**PRESERVE** - Pan London Early Rectal Cancer Meeting

**The Royal Marsden**
NHS Foundation Trust

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**PRE**-therapeutic MRI assessment of Early Stage Rectal Cancer and significant Rectal Polyps to avoid major resectional surgery: A new approach to the management of Early stage rectal cancer

Annabel Shaw
Pan London Clinical Research Fellow

Pan London Early Rectal Cancer Meeting

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**Investigators and Collaborators**

<table>
<thead>
<tr>
<th>Name</th>
<th>Role</th>
<th>Department</th>
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<tbody>
<tr>
<td>Gina Brown</td>
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<td>Radiology</td>
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<tr>
<td>Annabel Shaw</td>
<td>Clinical Research Fellow</td>
<td>Surgery</td>
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<td>Ian Swift</td>
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<td>Must Abdul</td>
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<td>David Cunningham</td>
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<td>Paris Tekkis</td>
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<td>Hana Yal</td>
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<td>James Kieron</td>
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<td>Kerstin Munakata</td>
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<td>Prabdeep Bhainswal</td>
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<td>Sarah Mills</td>
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<td>Tony Miles</td>
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<td>Euan McNeil</td>
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<td>Helen Jones</td>
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<td>Andrea Tijssen</td>
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<td>Andreas Farrow</td>
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<td>Anna Frischkeutsch</td>
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<td>Monica Forlino</td>
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<td>Robert Goldblin</td>
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<td>Katherine Van Logs</td>
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<td>Stefania Bolyaiukova</td>
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<td>Paul O'Trude</td>
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<tr>
<td>Ken Webster</td>
<td>Patient Representative</td>
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RMH
Portsmouth
Oxford
Stoke
Imperial
Colchester

Croydon
West Middlesbore
Liverpool
Basingstoke
Chelsea & Westminster
Brighton & Sussex
Current problem

Current pathway following diagnosis of a rectal SPECC does not involve pre-op staging

Cancerous polyps that are removed endoscopically are mostly subjected to TME surgery afterwards

Lack of adequate surveillance following organ preservation

MINSTREL Update

MINSTREL – complete.
Prospective trial to validate the MRI reporting tool for ERC.

<table>
<thead>
<tr>
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<th>Pathology – suitable for LE</th>
<th>Pathology – not suitable for LE</th>
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<tbody>
<tr>
<td>MRI – suitable for LE</td>
<td>43</td>
<td>2</td>
</tr>
<tr>
<td>MRI – not suitable for LE</td>
<td>5</td>
<td>2</td>
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</table>

45/52 were correctly staged – 87%
PRESERVE

Multi-centred prospective randomised trial to increase rates of successful local excision of early rectal cancer.

Primary Objective

To demonstrate an improvement in rectal preservation rates in patients with pT1 and pT2 tumours.

Feasibility Study

Secondary Objectives

- To determine the safety of early rectal cancer MRI assessment by measuring the accuracy by comparing MRI T-staging with pathology
- Report to rates of missed lesions suitable for local excision
- Report on rates of lesions not suitable for local excision
- Compare costs to the NHS / other healthcare systems of major surgery versus local excision for pT1 / pT2 early rectal cancer
- Measure the impacts of local excision and rectal preservation on patient-reported QOL measures
- Measure relapse-free and survival rates and 1 year post-surgery / local excision
- Assess quality of local excision surgery
- Assess willingness to be randomised
Inclusion / Exclusion Criteria

Inclusion – based upon MRI features:
- Absence of EMVI
- T3b tumour or less on initial assessment
- CRM clear >1mm
- Significant polyp or rectal lesion as defined on MRI / endoscopy
- be over 18 years of age
- Of adequate performance status to be able to undergo surgery if necessary

Exclusion:
- require neoadjuvant therapy for MRI staged advanced rectal cancer
- have metastatic disease
- have a second malignancy where there is <95% certainty of survival from the treated disease
- are unable to consent or withhold consent
- Biopsy-proven malignancy which is not adenocarcinoma

MDT confirms significant polyp / ERC
£
T3b not requiring CRT
Rectal SPECC – ERC identified at endoscopy
MRI assessment for LE vs radical surgery
MR staged >1mm muscularis preserved & technically feasible to perform local excision
Technically feasible to do LE but MR staged <1mm muscularis preserved
Pathology Assessment ‡ (with confirmation of adenocarcinoma)

Local Excision
- Low Risk*
- Moderate Risk**
- High Risk***

RT & Surveillance

TME Surgery
Pathology Assessment ‡ (with confirmation of adenocarcinoma)

Surveillance RT &

Randomisation†

Clinic visit to discuss outcome of ERC

One Year Follow-up (from date of surgery)
QOL Assessment of primary endpoint at 1 year post-date of surgery of last patient recruited

Three monthly follow-up (from date of surgery)
Six monthly follow-up (from date of surgery)
Six monthly follow-up (from date of surgery)
Six monthly follow-up (from date of surgery)
Six monthly follow-up (from date of surgery)
The Royal Marsden
PRESERVE – Pan London Early Rectal Cancer Meeting

11/22/18

MR staged >1mm muscularis preserved & technically feasible to perform local excision

Pathology Assessment + (with confirmation of adenocarcinoma)

Low Risk**

Moderate Risk***

HIGH RISK

Randomisation †

Surgery

Surgery

Surgery

Six monthly follow-up (from date of surgery)

Three monthly follow-up (from date of surgery)

One Year Follow-up (from date of surgery)

QOL

Assessment of primary endpoint at 1 year post-date of surgery of last patient recruited

ACPGBI guidelines for management of ERC post-local excision

(a) Scoring the risk of residual disease following resection of a malignant polyp.

(b) Risk stratification based on sum of risk factors (Williams, Pullan, Hill, Horgan, Salmo, Buchanan, Rasheed, McGee, Haboubi, et al. 2013)

Criteria are based on histological description of endoscopically resected malignant polyp weighted for prognostic significance of each risk factor. When more than one risk factor is present, the degree of risk is added together to give a total risk score.

* Score 0 on PRESERVE Risk Score
** Score 1 – 2 on PRESERVE Risk Score
*** Score ³ 3 on PRESERVE Risk Score
† If any patient declines randomisation, then they will follow a surveillance only arm (as per TME surgery follow-up)
‡ If any patient is found to have benign disease / malignancies other than adenocarcinoma, they will follow sentinel surveillance

Reasons for unsuitability for LE:

1. Anteriorly positioned & above the peritoneal reflection
2. Too low for instrument access
3. Too large
4. Other
### PRESERVE Risk Score

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Risk Score</th>
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<tbody>
<tr>
<td>Margin clear - &gt;0mm from the diathermy margin</td>
<td>0</td>
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<tr>
<td>Margin positive - 0mm to the diathermy margin</td>
<td>1</td>
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<tr>
<td>Margin positive/or un-assessable due to piecemeal removal - 0mm to the</td>
<td>3</td>
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<tr>
<td>tumour margin</td>
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<tr>
<td>Sm1/2 or Haggitt 1/2</td>
<td>0</td>
</tr>
<tr>
<td>Sm3/ Haggitt 3/4</td>
<td>1</td>
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<tr>
<td>Poorly differentiated / mucinous</td>
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<tr>
<td>Tumour budding</td>
<td>1</td>
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<tr>
<td>LVI</td>
<td>1</td>
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<tr>
<td>T2</td>
<td>1</td>
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<td>Size of tumour &gt;4cm</td>
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<table>
<thead>
<tr>
<th>Total Score</th>
<th>Grade of Risk</th>
<th>Recommended Treatment</th>
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<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>Surveillance only</td>
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<tr>
<td>1 – 2</td>
<td>Moderate</td>
<td>Randomisation between surveillance or</td>
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<tr>
<td></td>
<td></td>
<td>radiotherapy</td>
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<tr>
<td>≥3</td>
<td>High</td>
<td>Radiotherapy and surveillance</td>
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</table>

Criteria are based on histological description of locally removed rectal lesions, weighted for prognostic significance of each risk factor. Where more than one risk factor is present, the degree of risk is added together to give a total risk score.

### Feasibility Statistical Design

- Sample size 146
- Single-stage Ahern design
- Show that >17% pT1/pT2 patients undergo local excision (assuming true rate is 35%)
- Total 51 patients with pT1/T2 (90% power, one-sided alpha 0.05)
- Expected 18/51 (35%) undergo LE

<table>
<thead>
<tr>
<th>Registered to trial</th>
<th>n = 146</th>
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<tbody>
<tr>
<td>LE</td>
<td>n = 18</td>
</tr>
<tr>
<td>pT1/T2</td>
<td>n = 18</td>
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<tr>
<td>pT3+</td>
<td>n = 0</td>
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<tr>
<td>pT1/T2</td>
<td>n = 33</td>
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<td>pT3+</td>
<td>n = 80</td>
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<td>No surgery /</td>
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<tr>
<td>withdrawn</td>
<td>n = 15</td>
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<tr>
<td>Low risk</td>
<td>n = 4</td>
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<tr>
<td>Medium risk</td>
<td>n = 7</td>
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<tr>
<td>High risk</td>
<td>n = 7</td>
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n = 146
Patient-reported Quality of Life Assessment Measures

- LARS (low anterior resection syndrome) score
- EQ-5D
- Stoma Care Quality of Life Questionnaire
- Sexual Function Questionnaires:
  - IIEF-5 Questionnaire
  - FSFI

The QOL forms will be completed at the following times during the trial:
- At PRESERVE registration
- 6 months following surgery
- 1 year following surgery
- 3 years following surgery
- 5 years following surgery
- 10 years following surgery

Safety – QA / QC

Imaging

Surgery

Pathology

Safety monitoring throughout the trial:
- TMG – 3 month intervals
- IDMC – annually

TMG – minimum of 1 x TEM surgeon, 1 x pathologist, CI
Radiology Assessment

All trial radiologists will require accreditation in ERC staging

QA:
QA of ERC staging will be ensured by training and pre-trial testing of the radiology PIs in staging ERC

Workshops / Training:
A prerequisite to opening a site is that the allocated radiologist is able to perform MRI staging of early rectal cancers using the new MRI scoring system and achieve a high Kappa agreement (k≥0.7). Only radiologists that have passed this threshold will be eligible to report the MRIs for the PRESERVE trial.
Pre-trial testing and provision of training materials for those who require it

Standardisation:
Scans will be standardised and reporting criteria will be pre-defined
The trial radiologists will report depth of tumour invasion into the bowel wall, the degree of preservation of the submucosa and muscularis propria layers.

If an MRI has been reported by another radiologist then it must be re-reported by the trained radiologist and this report must be discussed at MDT prior to surgery
The planned surgical plane required to achieve total removal with clear margins will be recommended using the MRI.

Surgical Techniques

Standardisation:
All surgical and endoscopic PIs at sites will demonstrate proof competency in local excision techniques by submission and audit of histopathology reports for central review prior to site opening and during the trial.

Training:
If there are any concerns regarding the operative ability / specimen quality, then there will be a requirement to undergo further training prior to site opening.

QA:
A minimum of 5 consecutive specimens from each surgeon at participating sites to be audited by local histopathology CRFs and photography of specimens for quality of excision and specimen orientation.
Assessment of pre-trial specimens will be used to determine whether surgeons / endoscopists are exciting the lesions completely, with clear margins, and in an en bloc manner.
Pathology

Standardisation:
Histopathology assessment will be carried out according to the Royal College of Pathologists guidelines for reporting of colorectal cancers and local excision specimens

PRESERVE Risk Score – to determine post-operative pathway

Phase II Trial

Primary Endpoint
To demonstrate 3-year organ preservation rates of >17% whilst ruling out an unsalvageable local recurrence rate of >5%.

Secondary Endpoints
- To measure organ preservation rates in T1/2 rectal cancers, measured as local excision only, with no major abdominal resection required overall and by randomisation arm.
- To measure relapse-free survival, defined as no evidence of recurrence relapse of colorectal cancer, or death from any cause at 1, 3, 5 and 10 years of follow-up in PRESERVE.
- To measure overall survival, defined as rate of survival 1, 3, 5 and 10 years following surgery in PRESERVE.
- To measure the quality of surgery, assessed by the pathologist using a proforma. Surgical resection margins and complete specimens will be assessed.
- To measure stoma rates, at 1, 3, 5 and 10 years of follow-up in PRESERVE.
- To measure Quality of life impact of local excision and rectal preservation assessed by the LARS scoring system and the EQ-5D and Stoma Care Quality of Life questionnaires at 3 years post-surgery.
- To measure the impact on sexual function of local excision and rectal preservation (in patients volunteering to complete sexual function questionnaires) at 3 years post-surgery.
- To identify radiological and histopathological biomarkers of relapse free survival.
- To measure cost savings to the NHS/other healthcare systems compared to the current costs of major surgery for ERC in pT1/T2 ERC.
Cost Per Patient

Based upon coding from one participating hospital
- TEM vs AR, 6/12 stoma

Saving per patient recruited into trial:

£13,532.40

PRESERVE – current status

Recruitment over 36 months

Sponsorship in Principle approved

Aim for recruitment to start 2018/2019

Funded by Pelican Cancer Foundation Grant

Sponsored by the Pan London Cancer Research Fellowship

Supported by Biomedical Research Centres, RM Partners, UCLH Cancer Collaborative, and South East London Accountable Cancer Network (SEL ACN)
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