr>
<tr>
<td>Presacral space</td>
<td>15 (36)</td>
<td>42</td>
<td>2.35</td>
</tr>
<tr>
<td>Lateral nodes</td>
<td>5 (14)</td>
<td>14</td>
<td>0.78</td>
</tr>
<tr>
<td>Central pelvis</td>
<td>6 (17)</td>
<td>17</td>
<td>0.95</td>
</tr>
<tr>
<td>Lateral pelvis</td>
<td>1 (3)</td>
<td>3</td>
<td>0.16</td>
</tr>
<tr>
<td>Obturator/iliac nodes</td>
<td>3 (8)</td>
<td>8</td>
<td>0.44</td>
</tr>
<tr>
<td>Anastomosis</td>
<td>5 (14)</td>
<td>14</td>
<td>0.78</td>
</tr>
<tr>
<td>Perineum</td>
<td>0 (0)</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>1 (3)</td>
<td>3</td>
<td>0.16</td>
</tr>
</tbody>
</table>
What other categories?
CR07 Study: local recurrence per TNM stage and treatment arm

<table>
<thead>
<tr>
<th>TNM</th>
<th>number</th>
<th>RT + TME</th>
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</tr>
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Do upper rectal cancers benefit from neoadjuvant radiotherapy?
CR07: 3 year local recurrence rate by tumour position (cm)

<table>
<thead>
<tr>
<th>Position</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10-15</td>
<td>1.2%</td>
<td>6.2%</td>
</tr>
<tr>
<td>&gt;5-10</td>
<td>5%</td>
<td>9.8%</td>
</tr>
<tr>
<td>0-5</td>
<td>4.8%</td>
<td>10.4%</td>
</tr>
</tbody>
</table>
Avoiding Radiotherapy

- What data do we have?
Japanese studies without preoperative RT

- 817 patients 1988-2002
- 5 year local recurrence rate 6.2%

Fujita S et al., Int J Colorectal Dis 2008;23(11):1073-9
In terms of local recurrence

- SCPRT + Surgery = LPLND + Surgery
But you need this
Lateral node dissection of right side pelvic wall
Local Recurrence < 6%

- Frasson 2011
- Taylor 2011
- Mathis 2012

- SELECTED FOR NO RADIOTHERAPY
you need this
Total Mesorectal Excision
<table>
<thead>
<tr>
<th>Study</th>
<th>Eligible</th>
<th>Good Quality Mesorectal plane</th>
<th>Local Recurrence</th>
<th>Actuarial</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR07 overall (592) Quirke 2009</td>
<td>T any  N any</td>
<td>51%</td>
<td>59/592</td>
<td>11%</td>
</tr>
<tr>
<td>Dutch TME (180) Nagtegaal 2005</td>
<td>T any  N any</td>
<td>56%</td>
<td>Not stated</td>
<td>8.7% at 2 years</td>
</tr>
<tr>
<td>CR07 (301) Quirke 2009</td>
<td>T any  N any</td>
<td>100%</td>
<td>27/301</td>
<td>7% at 3 years</td>
</tr>
<tr>
<td>Mercury Taylor 2011</td>
<td>T3a/b  N any crm-</td>
<td>70%</td>
<td>4/122</td>
<td>3.3% at 5 years</td>
</tr>
<tr>
<td>Study</td>
<td>Eligible</td>
<td>Good Quality Mesorectal plane</td>
<td>+CRM</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>--------------</td>
<td>-------------------------------</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>CR07 (301) Quirke 2009</td>
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<td>100%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Eligible</td>
<td>Good Quality Mesorectal plane</td>
<td>+CRM</td>
<td></td>
</tr>
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<td>-------------------------------</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>CR07 (301) Quirke 2009</td>
<td>T any N any</td>
<td>100%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No MRI till</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>end of study</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Good quality mesorectal plane: CRM + rate no RT

<table>
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<th>Eligible</th>
<th>Good Quality Mesorectal plane</th>
<th>+CRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR07 (301) Quirke 2009</td>
<td>T any N any</td>
<td>100%</td>
<td>9%</td>
</tr>
<tr>
<td>MRI directed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mercury Taylor 2011</td>
<td>T3a/b N any cRM-</td>
<td>70%</td>
<td>4/122</td>
</tr>
<tr>
<td>German Strassburg 2011</td>
<td>&lt;6cm T3 N any &gt;6cm cRM-</td>
<td>90%</td>
<td>2/134</td>
</tr>
</tbody>
</table>
Good Quality MRI

- So you should cut + CRM rate by 60% with MRI

- And that would reduce the local recurrence even further
CR07: Local recurrence by T3 substage

- T3a ≤1mm: 3% vs 6%
- T3b >1-5mm: 3% vs 10%
- T3c >5-15mm: 10% vs 22%
Again MRI now will help

- The greater extent through muscularis the higher the risk of CRM +
- Will tell you the risk of lymph node involvement (better predictor than direct)
CR07 Multivariate analysis

- higher tumour (T) stage ($p<0.0001$)
- nodal (N) stage ($p<0.0001$),
- an anterior component (involved: 13%; not involved: 7%, $p=0.001$).

...independently associated with an involved circumferential resection margin.
Valentini 2012.

- 5 European CRT trials were pooled to give a total of 2795 patients,

- local control was no different 93% vs 94% for cN0 versus CN1-2,

- difference in 5 year distant control was significant (p=0.009), but small 78% versus 72% respectively
Is Gina Brown any better?
Table 1.

Patient Demographics and Survival Outcomes in 111 Patients Undergoing Preoperative Therapy in the MERCURY Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>No.</th>
<th>OS</th>
<th>DFS</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Rate</td>
<td>95% CI</td>
<td>P</td>
</tr>
<tr>
<td>MRI node stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>68</td>
<td>52</td>
<td>36 to 69</td>
<td>56</td>
</tr>
<tr>
<td>N1-2</td>
<td>41</td>
<td>54</td>
<td>42 to 66</td>
<td>54</td>
</tr>
<tr>
<td>Variable</td>
<td>No.</td>
<td>OS</td>
<td>DFS</td>
<td>LR</td>
</tr>
<tr>
<td>-------------------</td>
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</tr>
<tr>
<td></td>
<td></td>
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</tr>
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<td>MRI node stage</td>
<td></td>
<td></td>
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<td>56</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>to 69</td>
<td>to 38</td>
</tr>
<tr>
<td>N1-2</td>
<td>41</td>
<td>54</td>
<td>42</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>to 66</td>
<td>to 66</td>
</tr>
</tbody>
</table>

What is the risk in this patient of N1 or N2 histology?
<table>
<thead>
<tr>
<th>Stage</th>
<th>Number</th>
<th>%</th>
<th>5-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3N0</td>
<td>10615</td>
<td>53%</td>
<td>64%</td>
</tr>
<tr>
<td>T3N1</td>
<td>5787</td>
<td>28%</td>
<td>52.4%</td>
</tr>
<tr>
<td>T3N2</td>
<td>3755</td>
<td>19%</td>
<td>37.5%</td>
</tr>
<tr>
<td></td>
<td>20157</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
New Zealand audit (Vather 2010)

<table>
<thead>
<tr>
<th>Node positive</th>
<th>895 patients</th>
<th>48%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 node</td>
<td>278</td>
<td>31%</td>
</tr>
<tr>
<td>2-3 nodes</td>
<td>272</td>
<td>30.4%</td>
</tr>
<tr>
<td>4 or more (N2)</td>
<td>345</td>
<td>38.5% (19%)</td>
</tr>
</tbody>
</table>
- 50% likely to be node negative
- 30% N1
- 20% N2
N2 associated with

- T3c
- CRM threatened
- EMVI
pT3<5mm, N any
- T2 and T3 tumours <5mm have 85-90% 5 year cancer specific survival

Poor risk T3/T4

- High risk of systemic failure for poor risk patients: T3 > 5mm,
- Combined systemic Chemotherapy followed by Chemoradiotherapy:
  - Expert Trial (phase II)
  - Expert C trial (phase II randomised)
  - BACCHUS trial (randomised phase II)
Problems with RT/CRT

- Faecal incontinence
- Urinary incontinence
- Sexual problems
- Insufficiency fractures
- Small bowel effects
- Second malignancies
What if the mesorectal fascia is not threatened

- cT3
- cN+
- Extramural vascular invasion (EMVI)
Extramural vascular invasion

- Present in 30-40% of specimens resected
- Associated with synchronous metastatic disease
- MRI detection is an independent prognostic factor for poor survival
Extramural venous invasion

With thanks to Gina Brown
Maughan NJ et al., Br J Cancer. 2007

Royal College of Pathologists' colorectal cancer minimum dataset: 5947 resected patients
n = 135. Median follow-up = 3.12 (0.9-5.7) years.

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

p = 0.0015
T3 tumours >5mm spread 54% 5 year cancer specific survival

Merkel et al 2001
Principle 1: You only need RT/CRT

- If you are going to resect the primary and metastases
- Palliation of symptoms (avoidance of stoma)
Of 15-20% presenting with synchronous metastases
If metastatic to liver

- 20% now surgically treatable at presentation
- 15-20% may become resectable
- 60% will never be resected

Rectal cancer is a heterogenous/complex entity – outcomes depend on

- Upper/middle/lower
- Anterior/posterior
- Male/female
- Resectability/CRM
- T stage and T substage
- N stage
- EMVI/LVI/PNI
- Extranodal deposits
# Rectal cancer

<table>
<thead>
<tr>
<th>LOW RISK</th>
<th>INTERMEDIATE RISK (BAD)</th>
<th>HIGH RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Define by MRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk local recurrence/ Low risk metastases T1,T2,T3a</td>
<td>Low risk local recurrence/ moderate risk metastases</td>
<td>Moderate risk of local recurrence / high risk metastases</td>
</tr>
<tr>
<td><strong>GOOD</strong> CEA &gt; 5</td>
<td></td>
<td><strong>UGLY</strong></td>
</tr>
<tr>
<td>Clinical factors</td>
<td>Obesity Male /with anterior tumours Narrow pelvis Previous pelvic surgery Large bulky tumour/circumferential tumour</td>
<td>CEA</td>
</tr>
</tbody>
</table>
Rectal Cancer : The Message

- The old paradigm simply thinking in terms of local recurrence is no longer relevant in 2013
- We need to think in terms of risk adaptive strategies, i.e. individualize
- We need to consider late effects more
- We need a more balanced/broader discussion of pros and cons of pre-operative radiotherapy
Number needed to treat (NNT)

- Local recurrence NNT for moderate risk 20-25
- ? NN harm 20-30 for second malignancy
- NN Harm 10-12 for severe G3/G4 late toxicity
What is still difficult?

- Uncertainty re clinical nodal status
- Difficulty in accurate T staging in low rectal cancer
What does a Scotsman wear under his kilt!
Conclusions

- Modern MRI can define T substage and CRM
- Individualize decisions rather than one size fits all
- Low risk of local recurrence if good quality TME
- Without RT commonest site central/anastomotic which is salvageable surgically
- Are we back to advising RT to compensate for poor surgery?
- ? If we avoid - ? more proactive surveillance?
The End