Rectal cancer – treatment options and clinical trials

Matt Walker
Nick Battersby
Diana Tait
Matt – *Deferral of Surgery experience*

- Diagnosed in April 2012 at the age of 44 – married with two young children.
- Stage 3 with 4 cm tumour, located 4 cm up the rectum. T3N?M0.
- Offered immediate surgery, with permanent stoma, or chemo/radiotherapy then surgery. Opted for chemo/radio first.
- 3 months chemo – Capecitabine plus Oxaliplatin.
- Radiotherapy - 25 sessions IMRT - Intensity Modulated Radiotherapy, plus Capecitabine.
- 3 months later – Colonoscopy shows no remaining tumour. CT shows no spread, MRI shows only scar tissue.
- Referred to the Royal Marsden *Deferral of Surgery Trial* in January 2013, under Dr. Tait and Dr. Brown.
- 3 months more Capecitabine.
- On the Trial for 3 years to date – with very frequent CT’s, MRI’s, colonoscopies, PET scans, CEA blood tests, and digital rectal examinations to detect any signs of recurrence.
Matt – Deferral of Surgery experience

• Why am I on the trial?
  ✓ Close monitoring to identify recurrence early
  ✓ A chance to help future patients avoid potentially unnecessary surgery
  ✓ Nervous of major surgery and a permanent stoma, which I have avoided so far!

• Risks/downsides
  ✦ Tumour has not been removed. Risk of recurrence not identified? Should be mitigated by frequent checks
  ✦ Scan anxiety? Would experience regardless of the Trial.

• Personal Conclusion – strongly recommend to investigate Deferral of Surgery as an option.
Walking together for a future beyond cancer.
#MarsdenMarch
Rectal Cancer
Treatment Options & Clinical Trials

Nick Battersby
Surgical Registrar
Pelican Research Fellow – Basingstoke & RMH
Ben, 39 – locally advanced low rectal cancer

6 weeks chemo-radiation →

‘complete response!’...

Planned...APR (colostomy), followed by 4 months chemotherapy

“The hard part is knowing that hundreds of people out there (in Brazil, Holland and elsewhere) were in my position and chose to defer surgery and are now disease-free and bag-free. Those people exist and I envy them.”
Outline

AIM

• Raise awareness about Deferral of Surgery

• Outline when this might be suitable
Improved Rectal Cancer Survival

% 10 year Survival in UK

- 1970s
- 1980s
- 1990s
- 2000s
- 2010s

Improved Rectal Cancer Survival
Rectal Cancer - Background

Side effects...

TME
Total Mesorectal Excision
Rectal Cancer - Background

Affect of Bowel Function on Quality of Life?

Also consider...
1) Stoma
2) Side Effects
3) Self-awareness body image
Rectal Cancer - Background

Improve outcomes through selection?
Rectal Cancer - Background

Expect fewer symptoms?

....or with no excision! (Deferral of Surgery)

local excision

Expect fewer symptoms?
Outline

• Background

• Rectal Preserving Management
  – Selection by Stage
  – Deferral of Surgery
    • Rationale
    • Identifying who’s suitable
    • Problems
    • Evidence base
Rectum Preservation – who is eligible?

- 29,000 colon cancers in the UK/year
- ~30% rectal cancers, 12,000/yr

Bowel Cancer ≈ 30% Rectal
Rectum Preserving Management

**DUKES A**  
STAGE 1 (I)*  
T1 OR T2 N0 M0

**DUKES B**  
STAGE 2 (II)  
T3 OR T4 N0 M0

**DUKES C**  
STAGE 3 (III)  
ANY T N1 or N2 M0

**DUKES D**  
STAGE 4 (IV)  
ANY T ANY N M1

**Tumour has invaded several layers of bowel but has not spread outside the wall.**

**tissue, but has not spread to the lymph nodes.**

**where it started in the colon or rectum, to other organs often the liver and lung.**

(© Christian Josef – ch.josef@gmx.de)
Rectum Preservation – polyp (no cancer)

- Remove polyp endoscopically
- Pathology – complete removal?
- Monitor / no further surgery
Rectum Preservation – early cancer

- Stage
- Discuss at MDT + Patient
- Node Involvement ~ 20% risk
Rectum Preservation – early cancer

- Mainstay - TME surgery
- TME Vs Local excision +/- (C)RT

...STAR-TREK trial

Trade off – overtreatment V uncertainty
Rectum Preservation – locally advanced

**DUKES B**
- STAGE 2 (II)
  - T3 OR T4 NO M0

**DUKES C**
- STAGE 3 (III)
  - ANY T N1 or N2 M0

**Stage tumour – MRI**

Cancer has grown through the muscle layer of the bowel or rectum and invaded nearby tissue, but has not spread to the lymph nodes.

Cancer has spread to nearby lymph nodes, but not to other parts of the body.
Complete response

- 19-50% chance?

Chances altered by: CRT-surgery timing, stage, tumour site, treatment
Watchful waiting?

São Paulo, Brazil - Habr-Gama & Perez

Spread to...

• UK: Deferral of Surgery
• Dutch: Watch and Wait
• USA: Non-Operative Management
Deferral of Surgery – Concern I

DOES RADIOLOGY REFLECT PATHOLOGY?

? =

The challenge of identifying and monitoring responders
Tumor Regression Grading After Preoperative Chemoradiotherapy for Locally Advanced Rectal Carcinoma Revisited: Updated Results of the CAO/ARO/AIO-94 Trial


Disease-Free Survival (probability)

Time (months)

No. at risk

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P = .008

Fokas et al, 2014, JCO
Pathology $\approx$ MRI for predicting survival

![Graphs showing disease-free survival over time for ypT and mrTRG, with favorable and unfavorable categories, and p-values for statistical significance.](image)
Deferral of Surgery – Concern II

What if the tumour ‘regrows’?
Can a ‘regrowth’ be completely excised?

Still relatively little follow up data? Better outcomes
183 rectal cancer pts
cT2-4, non-metastatic
CRT 50.4Gy + 5FU

----------------------------------

90 pts: cCR at 8wks

Med fup 60 mos (12-233)

Lost to fup:
14 (15%) at 3 yrs
25 (27%) at 5 yrs

28 local or pelvic recurrences
25 salvage surgery
1 salvage brachy
2 unresectable

4 LR after salvage

6 pts LOCAL FAILURE

Habr-Gama et al, IJROBP 2014.
Deferral of Surgery – Which patient???

The anxiety of regrowth?

Discuss early - at time of CRT decision

MRI suggests ‘good response’ – re-explore deferral of surgery
Key Messages

• Great potential for organ preservation in rectal cancer
• If you need chemoradiotherapy
  – Repeat MRI is encouraged
  – Re-assess response
• Good response?
  ?? Non-operative management
Key Messages

EARLY DAYS

We need more evidence about....

• Case selection
• Safety
• Best way to achieve a complete response
• How best to follow patients up
Beating Bowel Cancer – Patient Day

Royal College of Surgeon
April 16th 2015

Dr Diana Tait
Consultant Clinical Oncologist
Royal Marsden Hospital

Mr Nicky Battersby
Pelican Surgical Research Fellow
Pelican Cancer Foundation
RT Responsiveness
Timing after CRT? When is maximum response reached?

- **Baseline**: mrT4
- **6 weeks**: mrT3b
- **12 weeks**: mrT2

*Final Pathology: ypT2N0*
Watch & Wait Philosophy

AVOID SURGERY

MAINTAIN SPHINCTER & FUNCTION

Local Control

Equivalent Survival

Philosophy of Anal Cancer Management
Decision Making .......
Strategy and Decision Making

AGE

PERFORMANCE STATUS

PATIENT WISHES
Is that agist?
30-day post-operative mortality in relation to Age

< 50 | 51-60 | 61-70 | 71-80 | >80

- Day post-operative mortality decreases as age decreases.
30-day post-operative mortality in relation to co-morbidities
MRI Tumour Regression Grading

MRI After Treatment of Locally Advanced Rectal Cancer: How to report Tumor Response - The MERCURY Experience (AJR 199: 2012)
DEFERRAL OF SURGERY STUDY

(Watch & Wait study)

Dr Diana Tait
Professor Gina Brown
Professor Bill Heald
Dr Sue Chua
Dr Andy Wotherspoon
Dr Irene Chong
Mr Nick Battersby

Referring Clinicians
Patients
Fig. 1 ‘DEFERRAL OF SURGERY’ TRIAL OUTLINE

**Screening Log** – capture reasons why patients refuse to enter study

MRI at 4-8 week post pre-operative therapy (CRT):
- mTRG 1-3
- APE considered likely or likely ultralow Anterior Resection
- Resectable disease
- No metastatic disease
- Patient fit for surgery

**Consideration of Trial and Consent by 10 weeks after CRT**

Further MRI and FDG-PET before 12 wks post CRT)
- mTRG1-2 to confirm eligibility
- PET-CT showing absence of definite disease activity
- Adjuvant Chemotherapy to start by 12 weeks post CRT (for node positive patients)

mrTRG 1-2 & no mets
- Register and Follow up as per protocol (see 7.1 Follow-Up Schedule)

mrTRG 3 – 5 or mets
- Eligibility failures
- Refer for Surgery

Re-growth suggested by either Flexible Sigmoidoscopy, MRI, PET-CT or clinical assessment/CEA

MDT Review of MRI/PET-CT and clinical assessment/CEA

Biopsy

Biopsy positive
- Refer for surgery

Follow-up as per protocol (7.2 Post Surgical FU Schedule)

Patient refuses surgery / Patient not fit for surgery
- Patient withdrawn

Patient refused surgery / Patient not fit for surgery
- Continue follow up as per protocol (see 7.1 Follow-Up Schedule)

Pelvic/distant relapse suspected

Pelvic/distant relapse discussed at MDT

Curative
- Further Treatment

Palliative
- End of Study
### Follow Up Protocol in Deferral of Surgery

<table>
<thead>
<tr>
<th>Timeline from end of CRT (A and B)</th>
<th>Toxicity Scales</th>
<th>DRE</th>
<th>CEA</th>
<th>Scans</th>
<th>Endoscopy</th>
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<tbody>
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<td>4-8 weeks* Inform / consent and register</td>
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<td>DRE</td>
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<td>MRI</td>
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<td>8-12 weeks*</td>
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<td>MRI, FDG-PET</td>
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<td>CEA</td>
<td>MRI</td>
<td>Flex Sig</td>
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<td>DRE</td>
<td>CEA</td>
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</table>

DRE refers to “digital rectal examination”. Flex Sig refers to “Flexible Sigmoidoscopy”. CEA refers to “CarcinoEmbryonic Antigen”.

Visit windows * +/- 1 week; ** +/- 1 month; *** +/- 2 months; **** +/- 3 months

A, B refer to patient cohorts
THE BIOPROBE

PORTABLE
QUICK
CHEAP

Operator Dependent
Documentation Dependent
Location Dependent
What should you do with an apparent complete responder?

- complete response
- when should you biopsy?
- how predictive is a small sample of the scar for tumour status?
Recruitment by time

![Graph showing recruitment by time with X-axis representing dates from 2006 to 2016 and Y-axis representing numbers. There are two lines: one for N Eligible and one for N Ineligible. The N Eligible line starts lower and then rises sharply, while the N Ineligible line starts higher and rises more gradually.]
Deferral - Statistics

- Sample size 59

1. We wish to show that the % of pts that can successfully omit surgery is at least 10%, with a true expected rate to be at least 25%

2. 2 year failure rate is assumed to be no more than 5%

3. Failure rate of 15% or more would be considered unacceptable

4. To be judged a success overall the trial must have no more than 4 pts with LF and at least 11 safely omitting surgery
Local Regrowth

- 12 pts had a regrowth
- 10 underwent surgery (R0)
- 2 did not have surgery
  - 1 – pt refusal
  - 1 – distant mets (lung)
OPTIMAL SURGERY

RO Resection

Functional Disturbance FDo
Summary

❖ Trial stopping rules
  • $\leq 48/59$ pts to have LR by 2 years and
  • $\leq 4/59$ pts to have LF by 2 yrs

❖ To date
  • 12/47 LR by 2 yrs
  • 0/47 LF by 2 yrs
To evaluate mrTRG as an imaging biomarker for the stratified management of patients with locally advanced rectal carcinoma

**RATIONALE FOR FEASIBILITY STUDY**

- To assess patient recruitment rate
  - Target: 6/month during last 4 months of recruitment
- To assess safety of offering consolidation chemotherapy to ‘poor responders’ and deferral of surgery to ‘good responders’
Patient Pathway Control Arm

- Post-CRT MRI within 4-6 weeks (no later than 10) from CRT completion
  - mrTRG not reported

- Surgery within 6-12 weeks from CRT completion:
  - Surgical Morbidity: 6 weeks post surgery and 12 months

- Chemotherapy 24 weeks:
  - Toxicity: end of each cycle and residual toxicity at 12 months

- Annual follow up for 3 years
- QoL: Registration, 12 months, 36-months
Intervention Arm – mrTRG I/II Good Responders

- Post-CRT MRI within 4-6 weeks (no later than 10) from CRT completion.
- mrTRG I/II
- 24 weeks of chemotherapy to commence within 12 weeks of CRT:
  - Toxicity: end of each cycle and residual toxicity at 12 months
- 5 year Surveillance Schedule
- Suspected Regrowth Pathway
- QoL: Registration, 12, 36 and 60 months
Intervention Arm – mrTRG III-V Poor Responders

- Post-CRT MRI within 4-6 weeks (no later than 10) from CRT completion
  - mrTRG reported

- 12 weeks of chemotherapy to commence within 12 weeks of CRT:
  - Toxicity: end of each treatment cycle

- REPEAT MRI
5 year Surveillance Schedule

**MRI**
- **Year 1:** 6, 9, 12 mths
- **Years 2 & 3:** 6 monthly
- **Years 4 & 5:** annually

**CT**
- 12, 24 & 36 months

**Endoscopy**
- **Year 1:** 6, 9, 12 mths
- **Year 2:** 6 monthly
- **Years 3-5:** annually
Our Inspiration