NCRN Clinical trials Meeting
24th March 2010

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PulMiCC: A Randomised trial of Pulmonary Metastasectomy in Colorectal Cancer

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Royal Brompton & Harefield NHS Foundation Trust
Aim of study

- Feasibility of enrolling patients into a randomised trial comparing pulmonary metastasectomy to no surgery
- If feasibility demonstrated - conduct a larger randomised trial of survival

Background (1)

- Colorectal cancer is one of the three commonest solid tumours
- >37,000 cases diagnosed in 2006
- Use of CT has led to earlier diagnosis of isolated or sub-clinical lung nodules
- Widespread adoption of pulmonary metastasectomy in selected cases
- Approx 300 operations in UK per year
- 5yr survival data of up to 50% (Pfannschmidt 2007)
- No matched data for pts who did not have surgery (Aberg 1980)
- Post-op complications not trivial: pleural effusion, respiratory insufficiency, wound abscesses
- Quality of life & effects on lung function not reported
- Need for RCT to confirm improved survival
Background (2)

- Survey on surgeons practice revealed widespread variation in types of patients considered
- Related to lack of good quality evidence
- Practice relates to known favourable or unfavourable prognostic criteria
  - Number of metastases
  - Length of time to become evident radiologically (eg rare to operate when multiple metastases apparent at time of surgery for 1st colorectal cancer but solitary nodule appearing after long interval will be operated on)
  - Difficult to know about strategy for pts inbetween these extremes
- Trials with very different treatments may be difficult eg surgery vs no surgery
  - Participants may have strong preference
  - Potential bias if one option explained before other
- PulMICC designed to overcome these potential difficulties
  - 2 stage consent process
  - Trial specific DVDs for pts & those consenting pts

Basic premise

<table>
<thead>
<tr>
<th>Feature &amp; its relationship to survival</th>
<th>Favourable</th>
<th>Intermediate</th>
<th>Adverse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time interval since primary resection</td>
<td>&gt;36 m</td>
<td>12-36m</td>
<td>Synchronous to 12m</td>
</tr>
<tr>
<td>Number of metastases</td>
<td>1</td>
<td>2-5</td>
<td>&gt;5</td>
</tr>
<tr>
<td>Laterality</td>
<td>unilateral</td>
<td>bilateral</td>
<td></td>
</tr>
<tr>
<td>CEA</td>
<td>&lt;5</td>
<td>5-10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Liver mets</td>
<td>None</td>
<td>Resected</td>
<td></td>
</tr>
</tbody>
</table>
Outcomes

Primary

- A monthly recruitment rate from ~11 centres

Secondary

- Overall survival
- Relapse free survival
- Lung function
- Patient reported quality of life
- Health economic assessment

Inclusion criteria for registration

- Patients with primary colorectal cancer who have undergone resection of the primary cancer with intent to cure
- Local control has been confirmed
- No clinical indications of other active colorectal cancer other than the known lung metastases
Exclusion criteria for registration

- Previous malignancy likely to interfere with protocol treatment or measurement of endpoints
- Any concurrent illness which could interfere with the treatment protocol or confound survival
- Unavailable for follow up and assessment according to protocol
- Psychiatric or mental incapacity that precludes fully informed consent

Procedure for registration

1. Explain uncertainty to pt
2. Pt given DVD & PIS to take home
3. Follow up discussion
4. Pt willing to join stage 1 of trial – sign consent
Helping the discussion

- Patients’ decisions might be heavily influenced by nuance or inadvertent bias by one team member
- Terminology very important – active monitoring
- Feasibility study includes an interactive DVD session for centres to facilitate ‘even-handed’ trial discussions
- An information DVD for patients

2-stage consent

Stage I
- Discuss scan findings, implications and options
- Explain uncertainty and PulMiCC trial in outline
- Invite patient to discuss with research nurse,
- Register interest and consent to further tests
- PIS and DVD given to take away

Stage II
- If tests show treatment still uncertain and patient fit for either arm of study – active monitoring +/- metastasectomy, consent to PulMiCC invited
Healthcare Professional DVD

- Shows oncologist, research nurse and thoracic surgeon describing each stage of trial with simulated patient and his wife
- Meant to stimulate discussion amongst all HCPs likely to be involved and help them organise local procedures for optimal recruitment

Patient Information DVD

- Contains clips from HCP DVD, cartoons and graphics
- Permits patients to take their time, replay parts and make informed unbiased decisions

Professor Tom Treasure describes the lung surgery

Oncologist Dr Pauline Leonard, explains trial rationale

Hayley Tapping, research nurse discussing the trial tests
Evaluation following registration

- ECOG performance status assessment
- PET-CT (half body)
- Histology/cytology to confirm the nature of the nodules if there is clinical uncertainty concerning their nature *(this is not mandatory)*
- Full blood count, serum biochemistry & liver function tests
- CEA measurement
- Lung spirometry
- Further lung function tests if there is uncertainty about fitness for surgery according to BTS guidelines
- Weight

Evaluation for randomisation

Investigations complete

Pt evaluated & systemic Rx given if required

Course of action clear to MDTs (lung & colorectal) pt not continued

Uncertainty then consider for 2nd stage

MDT Follow up at 1 yr

Pt eligible consent for 2nd stage & complete accept or decline questionnaire
Eligibility criteria for randomisation

- **Inclusion criteria**
  - One or more nodules histologically/cytologically confirmed as metastases from colorectal cancer OR >90% likelihood of being metastases from colorectal cancer
  - Pulmonary function adequate to sustain good performance after the largest likely loss of parenchyma (calculated as the predicted postoperative FEV1 according to BTS guidelines)
  - ECOG performance status 0-1
  - Any recommended systemic or other non surgical treatment has been completed
  - Available for trial assessments & follow up
  - Consent form has been signed

- **Exclusion criteria**
  - Patients with a nodule which is proven or is likely to be lung cancer
  - Concurrent disease that may interfere with protocol treatment or measurement of endpoints

Baseline questionnaires

- FACT-An-L
- STAI
- EQ-5D
Randomisation

- Allocation will be carried out electronically
- Factors for minimisation
  - Age
  - Sex
  - Number of metastases
  - CEA level
  - Prior liver metastasectomy
  - Time since resection of the colorectal primary cancer
  - T stage
  - N stage
  - Randomisation will also be stratified by local site

Randomisation

- Active monitoring following local practice guidelines
- Active monitoring following local practice guidelines PLUS pulmonary metastasectomy*

* RFA is not a treatment option
## Timetable

<table>
<thead>
<tr>
<th>Month</th>
<th>Event</th>
</tr>
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<tbody>
<tr>
<td>Oct 2009</td>
<td>Grant awarded</td>
</tr>
<tr>
<td>Dec 2009</td>
<td>Ethics submitted</td>
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<tr>
<td>Jan 2010</td>
<td>Ethics approval</td>
</tr>
<tr>
<td>Feb 2010</td>
<td>SSI forms and Agreements sent to centres</td>
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<tr>
<td>Mar 2010</td>
<td>Investigator’s meeting</td>
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<tr>
<td>Apr/May 2010</td>
<td>Centre Training</td>
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<tr>
<td>Jun 2010</td>
<td>Start of recruitment</td>
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<tr>
<td>Sep 2011</td>
<td>End of feasibility grant</td>
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## Centres

<table>
<thead>
<tr>
<th>Centres</th>
<th>Location</th>
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<tbody>
<tr>
<td>Miss Karen Harrison-Phipps</td>
<td>Guy's &amp; St Thomas'</td>
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<tr>
<td>Mr Peter O'Keefe</td>
<td>Cardiff</td>
</tr>
<tr>
<td>Mr Mike Shackcloth</td>
<td>Liverpool</td>
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<tr>
<td>Dr Pauline Leonard</td>
<td>Whittington</td>
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<tr>
<td>Mr Ian Morgan</td>
<td>Wolverhampton</td>
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<tr>
<td>Mr Aman Coonar</td>
<td>Papworth</td>
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<tr>
<td>Mr Babu Naidu</td>
<td>Birmingham</td>
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<tr>
<td>Mr Apostolos Nakas</td>
<td>Glenfield</td>
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<tr>
<td>Mr John Edwards</td>
<td>Sheffield</td>
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<tr>
<td>Mr Mark Jones</td>
<td>Manchester</td>
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<tr>
<td>Mr Antonio Martin-Ucar</td>
<td>Nottingham</td>
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<tr>
<td>Mr Hugo Taylor</td>
<td>Basildon</td>
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<tr>
<td>Mr Ed Black</td>
<td>Oxford</td>
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<tr>
<td>Professor J Dark/Mr Sion Barnard/Mr Jonathon Forty</td>
<td>Newcastle</td>
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<tr>
<td>Mr Simon Kendall</td>
<td>Middlesbrough</td>
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<tr>
<td>Mr Ian Hunt and Ms Carol Tan</td>
<td>St Georges</td>
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<tr>
<td>Mr Kieran McManus</td>
<td>Belfast</td>
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<tr>
<td>Ms Mathilda Cominos</td>
<td>Maidstone &amp; Tunbridge Wells</td>
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<tr>
<td>Professor Brian Davidson</td>
<td>Royal Free</td>
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<tr>
<td>Mr David Simon-Montefiore</td>
<td>Leeds</td>
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PulMiCC Web site

http://www.rbht.nhs.uk/PulMiCC/