A Randomised Phase III Trial of Highly Conformal Hypofractionated Image guided (“Stereotactic”) Radiotherapy vs Conventionally Fractionated Radiotherapy for Inoperable Early stage I Non-Small Cell Lung Cancer (NSCLC)

CHISEL 2013 – An update on TROG trial 09.02

M Enge, D Ball, T Kron, B Chesson
CHISEL 09.02 Update

- Trial background
- Original study design and new trial amendments
- Changes to Quality Assurance Processes
- Trial credentialing and enrolment status
- Conclusion
Trial Background

Study Hypothesis

Highly conformal hypofractionated image guided radiotherapy (HypoRT) for peripherally located inoperable T1 and T2a NSCLC will result in superior control of disease at the primary site compared with conventionally fractionated RT.
Endpoints

Primary
- Time to local failure

Secondary
- Overall Survival
- Cancer specific survival
- Toxicity (CTCAE v 4.0)
- Quality of Life
  - EORTC QLQ C30 and LC 13
  - State Trait Anxiety Inventory
  - Distress Thermometer
  - Cancer Worry Scale

Statistical analysis will be performed at the end of the 24 month follow-up period. No interim analyses are planned.
Original Trial Design

Patient population
T1N0 or T2aN0 NSCLC based on FDG PET/CT (Histological/cytologically confirmed)
Peripherally located tumour (1cm beyond the mediastinum & 2cm beyond bifurcation of the lobar bronchi)
Medically inoperable or patient refuses surgery

RANDOMISATION
1:1

ARM 2 (Control)
Conventional RT
Conventional RT 66 Gy in 33 daily 2 Gy fractions prescribed to the isodose line covering the PTV over 6.5 weeks.

ARM 1 (Investigational)
Hypofractionated RT
- See next slide
HypoRT Treatment Arm

ITV ≥ 2cm from chest wall

54 Gy divided into 3 fractions of 18 Gy each, delivered weekly on days 0, 7 & 14. Maximum deviation of ±2 days from the specified time is allowable.
Sample Size, Randomisation & Duration

- 100 evaluable patients
- Initial randomisation allocation ratio was 1:1
- Total duration of accrual was anticipated as being three years
- All patients will be followed up until two years after the last patient completes treatment
Trial Amendments

- Randomisation
- Central tumour dose/fractionation
- Chest wall dose constraint
- Physics QA
Trial Amendments

- Randomisation
- Patient population: T1N0 or T2aN0 NSCLC based on FDG PET/CT (Histological/cytologically confirmed)
  Peripherally located tumour (1cm beyond the mediastinum & 2cm beyond bifurcation of the lobar bronchi)
  Medically inoperable or patient refuses surgery

RANDOMISATION 2:1

**ARM 1 (Investigational)**
Hypofractionated RT
54 Gy divided into 3 fractions of 18 Gy each, delivered weekly on days 0, 7 & 14

**ARM 2 (Control)**
Conventional RT
Conventional RT 66 Gy in 33 daily 2 Gy fractions prescribed to the isodose line covering the PTV over 6.5 weeks.
Trial Amendments

- Randomisation
- Central tumour dose/fractionation
- Chest wall dose constraint
- Physics QA
Dose Fractionation

- Peripherally located at least 1cm beyond mediastinum and 2cm beyond bifurcation of the lobar bronchi

- Originally not allowed tumours <1.0cm from chest wall

- Now allowed with altered dose fractionation schedule: 48Gy in 4 fractions

Timmermann et al. JCO, 2006 24;4833-4839
Exclusion Zone

Tumour Diameter

1.0 cm

3.0 cm

5.0 cm

CW restriction

No CW restriction

QuickTime™ and a decompressor is needed to see this picture.
| 3 cm cancer | 642/20.01 | 1142/35.60 | 15.59 | 77.88 |
Trial Amendments

- Randomisation
- Central tumour dose/fractionation
- Chest wall dose constraint
- Physics QA
Chest Wall Dose Constraint

- Definition of chest wall (RTOG interpretation)
- Dose only ‘observed’ in other trials
- Original dose constraint
  - Unachievable
- Resulted in several minor/major deviations
- New chest wall constraint = 30Gy to 30cc Max
<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>No. of patients</th>
<th>Median F/U (months)</th>
<th>Selection criteria specific to CW</th>
<th>Dose range</th>
<th>No. of fractions</th>
<th>Measurement method</th>
<th>CW toxicities</th>
<th>Follow-up and reporting</th>
<th>Statistical analysis and prognostic factors reported</th>
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</thead>
<tbody>
<tr>
<td>Dunlap5</td>
<td>Retrospective</td>
<td>60</td>
<td>11.1</td>
<td>targets ≤2.5 cm from CW</td>
<td>21 Gy–60 Gy</td>
<td>3–5</td>
<td>3 cm expansion from external lung contour</td>
<td>17/28.3%</td>
<td>20/33.0%</td>
<td>5 patients</td>
</tr>
<tr>
<td>Stephens10</td>
<td>Retrospective</td>
<td>45</td>
<td>18.8</td>
<td>nil</td>
<td>60 Gy</td>
<td>3</td>
<td>Rib, intercostal muscle and soft tissue</td>
<td>0/0.0%</td>
<td>10/22.2%</td>
<td>Not reported</td>
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<tr>
<td>Welsh13</td>
<td>Retrospective</td>
<td>265</td>
<td>10.3</td>
<td>targets ≤2.5 cm from CW</td>
<td>50 Gy</td>
<td>4</td>
<td>volume between skin surface and lung</td>
<td>2/0.8%</td>
<td>45/16.2%</td>
<td>8 patients</td>
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<tr>
<td>Mutter14</td>
<td>Prospective</td>
<td>126</td>
<td>16</td>
<td>nil</td>
<td>40 Gy–60 Gy</td>
<td>3–5</td>
<td>A) 3 cm expansion from external lung contour B) 2 cm expansion from external lung contour</td>
<td>19/15.0%</td>
<td>35/27.8%</td>
<td>5 patients/8 ribs</td>
</tr>
<tr>
<td>Andolino15</td>
<td>Retrospective</td>
<td>347</td>
<td>19</td>
<td>nil</td>
<td>18 Gy–72 Gy</td>
<td>2–5</td>
<td>3 cm expansion from external lung contour</td>
<td>3/0.9%</td>
<td>51/14.7%</td>
<td>18 ribs</td>
</tr>
<tr>
<td>Pettersson6</td>
<td>Retrospective</td>
<td>33</td>
<td>29</td>
<td>nil</td>
<td>45 Gy</td>
<td>3</td>
<td>Individually contoured ribs</td>
<td>N/A</td>
<td>N/A</td>
<td>7 patients/13 ribs</td>
</tr>
<tr>
<td>Voroney7</td>
<td>Prospective</td>
<td>42</td>
<td>17</td>
<td>nil</td>
<td>54 Gy–60 Gy</td>
<td>3</td>
<td>Individually contoured ribs</td>
<td>N/A</td>
<td>N/A</td>
<td>9 patients/15 ribs</td>
</tr>
<tr>
<td>Bongers16</td>
<td>Retrospective</td>
<td>500</td>
<td>33</td>
<td>nil</td>
<td>60 Gy</td>
<td>3–8</td>
<td>not described</td>
<td>5/1.0%</td>
<td>27/5.4%</td>
<td>8 patients</td>
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<td>Woody17</td>
<td>Retrospective</td>
<td>102</td>
<td>25.5</td>
<td>nil</td>
<td>48 Gy–60 Gy</td>
<td>3–10</td>
<td>3 cm expansion from external lung contour</td>
<td>1/0.9%</td>
<td>19/18%</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

**Notes:**
- CW: Critical structures.
- CTCAE: Common Terminology Criteria for Adverse Events.
- F/U: Follow-up.
- CI: Confidence interval.
- N/A: Not applicable.
## Chest Wall Dose Constraint

<table>
<thead>
<tr>
<th>ORGAN</th>
<th>PARAMETER</th>
<th>CONVENTIONAL ARM</th>
<th>INVESTIGATIONAL ARM</th>
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</thead>
<tbody>
<tr>
<td>Lung</td>
<td>V 20</td>
<td>35%</td>
<td>15%</td>
</tr>
<tr>
<td>Heart</td>
<td>Maximum dose</td>
<td>65 Gy</td>
<td>30 Gy</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>Maximum dose</td>
<td>65 Gy</td>
<td>27 Gy</td>
</tr>
<tr>
<td>Spinal Canal</td>
<td>Maximum dose</td>
<td>45 Gy</td>
<td>18 Gy</td>
</tr>
<tr>
<td>B Plexus</td>
<td>Maximum dose</td>
<td>65 Gy</td>
<td>24 Gy</td>
</tr>
<tr>
<td>Chest Wall</td>
<td>Maximum dose</td>
<td>65 Gy (30cc maximum)</td>
<td>30Gy (30cc maximum)</td>
</tr>
</tbody>
</table>
Site Radiotherapy Credentialing

- **Link Sites:** to deliver both Con-RT and Hypo-RT
  - Facility Questionnaire
  - Benchmarking plans
  - Dosimetric phantom study
  - Site visit (Phantom Dose Measurements/Site specific IGRT)

- **Base Sites:** to deliver Con-RT only
  - an abbreviated credentialing
  - the creation of ITVs based on PET rather than 4D CT is acceptable
Credentialing of participating centres

The four steps to successful site activation:

1. Completion of a facility questionnaire
Facility Questionnaire

Assesses the departments suitability to enroll patients based upon requirements for:

• Stabilisation
• Simulation/Image guidance images
• Treatment planning, dosimetry and verification
• Quality assurance
• Motion management
• Capability and patient support endpoints
Credentialing of participating centres

The four steps to successful site activation:

1. Completion of a facility questionnaire

2. Participation in a planning study that requires centres to develop plans for a phantom and two test cases of different complexity.
Benchmarking

- Plans will be reviewed prior to treatment using SWAN and TROG CQMS software
- Anticipated turnaround < 2 working days
- Peer review by:
  - Radiation oncologist (eligibility, contours)
  - Radiation Therapist (dose/volume constraints, technical parameters)
Credentialing of participating centres

The four steps to successful site activation:

1. Completion of a facility questionnaire

2. Participation in a planning study that requires centres to develop plans for a phantom and two test cases of different complexity.

3. Participation in a level III dosimetric phantom study.
Physics Quality Assurance

QA is essential in hypofractionated image guided RT

Verification is done to ensure:

1. Motion management strategies are appropriate
2. Margins are appropriate
3. Treatment plans are accurately calculated
4. Stabilisation is appropriate
5. Image guidance is accurate
6. Dose is delivered as expected
Patient Specific Quality Assurance
PMCC Patient Specific QA

1. Patient plan is mapped onto phantom
2. Stationary and moving measurements
3. Film and dose readings
4. Final review
PMCC Patient Specific QA

Individual QA (n=33) has picked up:
- Non-deliverable fields
- Need to consider couch
- One incorrect factor entered for a single field (20% difference in this field)
Physics Quality Assurance

- Essential for complex radiotherapy such as SABR.

- Growing confidence in hypofractionated treatment delivery gives way to a more relaxed approach to QA.

- More important for
  1. Located at air/tissue/bone interfaces
  2. Highly mobile (ie. >1.0cm in any direction)
  3. In close proximity to critical structures.
Credentialing of participating centres

The four steps to successful site activation:

1. Completion of a facility questionnaire

2. Participation in a planning study that requires centres to develop plans for a phantom and two test cases of different complexity.

3. Participation in a level III dosimetric phantom study.

4. Site visit to be performed by members of the project team
Current Status - sites

- **Open**
  - Alfred
  - Peter Mac: E. Melb, Bendigo, Box Hill & Moorabbin
  - Royal North Shore
  - Royal Prince Alfred
  - Princess Alexandra
  - Prince of Wales
  - Liverpool

- **Approval pending /Interested sites**
  - **NSW**: Mater Newcastle, Nepean, Westmead
  - **Qld**: Townsville
  - **SA**: Royal Adelaide
  - **Tas**: Royal Hobart
  - **WA**: Sir Charles Gairdner
  - **NZ**: Auckland, Christchurch, Palmerston Nth
09.02 Accrual to Date

Time since activation (months)

Patients Enrolled

Projected = 100
Actual = 36
Conclusion

- Challenges involved in complex trials calls for constant adaptation
- Successful trials require buy in from MDT
- Technical QA is essential


Acknowledgements

- PeterMac SABR Team
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