A multidisciplinary approach to locoregionally advanced rectal cancer

Radiotherapy: Which type and for whom?

Rob Glynne-Jones
Mount Vernon Cancer Centre
Disclosures: last 5 years

- **Speaker:** Roche, Merck Serono, Sanofi Aventis, Pfizer
- **Advisory Boards:** Roche, Merck Serono, Sanofi Aventis, Astra Zeneca
- **Funding to attend meetings:** Roche, Merck Serono, Sanofi Aventis
- **Research funding:** Roche, Merck Serono, Sanofi Aventis
Areas to cover

- Adjuvant radiotherapy evidence (NB mainly conventional surgery)
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- Preoperative versus postoperative
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- Allcomers or Selective approach using MRI (ie individualized)
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- SCPRT (5x5Gy) versus Chemoradiation
Areas to cover

- Adjuvant radiotherapy evidence (NB mainly conventional surgery)
- Preoperative versus postoperative
- Allcomers or Selective approach using MRI (ie individualized)
- SCPRT (5x5Gy) versus Chemoradiation (CRT)
- Postoperative Chemoradiation
Which type?
Radiotherapy evolution

.........the machines

Radium moulds
Superficial 50-150kV x-rays
1920

Orthovoltage 300kV x-rays

Megavoltage Cobalt 2MV gamma rays

Dosimetry has improved
So we can be more accurate

1990

Megavoltage Linac
4-20MV x-rays and
Many Options for External Beam

- Preoperative long course radiotherapy or long course CRT and surgery at 6-12 weeks
- Short course preoperative radiotherapy (5X5Gy) and immediate surgery
- Short course preoperative radiotherapy and delayed surgery at 6-12 weeks
- Postoperative CRT
Simultaneous integrated boost low acute toxicity
RTOG 0822

- Phase II
- 79 patients
- Deliverable
- Efficacy Results with IMRT comparable to standard RT

Hong TS et al. abstract 36 ASTRO 2014
But NB Grade $\geq 3$ late toxicity.

- Gastrointestinal 9%
- Urinary 4%
- Any 13%

Engels B et al. Radiother Oncol 2014
Additional Options for Contact or Brachytherapy or cyberknife as boost

Papillon50™:
- intraluminal rectal
- X-ray brachy 50 kv
Cyberknife Theory

- High doses of radiation (15-45 Gy) given over a shorter period of time (1-5 days)
- can more effectively destroy cancer cells when compared to conventional radiation (50 Gy) given over a 5 week period.
What type for LARC

- External beam -3D – role for IMRT unproven
What type for LARC

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- Evidence base / guidelines 45-50 Gy preop as CRT (capecitabine or 5FU)
What type for LARC

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- or 5x5Gy SCPRT
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- External beam -3D – role for IMRT unproven
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- Brachytherapy alternative for resectable cancers
What type for LARC

- External beam -3D – role for IMRT unproven
- Evidence base /guidelines 45-50Gy preop as CRT (capecitabine or 5FU)
- or 5x5Gy SCPRT
- Brachytherapy alternative for resectable cancers
- Boost not routine (unless unresectable or extends outside MRF or no surgery planned)
For whom?
“Chemoradiation is the standard treatment for locally advanced, clinically resectable (T3 and/or N+) rectal cancer.”

Bruce Minsky 2013
“With a blanket approach to SCPRT and good surgery we can virtually eliminate local recurrence in rectal cancer”

David Sebag-Montefiore 2009
There is always a tension

- Between evidence based medicine

And

- Individualized selection
Individualized Medicine in 2014

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

- most likely
- and least likely

to benefit from a particular intervention
Rectal Cancer and Radiotherapy: my mission statement

- I want the best chance of long-term survival
- Ideally avoiding permanent stoma
- Good function
- Minimal long term sequelae
- Good Quality of Life
- I want informed decision making for the patient
Patient and Oncologist preferences are different Pieterse et al., 2007
My Principles

- T4 CRT is a no brainer
- 75% of rectal cancer are T3
- All T3 are not created equal so do they all need RT?
- Preoperative SCPRT and CRT do not benefit all rectal cancer patients.
- No impact from CRT on DFS or OS
- Quality and Selection are the keys
Locally Advanced Rectal Cancer (LARC)

- Stage and rationale for CRT defined by MRI
Margin at risk disease /T4 a ‘no brainer’
CR07 Local recurrence by T3 substage

- T3a: <=1mm
- T3b: >1-5mm
- T3c: >5-15mm

N=184 for T3a
N=309 for T3b
N=150 for T3c

3% vs 6% for T3a
3% vs 10% for T3b
10% vs 22% for T3c
Extramural venous invasion

With thanks to Gina Brown
The problems

- Not all using MRI (or good quality MRI)
- Not all using pro forma for MRI
- Not all surgeons are doing high quality resections TME/APER

- Low rectal cancer T2/T4 different entity
- It is more difficult to predict levator involvement
- MRI technique/plane is more critical
- 15% LPLN for low tumours
Radiotherapy

- Is always going to be required to compensate for poor surgery
Rectal cancer is a heterogenous entity – outcomes may depend on

- Upper/middle/lower
- Anterior/ posterior
- Male/female
- Resectability/CRM
- T stage
- N stage
- EMVI/LVI/PNI
- Extranodal deposits
Relevant Endpoints in rectal cancer

- Local recurrence
- Disease-free survival
- Overall survival
- Sphincter sparing/organ sparing
- Late effects
- QOL
- Second malignancies
In decisions re SCPRT/CRT

So does the risk of local recurrence trump everything else?
Problems with SCPRT

- Faecal incontinence
- Urinary incontinence
- Sexual problems
- Insufficiency fracture
- Small bowel effects
- Second malignancies
Don’t you have to explore these with the patient to find their priorities

ie informed decision making
What is the evidence?
Pre- vs post-operative chemoradiation CAO/ARO/AIO-94

Locoregional Recurrences

Acute G3/4 adverse events
27% vs 40% (p=0.001)

Long-term G3/4 adverse events
14% vs 24% (p=0.01)

Pre- vs post-operative chemoradiation
CAO/ARO/AIO-94

Locoregional Recurrences

<table>
<thead>
<tr>
<th>Months</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>12</td>
<td>6%</td>
<td>13%</td>
</tr>
<tr>
<td>24</td>
<td>6%</td>
<td>13%</td>
</tr>
<tr>
<td>36</td>
<td>6%</td>
<td>13%</td>
</tr>
<tr>
<td>48</td>
<td>6%</td>
<td>13%</td>
</tr>
<tr>
<td>60</td>
<td>6%</td>
<td>13%</td>
</tr>
</tbody>
</table>

Acute G3/4 adverse events
27% vs 40% (p=0.001)

Long-term G3/4 adverse events
14% vs 24% (p=0.01)

There is a standard for chemoradiation

Pre- vs post-operative chemoradiation
CAO/ARO/AIO-94

Overall Survival (%)

Time (months)

No. at risk
Preop. CRT 404 351 305 268 174 67 6
Postop. CRT 395 342 295 262 172 70 6

Preoperative treatment arm, 59.9%
Postoperative treatment arm, 59.6%
P = .85
What if you decided to omit preoperative radiotherapy/chemoradiotherapy?
Impact on overall survival of 6 methods of treatment in rectal cancer pooled analysis

S alone and S+RT
### RT vs CTRT: local recurrence

<table>
<thead>
<tr>
<th></th>
<th>RT alone %</th>
<th>CTRT %</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFCD</td>
<td>16.5</td>
<td>8</td>
</tr>
<tr>
<td>EORTC 22921</td>
<td>17.1</td>
<td>8.7</td>
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</table>
**Effect of neoadjuvant chemoradiation**

<table>
<thead>
<tr>
<th>Study</th>
<th>Journal and Reference</th>
<th>Pathologic Response cT3-T4</th>
<th>RT</th>
<th>RT + 5-FU</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosset JF et al.</td>
<td>J Clin Oncol 2005 EORTC 22921</td>
<td></td>
<td>5.3%</td>
<td>13.7%</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Gerard JP et al.</td>
<td>J Clin Oncol 2006 FFCD 9203</td>
<td></td>
<td>3.6%</td>
<td>11.4%</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>
EORTC 22921 – Overall Survival
- Preop CRT rather than RT alone
- Preop CRT rather than RT alone
- Postop CRT rather than RT alone
What about SCPRT?

- Huge evidence base that SCPRT reduces local recurrence
Polish trial Bujko et al Radiother Oncol 2004

T3/T4, resectable  n=316 palpable on DRE,<75yrs

Planned operation recorded

SCPRT (5x5Gy)

Pre-op CRT 50.4 + 5FU/LV

Immediate surgery

6-8 week interval

Surgery
### Polish trial – outcomes

<table>
<thead>
<tr>
<th></th>
<th>SCPRT</th>
<th>CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute toxicity</td>
<td>3%</td>
<td>18%</td>
</tr>
<tr>
<td>Severe late toxicity</td>
<td>10%</td>
<td>7%</td>
</tr>
<tr>
<td>Sphincter sparing</td>
<td>61%</td>
<td>58%</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>9%</td>
<td>14%</td>
</tr>
<tr>
<td>DFS</td>
<td>58%</td>
<td>56%</td>
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</tbody>
</table>
Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer

K. Bujko¹, M. P. Nowacki², A. Nasierowska-Guttmejer³, W. Michalski⁴, M. Bebenek⁵ and M. Kryj⁶ for the Polish Colorectal Study Group

![Graph showing long-term survival rates for short-course radiotherapy and chemoradiation. The graph indicates that long-term outcomes are the same for both methods.](image-url)
Randomized Trial of Short-Course Radiotherapy Versus Long-Course Chemoradiation Comparing Rates of Local Recurrence in Patients With T3 Rectal Cancer: Trans-Tasman Radiation Oncology Group Trial 01.04

No benefit in LR comparing 5x5 Gy to CRT
In locally advanced rectal cancer if CRM/MRF not threatened

SCPRT = CRT??
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

Consider SCPRT

Proceed immediately to surgery

Moderate risk

Consider

High risk (locally advanced)¹

Chemoradiotherapy²

Interval before surgery to allow shrinkage and response

Surgery

See algorithm on “Post-operative care”
NICE GUIDANCE from MRI

High-risk locally advanced

a) a threatened resection margin,
b) more than 5mm - 15mm (cT3c and cT3d) extension,
c) more than 4 involved nodes (cN2), or
d) the presence of macroscopic extramural vascular invasion;

CRT recommended
NICE GUIDANCE from MRI

Moderate-risk locally advanced

a) up to 5mm (cT3a and cT3b) extension into the muscularis propria, or

b) up to 4 involved nodes (cN1).

SCPRT or CRT
STOCKHOLM III

Resectable Rectal AdenoCa 303

Randomise

25 Gy in 5 F → Surgery

25 Gy in 5 F

50 Gy in 25 F

Surgery (delayed)

Surgery (delayed)

Primary endpoint: sphincter preservation rate

Pettersson et al BJS 2010
RAPIDO Trial

N = 885 patients

T4 EMVI + N2 CRM + RANDOMIZATION

SCPRT 5X5 GY

Standard CRT

CapOx + 6

Primary endpoint 3 year DFS

Capcitabine: 825 mg/m2
Oxaliplatin: 130 mg/m2
How do we decide?
Alan Sokal 1996

- "Transgressing the Boundaries: Towards a Transformative Hermeneutics of Quantum Gravity",

- proposed that quantum gravity is a social and linguistic construct.
The value of radiotherapy

- Varies according to the historical context
The value of radiotherapy

- Varies according to the historical context
- and the surgeons skill
Total Mesorectal Excision

Optimal TME

Moderate, irregularity of mesorectal surface

Poor TME
### CRM associations with plane of surgery

<table>
<thead>
<tr>
<th>Plane of surgery</th>
<th>Mesorectal</th>
<th>Intra-mesorectal</th>
<th>Muscularis propria</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRM +ve rate</td>
<td>9%</td>
<td>12%</td>
<td>19%</td>
</tr>
<tr>
<td>Stage I</td>
<td>29%</td>
<td>24%</td>
<td>27%</td>
</tr>
<tr>
<td>Stage II</td>
<td>27%</td>
<td>32%</td>
<td>30%</td>
</tr>
<tr>
<td>Stage III</td>
<td>44%</td>
<td>43%</td>
<td>41%</td>
</tr>
</tbody>
</table>

With thanks to Phil Quirke
# TME Northern Europe: Good quality mesorectal plane: no RT

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligible</th>
<th>Good Quality Mesorectal</th>
<th>Local Recurrence</th>
<th>Actuarial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swedish Rectal Cancer Trial 1997 (574)</td>
<td>T any, N any</td>
<td>&lt;10%</td>
<td>150/557, 27%</td>
<td>&gt;30%</td>
</tr>
<tr>
<td>CR07 overall (592) Quirke 2009</td>
<td>T any, N any</td>
<td>51%</td>
<td>59/592, 10%</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% (MRI not routinely used)</td>
<td>27/301, 9%</td>
<td>7% at 3 years</td>
</tr>
<tr>
<td>Mercury* (122) Taylor 2011</td>
<td>T3a/b, N any, crm-</td>
<td>70%</td>
<td>4/122, 3%</td>
<td>3.3% at 5 years</td>
</tr>
</tbody>
</table>

* NB MRI directed
NNT in rectal cancer

- Local recurrence NNT for moderate risk 20-25
- NN Harm 10-12 for severe G3/G4 late toxicity
- NN Harm 20 for second malignancy
# Randomised trials SCPRT

<table>
<thead>
<tr>
<th>Trial</th>
<th>MRI mandated</th>
<th>EUS mandated</th>
<th>TME mandated</th>
<th>Good Quality TME</th>
<th>Median no of nodes resected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swedish Rectal</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>?No</td>
<td>Not stated</td>
</tr>
<tr>
<td>Dutch TME</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>50%</td>
<td>7</td>
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<tr>
<td>Polish</td>
<td>No</td>
<td>No</td>
<td>Yes?</td>
<td>?</td>
<td>9</td>
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<tr>
<td>CR07</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>50%</td>
<td>11</td>
</tr>
<tr>
<td>TROG-0104</td>
<td>If US not possible</td>
<td>Yes</td>
<td>No</td>
<td>?</td>
<td>Not stated</td>
</tr>
<tr>
<td>Trial</td>
<td>MRI mandated</td>
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<td>TME</td>
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<tr>
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<td>-----</td>
<td>------------------</td>
<td>----------------------------</td>
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<tr>
<td>German (Sauer 2004)</td>
<td>No</td>
<td>Yes</td>
<td>?</td>
<td>?</td>
<td>Collected but not stated</td>
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<tr>
<td>EORTC 22921</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>7 after CRT</td>
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<td>FFCD 9203</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Not stated</td>
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<td>NSABP R03</td>
<td>No</td>
<td>?</td>
<td>No</td>
<td>No</td>
<td>Not stated</td>
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<tr>
<td>Polish</td>
<td>No</td>
<td>No</td>
<td>?</td>
<td>?No</td>
<td>8</td>
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<tr>
<td>TROG-0104</td>
<td>some</td>
<td>Yes</td>
<td>?</td>
<td>?</td>
<td>Not stated</td>
</tr>
</tbody>
</table>
How can I use these trials data as my evidence base and relate the data to my practice in 2014

When ....

No MRI/poor TME/ few nodes
Significant number elderly > 70
For individualized therapy we need

- Accurate Clinical staging (TNM) - precise risks for local recurrence and metastases.
For individualized therapy we need

- Accurate Clinical staging (TNM) - precise risks for local recurrence and metastases.
- Other imaging characteristics (EMVI+, CRM)
For individualized therapy we need

- Accurate Clinical staging (TNM) - precise risks for local recurrence and metastases.
- Other imaging characteristics (EMVI+, CRM)
- Pathology (adenoca, mucinous, signet ring etc)
For individualized therapy we need

- Accurate Clinical staging (TNM) - precise risks for local recurrence and metastases.
- Other imaging characteristics (EMVI+, CRM)
- Pathology (adenoca, mucinous, signet ring etc)
- The associated clinical characteristics which also define risks and different subpopulations (frailty/morbidity site etc…
For individualized therapy we need

- Accurate Clinical staging (TNM) - precise risks for local recurrence and metastases.
- Other imaging characteristics (EMVI+, CRM)
- Pathology (adenoca, mucinous, signet ring etc)
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- The molecular pathways underpinning the disease
For individualized therapy we need

- Accurate Clinical staging (TNM) - precise risks for local recurrence and metastases.
- Other imaging characteristics (EMVI+, CRM)
- Pathology (adenocarcinoma, mucinous, signet ring etc)
- The associated clinical characteristics which also define risks and different subpopulations (frailty/morbidity site etc…
- The molecular pathways underpinning the disease
- Patient preferences
- And…. 
For individualized therapy we need

- The input from all members of the MDT
- And...
For individualized therapy we need

- The input from all members of the MDT
- And…
- The wishes and input of an informed patient for decision making
Pre-operative radiotherapy algorithm
NICE guidelines 2011

Pelvic MRI

Risk of local recurrence

Low risk

Moderate risk

Consider
Consider

SCPRT

CRT

High risk

Surgery
Pre-operative radiotherapy algorithm
My guidelines 2014

Pelvic MRI

Risk of local recurrence

Low risk

Moderate risk

Consider

Consider

SCPRT

CRT

Threatened CRM/T4
Low anterior tumours

Surgery
Pre-operative radiotherapy algorithm
My guidelines 2014

Pelvic MRI

Risk of local recurrence

Low risk

Mid rectum EMVI (T3c), T3d Clear cN2

Threatened CRM/T4
Low anterior tumours

SCPRT
CRT

Surgery
Pre-operative radiotherapy algorithm
My guidelines 2014

Pelvic MRI

Risk of local recurrence

- T2, Mid rectum T3a,T3b, T3c cN1,?cN2
- Mid rectum EMVI (T3c),T3d Clear cN2
- Threatened CRM/T4 Low anterior tumours

SCPRT

CRT

Surgery
Postoperative CRT

• CRM +

If poor mesorectal quality
• Gross EMVI
• pN2
• Extracapsular spread
• Extranodal deposits
Conclusions: Radiation has a role in Unresectable cancer

For improving resectability
Conclusions: Radiation has a role in Resectable LARC

- Reducing recurrence in high risk but not low risk
- Both SCPRT and pre-op CRT are acceptable, but not necessary for all patients.
- Patients need to be informed and part of the decision making
- Each unit needs to audit results and feedback loop
The End