Recent advances in radiotherapy

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Consultant Clinical Oncologist
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Overview

- What is radiotherapy?
- A brief history of radiotherapy
- Advances in the technology - SABR/SBRT, IMRT/VMAT, MR Linac, Protons
- Clinical advances, practice changes, current standards of care, clinical trials in radiotherapy for NSCLC, SCLC, Mesothelioma
- Conclusions and take home messages
Radiotherapy

The practice of using ionising radiation to treat malignant disease

- External beam radiotherapy (EBRT) – X-rays
- Particle therapy eg protons and heavy ions
- Brachytherapy – Interstitial, intracavitary
- Radionuclides eg Ra223, I-131, Sr89
“Holy Grail” of radiotherapy

“To deliver a curative radiation dose to the tumour, without causing significant damage to normal tissues”

The goal
- 100% local tumour control
- No acute or late side effects

The challenges
- Tumour isn't just the visible component. Microscopic disease
- Critical structures located next to tumours
- The patient and their organs move – moving targets
A Brief History of Radiotherapy
The discovery of X-rays - 1895

- Wilhelm Conrad Roentgen – 8th Nov 1895. Nobel prize
- First radiation therapy by Emile Grubbe on Jan 29th 1896
First diagnostic X-ray 3rd Feb 1896 by Frost. Colles fracture
X-ray fluoroscopy
Early treatment lab
The Curies, Bequerel and Radium

- 1896. Bequerel discovers uranium salts produce a similar type of radiation to X-rays
- 1898. Curies isolate radium from pitchblende in a shed. Nobel prize 1903
- Pierre Curie developed an ulcer on his chest where he kept a sample of radium in his waistcoat! He suggested that radium could be used for cancer treatment - brachytherapy
- Original research papers remain radioactive!
Early radium treatments – brachytherapy
Consequences for early radiation pioneers
Evolution of radiotherapy equipment

- 1950. Cobalt 60 unit (1.2MeV). Started the era of “deep” external beam radiotherapy

- Development of linear accelerators 1950-70’s. Initially very cumbersome!
“Modern” linear accelerator - 1980s
Multi-leaf collimator (MLC) - Conformal RT Beam shaping - 1990s
IMRT (Intensity modulated radiotherapy)
Sparing oesophagus, cord, and contralateral lung
Cardiac sparing
Image-guided radiotherapy (IGRT) linacs 1990s-current
PDG-PET for target definition – functional planning

FDG-PET in treatment planning:
+ Differentiation between tumor and atelectasis
+ Definition of GTV
+ Proven to reduce normal lung volumes
“Dose painting” using combined IMRT and PET-CT
Motion management advances
Hitting the Target: Motion Strategies

Static Tumor

Moving Tumor No margin

Moving Tumor with margin

Moving Tumor Gating

© Steve B. Jiang
Adaptive radiotherapy (ART) planning

- If tumours shrink or other changes occur during treatment, this can be picked up on repeat cone beam CT imaging
- This allows plan to be adapted to new tumour volume and organs at risk
MRI guided adaptive radiotherapy

Patient-controlled breath-hold gated SABR

When the tumor (blue) moves away from the boundary (red), the beam will automatically pause.

When the tumor (blue) move into the boundary (red), the beam will automatically resume.
Proton therapy
Lung cancer: Building hope in challenging times
Consensus Statement on Proton Therapy in Early-Stage and Locally Advanced Non-Small Cell Lung Cancer

Joe Y. Chang, MD, PhD,* Salma K. Jabbour, MD,#
Dirk De Ruyscher, MD, Steven E. Schöld, MD, Charles B. Simone, II, MD,
Ramesh Rengan, MD,* Steven Feigenberg, MD,# Atif J. Khan, MD,
Noah C. Choi, MD, * Jeffrey D. Bradley, MD, Xiaorong R. Zhu, PhD,#
Antony J. Lomax, PhD,* and Bradford S. Hoppe, MD, on behalf of the
International Particle Therapy Co-operative Group (PTCOG) Thoracic
Subcommittee

• Promising (comparable) indications for PBT:
  • Early-stage NSCLC
  • Larger tumors
  • Central tumors
  • Tumors near brachial plexus
  • Multiple tumors
  • Locally advanced NSCLC
  • Recurrence

Figure 1 Demonstrative cases comparing (A) 3D CRT, (B) IMRT, and (C) PBT.
Note: Images courtesy of Tatsuo Segawa.
Abbreviations: 3D CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; PBT, proton beam therapy.
Early stage medically inoperable NSCLC
How SABR/SBRT became the standard of care
Early stage NSCLC

- Surgery remains gold standard: cures 50-75%
- But 25% patients are unfit for surgery due to co-morbidities
- Conventional RT has been the main option
- Typically 20-30 fractions over 4-6 weeks
- Local control ~ 20-40%. Cure ~ 10-20%
- Dose is not high enough!
So what dose is required to eradicate NSCLC?

Reconstructed from Martel et al. Lung Cancer 1999;24:31-37
What is SABR/SBRT?

- SABR is the delivery of very focused, precise and biologically potent (ablative) doses of radiation to tumours in the chest abdomen and pelvis.
- Characterised by extreme hypofractionation (2-8 fractions)
- Made possible by advances in IGRT, advanced planning algorithms, and motion management techniques
### Meta-analysis

**Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: A meta-analysis**

Janneke P.C. Grutters\textsuperscript{a,*}, Alfons G.H. Kessels\textsuperscript{b}, Madelon Pijs-Johannesma\textsuperscript{a}, Dirk De Ruysscher\textsuperscript{a}, Manuela A. Joore\textsuperscript{b,1}, Philippe Lambin\textsuperscript{a,1}

*Radiotherapy and Oncology 95 (2010) 32–40*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>5-year overall survival</th>
<th>(95% CI)</th>
<th>p-Value**</th>
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<tr>
<td>CRT</td>
<td>0.195</td>
<td>(0.148–0.242)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBRT</td>
<td>0.421</td>
<td>(0.341–0.501)</td>
<td>0.014</td>
</tr>
<tr>
<td>Protons</td>
<td>0.397</td>
<td>(0.245–0.550)</td>
<td>0.782</td>
</tr>
<tr>
<td>Carbon-ions</td>
<td>0.421</td>
<td>(0.322–0.520)</td>
<td>0.985</td>
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<table>
<thead>
<tr>
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<th>5-year disease-specific survival</th>
<th></th>
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<tbody>
<tr>
<td>CRT</td>
<td>0.435</td>
<td>(0.311–0.559)</td>
<td>0.045</td>
</tr>
<tr>
<td>SBRT</td>
<td>0.627</td>
<td>(0.500–0.754)</td>
<td>0.389</td>
</tr>
<tr>
<td>Protons</td>
<td>0.521</td>
<td>(0.319–0.724)</td>
<td>0.999</td>
</tr>
<tr>
<td>Carbon-ions</td>
<td>0.643</td>
<td>(0.486–0.801)</td>
<td>0.353</td>
</tr>
</tbody>
</table>

**Accepted standard of care:** NCCN, ASTRO Emerging Technology Committee, EORTC, ACCP

**NHS funding:** Agreed by NHS CB April 2013

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**Lung cancer: Building hope in challenging times**
SBRT Vs Conventional RT. Randomised Phase III trial evidence

The CHISEL trial: Overall survival

HR = 0.531, 95% CI 0.301, 0.940

Ball et al WCLC 2017
How do we do SABR/SBRT?
Patient selection criteria for SABR (NSCLC)

- Medically inoperable peripherally located NSCLC or patient choice to avoid surgery
- PS 0-2
- Stage T1-3, N0 following PET-CT
- Ideally biopsy proven, but accept PET+ve growing lesion
- Max tumour size 5cm (UK guidelines). Peripheral location. Not adjacent to major vessels, heart, oesophagus.
- Able to lie flat for 30 mins
SBRT/SABR motion management techniques


Reduction of Tumor Movement

Free breathing

Diaphragm control

P = 0.0002
Generating the ITV (motion envelope) from 4D CT

End-exhalation

End-inhalation

ITV

5mm

PTV
Planning and dosimetry

- 7 field static IMRT
- VMAT
Treatment delivery, IGRT cone-beam CT correction and verification
Treatment delivery, IGRT cone-beam CT correction and verification
Current UK dose/fractionation for SABR/SBRT

- 54Gy in 3 fractions
- 55Gy in 5 fractions if adjacent to chest wall
- 60Gy in 8 fractions if adjacent to spine, aorta, close to “no fly-zone”
Comparing with International Series

**Middlesbrough Data**

- **Survival (%)**
  - Y-axis: 0 to 100
  - X-axis: 0.0 to 3.0 years
  - n=97

**Timmerman (RTOG 0236)**

- **SBRT for in-operable Early stage NSCLC**
- **JAMA 2010;303:1070-76**

- **Survival (%)**
  - Y-axis: 0 to 100
  - X-axis: 0.0 to 36 months
  - n=55

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Lung cancer: Building hope in challenging times
Lung cancer: Building hope in challenging times

KM plot showing overall survival

Cum Survival vs Time (months)

- 1yr: 87.20%
- 2yr: 67.30%
- 3yr: 56.90%
- 4yr: 48.70%
- 5yr: 44.00%
Technology delivers Faster treatment times!

**Treatment time (mins)**

<table>
<thead>
<tr>
<th>Patient</th>
<th>3DCRT 7 fields</th>
<th>VMAT 550 DR</th>
<th>VMAT FFF 1800 DR</th>
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<td>5.5</td>
<td>2.5</td>
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<tr>
<td>54 Gy in 3 (18Gy)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Patient 2</td>
<td>12</td>
<td>5.5</td>
<td>2.0</td>
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<tr>
<td>54 Gy in 3 (18Gy)</td>
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</tr>
<tr>
<td>Patient 3</td>
<td>13</td>
<td>3.5</td>
<td>1.5</td>
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<tr>
<td>55 Gy in 5 (11Gy)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Patient 4</td>
<td>12</td>
<td>4</td>
<td>1.5</td>
</tr>
<tr>
<td>55 Gy in 5 (11Gy)</td>
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<td></td>
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</tbody>
</table>
Lung cancer: Building hope in challenging times
Other advances and developments in early stage NSCLC

- Single fraction - SRS
- SABR in patients with interstitial lung disease (ILD)
- Operable NSCLC - SABR Vs Surgery
- Central disease and Ultra-central disease
Is there a role for single fraction radiosurgery?

- 30Gy and 34Gy single fractions both look to be safe and well tolerated with no G3 toxicities (n=80). (RTOG 0915, Videtic et al IJROBP 2014).
- RTOG taking forward 34Gy schedule in Phase III trial

NRG Oncology RTOG 0915 (NCCTG N0927): A Randomized Phase II Study Comparing 2 Stereotactic Body Radiation Therapy (SBRT) Schedules for Medically Inoperable Patients with Stage I Peripheral Non-Small Cell Lung Cancer

**Conclusion**

NRG Oncology RTOG 0915/NCCTG N0927 was a randomized phase II lung SBRT study of 34 Gy in 1 fraction versus 48 Gy in 4 fractions to find the least toxic yet still efficacious regimen for medically inoperable patients. Both regimens appeared safe with low rates of toxicity and high rates of PC at 1 year. Given a primary endpoint of pre-specified toxicity rates and a secondary endpoint of PC at 1 year, our results suggest that 34 Gy is an appropriate schedule for further investigation, most appropriately in a phase III trial involving a comparison with the RTOG standard of 54 Gy in 3 fractions.
Beware of interstitial lung disease

<table>
<thead>
<tr>
<th>MODALITY</th>
<th>MORTALITY</th>
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<tr>
<td>SABR</td>
<td>15.6%</td>
</tr>
<tr>
<td>RFA</td>
<td>8.7%</td>
</tr>
<tr>
<td>Surgery</td>
<td>2.2%</td>
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</table>

Chen et al IJROBP 2017; 98:622
ASPIRE-ILD
Assessment of precision irradiation in early non-small cell lung cancer and interstitial lung disease: A phase II trial

Study Question:
What are the survival and toxicity outcomes associated with the use of SABR in patients with ILD?

Principal Investigators:
Dr. David Palma (Radiation Oncology)
Dr. Alexander Louie (Radiation Oncology)
Dr. Chris Ryerson (Respirology)
Operable early stage NSCLC

Stage I: ASTRO Guidelines

Standard operative risk

Statement KQ 1B: For patients with “standard operative risk” (i.e., with anticipated operative mortality of <1.5%) and stage I NSCLC, SBRT is not recommended as an alternative to surgery outside of a clinical trial. Discussions about SBRT are appropriate, with the disclosure that long-term outcomes with SBRT >3 years are not well-established. For this population, lobectomy with systematic mediastinal lymph node evaluation remains the recommended treatment, though a sublobar resection may be considered in select clinical scenarios.

Recommendation strength: Strong
Quality of evidence: High
Consensus: 94%
541 potential SBRT candidates underwent surgical resection (Lobectomy and LND)

25% had occult nodes - 12.8% N1, 12.2% N2

Raises question of the need for invasive staging pre-SBRT?

<table>
<thead>
<tr>
<th>T / N category</th>
<th>N0</th>
<th>N1a</th>
<th>N1b</th>
<th>N2a1</th>
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<tbody>
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<td>32</td>
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<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td></td>
<td>(97.0%)</td>
<td>(3.0%)</td>
<td></td>
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<td></td>
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<td>1b</td>
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<td>7</td>
<td>1</td>
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<td>2</td>
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<tr>
<td></td>
<td>(88.1%)</td>
<td>(0.8%)</td>
<td>(5.9%)</td>
<td>(0.8%)</td>
<td>(2.5%)</td>
<td>(1.7%)</td>
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<tr>
<td>1c</td>
<td>86</td>
<td>7</td>
<td>15</td>
<td>5</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>(66.2%)</td>
<td>(5.4%)</td>
<td>(11.5%)</td>
<td>(3.8%)</td>
<td>(8.5%)</td>
<td>(4.6%)</td>
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<tr>
<td>2a</td>
<td>184</td>
<td>13</td>
<td>25</td>
<td>8</td>
<td>12</td>
<td>18</td>
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<tr>
<td></td>
<td>(70.8%)</td>
<td>(5.0%)</td>
<td>(9.0%)</td>
<td>(3.1%)</td>
<td>(4.6%)</td>
<td>(6.9%)</td>
</tr>
</tbody>
</table>

Conclusion:
In view of the high rate of lymph node metastasis in clinical stage I lung cancer, surgical resection is still the preferred treatment.
“Dose cloud s” ideal for knocking out microscopic disease
The case for a randomised clinical trial of SABR Versus Surgery in operable patients

- Encouraging SABR results in operable patients
  JCOG 0403 – 76.5% 3 yr OS (n=64)
  RTOG 0618 - 76.9% 3 yr OS (n=26)
  ACOSOG Z0030 – 76.2% 3yr OS (n=1000)

- Meta-analysis by Solda et al showed LC of 91% and OS of 70% SABR versus 68% Surgery.
- Recent pooled analysis of ROSEL and STARS closed phase III studies showed SABR likely to be as good as surgery. 3 yr OS 95% vs 79% in favour of SABR, but n=58
- Conclusion: direct comparison within a clinical trial is a priority
Randomised trials of SBRT versus Surgery

- Randomised trials have attempted to answer the question, but have failed to recruit. ROSEL, STARS, ACOSOG, SABRTooth
- However, 3 important ongoing trials:
  - VALOR (US) n=670
  - STABLE-MATES (US) n=258
  - POSTLIV (China) n=76
Veterans Affairs Lung Cancer Or Stereotactic Radiotherapy (VALOR)

- Phase III trial SBRT Vs Surgery (standard lobectomy or limited anatomic pulmonary resection)
- Peripheral tumours will receive either 18 Gy x 3, 14 Gy x 4, or 11.5 Gy x 5 fractions
- Central tumours will be treated with 10 Gy x 5
- Participants found to have incidental nodal involvement after surgery will be referred for adjuvant chemotherapy, with our without postoperative radiotherapy
- N=670
Joint Lung Cancer Trialist’s Coalition
JoLT - Ca

A Randomized Phase III Study of Sublobar Resection (SR) versus Stereotactic Ablative Radiotherapy (SAbR) in High Risk Patients with Stage I Non-Small Cell Lung Cancer (NSCLC)

The STABLE-MATES Trial

Major eligibility
• FEV1 ≤ 50% predicted
• DLCO ≤ 50% predicted

Minor eligibility (any two of)
• Age ≥ 75
• FEV1 = 51–60% predicted
• DLCO = 51-60%
• Pulmonary hypertension
• Ejection fraction ≤ 40%
• Arterial pO2 ≤ 55 mm Hg
• pCO2 ≥ 45 mm Hg
• MMRC dyspnoea scale ≥ 3
• Surgeon believes lobectomy/pneumonectomy would be poorly tolerated
What is “central” disease?

- Central disease encompasses a heterogeneous group
- No universally accepted definition
- ASTRO and ASCO, EORTC, NCCN guidelines:
  - Generally accepted that conservative SABR/SBRT schedules (5-10 fractions) can be safely used to treat central early stage lung tumours.
  - Avoid “ultra-central disease”
Systematic review

Outcomes of stereotactic ablative radiotherapy for central lung tumours: A systematic review

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Mortality

ABSTRACT

Background and purpose: Stereotactic ablative radiotherapy (SABR) has improved the survival for medically inoperable patients with peripheral early-stage non-small cell lung cancer (NSCLC). We performed a systematic review of outcomes for central lung tumours.

Material and methods: The systematic review was performed following PRISMA guidelines. Survival outcomes were evaluated for central early-stage NSCLC. Local control and toxicity outcomes were evaluated for any centrally-located lung tumour.

Results: Twenty publications met the inclusion criteria, reporting outcomes for 563 central lung tumours, including 315 patients with early-stage NSCLC. There was heterogeneity in the planning, prescribing and delivery of SABR and the common toxicity criteria used to define toxicities (versions 2.0–4.0). Tumour location (central versus peripheral) did not impact overall survival. Local control rates were ≥85% when the prescribed biologically equivalent tumour dose was ≥100 Gy. Treatment-related mortality was 2.7% overall, and 1.0% when the biologically equivalent normal tissue dose was ≤210 Gy. Grade 3 or 4 toxicities may be more common following SABR for central tumours, but occurred in less than 9% of patients.

Conclusions: Post-SABR survival for early-stage NSCLC is not affected by tumour location. SABR achieves high local control with limited toxicity when appropriate fractionation schedules are used for central tumours.

In summary, this systemic review suggests SABR offers a safe and effective curative treatment for patients with central tumours who unfit for surgery. Data from the ongoing RTOG 0813 trial will provide prospective data to determine more reliable normal organ constraints with respect to the SABR fractionation schedules being assessed.
IASLC Advanced Radiation Technology Committee

- “Findings from several large clinical series reporting long-term clinical outcomes after SABR for central lesions support the use of this technique for curative treatment of centrally located early stage NSCLC”
- Recognition of variation in definitions, techniques, dose/fractionation, definitions of failure etc
- “Tumours located at or involving the hilar structures, invading bronchial tree or mediastinum......are not considered safe targets”.
Ultra-central disease – SUNSET Phase I trial

<table>
<thead>
<tr>
<th>Dose Level</th>
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<tbody>
<tr>
<td>-1</td>
<td>4 Gy</td>
<td>15</td>
<td>60 Gy</td>
</tr>
<tr>
<td>0</td>
<td>6 Gy</td>
<td>10</td>
<td>60 Gy</td>
</tr>
<tr>
<td>1</td>
<td>7.5 Gy</td>
<td>8</td>
<td>60 Gy</td>
</tr>
<tr>
<td>2</td>
<td>10 Gy</td>
<td>6</td>
<td>60 Gy</td>
</tr>
<tr>
<td>3</td>
<td>12 Gy</td>
<td>5</td>
<td>60 Gy</td>
</tr>
</tbody>
</table>

Starting Level = Level 1

Required Sample Size: 30

**SUNSET**

Stereotactic body radiotherapy for ultra-central non-small cell lung cancer: A safety and efficacy trial

**Study Question:**
What is the maximally tolerated dose of radiotherapy for ultracentral non-small cell lung carcinoma associated with a 30% or lower rate of grade 3-5 toxicity occurring within 2 years of treatment?

**Principal Investigator:**
Dr. Meredith Giuliani (Radiation Oncology)

**Target Accrual:** 30 patients
Locally advanced NSCLC
Meta-analysis of concurrent versus sequential chemoradiotherapy (Auperin, JCO 2010)
Dose escalation in LA NSCLC

- Outcome of the phase III Radiation Therapy Oncology Group (RTOG) 0617 trial surprisingly disappointing
- Concurrent chemoradiotherapy to 74 Gy in 37 fractions led to worse survival, compared with the standard of care (60 Gy in 30 fractions)
- But did provide prospective evidence supporting IMRT for NSCLC (secondary analysis showed IMRT produced lower rates of severe pneumonitis and resulted in lower cardiac doses, compared with conventional RT)
Overall Survival with Durvalumab versus Placebo after Chemoradiotherapy in Stage III NSCLC: Updated Results from PACIFIC

Scott J. Antonia\(^1\), Augusto Villegas\(^2\), Davey Daniel\(^3\), David Vicente\(^4\), Shuji Murakami\(^5\), Rina Hui\(^6\), Takayasu Kurata\(^7\), Alberto Chiappori\(^1\), Ki Hyeong Lee\(^8\), Maike de Wit\(^9\), Byoung Chul Cho\(^10\), Maryam Bourhaba\(^11\), Xavier Quantin\(^12\), Takaaki Tokito\(^13\), Tarek Mekhail\(^14\), David Planchard\(^15\), Young-Chul Kim\(^16\), Christos S. Karapetis\(^17\), Sandrine Hiret\(^18\), Gyula Ostoros\(^19\), Kaoru Kubota\(^20\), Jhanelle E. Gray\(^1\), Luis Paz-Ares\(^21\), Javier de Castro Carpeño\(^22\), Corinne Faivre-Finn\(^23\), Martin Reck\(^24\), Johan F. Vansteenkiste\(^25\), David Spigel\(^26\), Catherine Wadsworth\(^27\), Giovanni Melillo\(^28\), Maria Taboada\(^29\), Phillip A. Dennis\(^28\), Mustafa Özgüroğlu\(^30\)

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PACIFIC Regimen – Mechanism of Action

**CHEMORADIATION**
- Chemoradiation induces tumor antigen release and an adaptive immune response
- Chemotherapy
- Radiation

**DURVALUMAB**
- Durvalumab reverses immune suppression and leads to a systemic antitumor response
- PD-L1 overexpression leads to immune cell evasion
- Durvalumab

**Antigens**
- Chemoradiation induces tumor antigen release and an adaptive immune response

**Chemotherapy**

**Radiation**

**Antigen-presenting Cell**

PACIFIC: Study Design
Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study

- Unresectable, Stage III NSCLC without progression after definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- If available, archived pre-cCRT tumor tissue for PD-L1 testing*

All-comers population (i.e. irrespective of PD-L1 status)
N=713 randomized

**Primary endpoints**
- PFS by BICR using RECIST v1.1†
- OS

**Key secondary endpoints**
- ORR, DoR and TTDM by BICR
- PFS2 by investigator
- Safety
- PROs

**Durvalumab**
10 mg/kg q2w for up to 12 months
N=476

**Placebo**
10 mg/kg q2w for up to 12 months
N=237

2:1 randomization, stratified by age, sex, and smoking history

1–42 days post-cCRT

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*Using the Ventana SP263 immunohistochemistry assay

†Defined as the time from randomization until the date of objective disease progression or death by any cause in the absence of progression. BICR, blinded independent central review; cCRT, concurrent CRT; PFS2, time to second progression; RECIST, Response Evaluation Criteria in Solid Tumors; TTDM, time to death or distant metastasis. ClinicalTrials.gov number: NCT02125461

Overall Survival* (ITT)

OS HR = 0.68
99.73% CI, 0.469–0.997†

P=0.00251

No. of events / No. of patients (%)
Durvalumab 183/476 (38.4) NR (34.7–NR)
Placebo 116/237 (48.9) 28.7 (22.9–NR)

Median OS (95% CI) months
Durvalumab NR 476 464 431 415 385 364 343 319 274 210 115 57 23 2 0 0
Placebo 237 220 198 178 170 155 141 130 117 78 42 21 9 3 1 0

*Median duration of follow-up for OS was 25.2 months (range 0.2–43.1)
†Adjusted for interim analysis

NR, not reached
### Subgroup Analysis by PD-L1 Status

<table>
<thead>
<tr>
<th>PD-L1 Status (pre-specified)</th>
<th>PFS HR (95% CI)</th>
<th>OS HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td><img src="image" alt="Graph" /></td>
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</tr>
<tr>
<td>≥25%</td>
<td><img src="image" alt="Graph" /></td>
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</tr>
<tr>
<td>&lt;25%</td>
<td><img src="image" alt="Graph" /></td>
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</tr>
<tr>
<td>Unknown</td>
<td><img src="image" alt="Graph" /></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PD-L1 Status (post-hoc)</th>
<th>PFS HR (95% CI)</th>
<th>OS HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1%</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
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<tr>
<td>1–24%</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>&lt;1%</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
</tbody>
</table>

- **Important facts regarding PD-L1 status:**
  - PD-L1 testing was not required
  - 37% of patients with unknown PD-L1 status
  - PD-L1 status was obtained pre-CRT (getting a sample post-CRT medically not feasible)
  - PD-L1 expression-level cutoff of 1% was part of an unplanned post-hoc analysis requested by a health authority

---

Note: PFS data based on data cutoff of Feb 13, 2017, and OS data based on data cutoff of March 22, 2018

Lung cancer: Building hope in challenging times
## Updated Safety Summary

<table>
<thead>
<tr>
<th></th>
<th>Durvalumab (N=475)</th>
<th>Placebo (N=234)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any-grade all-causality AEs, n (%)</td>
<td>460 (96.8)</td>
<td>222 (94.9)</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>145 (30.5)</td>
<td>61 (26.1)</td>
</tr>
<tr>
<td>Outcome of death</td>
<td>21 (4.4)</td>
<td>15 (6.4)</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>73 (15.4)</td>
<td>23 (9.8)</td>
</tr>
<tr>
<td>Serious AEs, n (%)</td>
<td>138 (29.1)</td>
<td>54 (23.1)</td>
</tr>
<tr>
<td>Any-grade pneumonitis/radiation pneumonitis, n (%)</td>
<td>161 (33.9)</td>
<td>58 (24.8)</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>17 (3.6)</td>
<td>7 (3.0)</td>
</tr>
<tr>
<td>Outcome of death</td>
<td>5 (1.1)</td>
<td>5 (2.1)</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>30 (6.3)</td>
<td>10 (4.3)</td>
</tr>
</tbody>
</table>
Conclusions

• Durvalumab demonstrated statistically significant and clinically meaningful improvement in OS versus placebo in the ITT population (HR = 0.68)

• Improvements in PFS, TTDM, and incidence of new lesions with durvalumab versus placebo were maintained, consistent with the prior report¹

• Durvalumab was well tolerated, with no new safety signals identified after longer follow-up

• PACIFIC study demonstrated a survival advantage for unresectable, Stage III NSCLC, supporting the PACIFIC regimen (CRT followed by durvalumab) as a new SoC

Other IO agents likely to offer similar benefit?

Phase II Trial of Concurrent Chemoradiation with Consolidation Pembrolizumab in Patients with Unresectable Stage III NSCLC

Hoosier Cancer Research Network LUN 14-179

Greg Durm1, Sandra Althouse2, Ahad Sadiq3, Shadia Jalal1, Salma Jabbour4, Robin Zon5, Goetz Kloecker6, William Fisher7, Karen Reckamp8, Ebenezer Kio9, Robert Langdon10, Barndele Adeunloye11, Ryan Gentzler12, and Nasser Hanna1

1 Indiana University Simon Cancer Center, 2 Indiana University Department of Biostatistics, 3 Fort Wayne Medical Oncology and Hematology, 4 Rutgers Cancer Institute of New Jersey, 5 Michigan Hematology/Oncology, 6 University of Louisville James Graham Brown Cancer Center, 7 IU Health Ball Memorial Hospital, 8 City of Hope Comprehensive Cancer Center, 9 Goshen Center for Cancer Care, 10 Nebraska Medical Hospital, 11 IU Health Arnett Cancer Center, 12 University of Virginia Cancer Health System
Ongoing studies

- **DETERRED**: Phase II Trial Combining Atezolizumab Concurrently with Chemoradiation Therapy in Locally Advanced Non-Small Cell Lung Cancer
- **ECOG EA5181 and SWOG S1910**
Other novel agents

CONCORDE

NSCLC: Platform study of novel agents in Combination with Conventional Radiotherapy in locally advanced disease

- Patients fit for radical RT with or without previous induction chemotherapy
- Patients suitable for concurrent CRT will be excluded (established risk of exacerbating normal tissue and systemic toxicities when combining DDRi with concomitant CRT)
- PS 0-2 as long as PS 2 is due to disease and not comorbidities

PARPi + 60-66 Gy
Weel + 60-66 Gy
ATRi + 60-66 Gy
ATMi + 60-66 Gy
60-66 Gy control arm

Translational research will be essential, but biomarker driven drug selection not planned because predictive biomarkers not yet sufficiently robust
ADSCaN
A Randomised Phase II study of Accelerated, Dose escalated, Sequential Chemo-radiotherapy in Non-Small Cell Lung Cancer

n=360 (120 standard, 60 each experimental arm)
“Cancer comprises a biological spectrum, extending from when a disease is localized to one that is systemic when first detectable but with many intermediate states.”

“An attractive consequence [of the] oligometastatic state is that some patients should be amenable to a curative therapeutic strategy”

Hellman and Weichselbaum, JCO 1995
Definition of synchronous oligometastasis: ESMO guideline st IV NSCLC

treatment of oligometastatic NSCLC

The term ‘oligometastases’ refers to a limited number of haematogenous metastases, although there is no consensus on what ‘limited’ means. Some groups propose a definition of up to three, others up to five metastatic lesions, yet others limit the number of organs in which these metastases are present [165]. The growing interest in oligometastases is based on the concept that long-term disease control, or even cure, may be achieved in some subgroups of these patients [166].
Types of oligometastatic disease

- Synchronous (at diagnosis)
- Metachronous (oligo-recurrence after successful treatment of primary)
- Oligo-progressive and oligo-persistent

Synchronous

Metachronous
Oligo-Persistent Disease

A clinical scenario in which, following response to systemic therapy, there are a limited number of persistent lesions.

Widespread Persistent Disease

- Untreated Distant Metastasis
- Untreated Primary Lesion
- Persistent Distant Metastasis
- Persistent Primary Lesion

Oligo-Persistent Disease
Oligo-Progressive Disease

A clinical scenario in which, following response to systemic therapy, progression of a limited number of lesions occurs while all other sites of disease remain controlled.
Clinical evidence to support idea and the treatment of the oligometastatic state is growing

- More patients being diagnosed with OM due to increased surveillance and improvements in imaging technology and cancer treatment
- The International Registry of Lung Metastases (n=5200). Lung metastectomy. 36% 5yr OS, 26% 10 yr OS. J Thorac Cardiovasc Surg 1997;113(1):37-49
- Liver resection. 30% alive after 5 years - 62% of those without evidence of failure. 2.8% mortality rate (30 studies - Simmonds et al- BJC, 2006)
- SABR/SBRT series consistently show high rates of LC, with encouraging PFS and OS rates, and low rates of toxicity (G3-4 <10%)
- SABR/SBRT now “standard practice” for management of oligometastatic disease in many countries
- Evidence base remains weak
- More clinical trials needed!
Clinical Commissioning Policy: The use of Stereotactic Ablative Radiotherapy (SABR) in the treatment of oligometastatic disease

Reference: NHS England: 16032/P

What we have decided
NHS England has carefully reviewed the evidence to treat oligometastatic disease with Stereotactic body radiotherapy. We have concluded that there is not enough evidence to make the treatment available at this time.
Lung cancer: Building hope in challenging times
Royal Mail & Radiotherapy

Royal Mail says its traditional job of delivering letters and parcels six days a week to every address in the UK for the same price is under threat. We hear from frontline postmen who fear for their jobs and claim rival postal businesses have an unfair advantage. But business analysts say the Royal Mail needs to be more efficient. And why are cancer patients being denied a radiotherapy treatment which leading doctors say is cheaper and more effective?
Victory for Dallaglio in cancer-care battle

Table 1. Indications for SABR to be included in Commissioning through Evaluation proposal.

- a) Oligometastases. (3 sites or fewer).
  Note that once the FIRST centre in England is open for recruitment to the CORE trial, patients eligible for the CORE trial will no longer be eligible for this CIE programme.
  - Spine metastases
  - Liver metastases
  - Adrenal metastases
  - Lymph node metastases
  - Lung metastases
  - Bone metastases

- b) Primary Hepatocellular carcinoma (HCC)

- c) Re-irradiation (pelvis and spine only)
Roy 'Chubby' Brown handed parking ticket after visiting hospital to present charity cheque

Blue comedian donated £5,000 to help cancer patients... then emerged to find he had been given a £50 parking ticket.

Dr Clive Peedel, a cancer specialist at James Cook University Hospital, tweeted: "Big thanks to Roy Chubby Brown for donating £5,000 to our cancer centre. Apologies for parking ticket, Roy!"

A spokeswoman for Chubby added: "Roy reckons the same guy put a parking ticket on the Queen's Rolls Royce outside Buckingham Palace."

Brown was fined £30 fine last month by magistrates in North Yorkshire after he was filmed behind the wheel of his luxury Lexus car on the A19 near Crathorne, North Yorkshire, on May 15 while reading a newspaper.
Lung cancer: Building hope in challenging times
Synchronous oligo-mets – lung cancer results

Stage IV NSCLC: OLIGOMET
Local ablative therapy

PFS 12 vs 4 months

IDMC closed study after 29pts
PFS 10 vs 4 months
Iyengar et al. JAMA Oncol 2017
"OLIGOMEZ" OS data presented at ASTRO 18

Overall Survival

Median 17.0 months
MT/O [HR=0.40, 95% CI 10.1–39.8, P=0.017] vs. 41.2 months LCT [95% CI 18.9–not reached]
Ongoing clinical trials: synchronous

<table>
<thead>
<tr>
<th>Trial number</th>
<th>country</th>
<th>phase</th>
<th>N</th>
<th>title</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02704777</td>
<td>China</td>
<td>3</td>
<td>420</td>
<td>The Optimal Intervention Time of Radiotherapy for Oligometastatic Stage IV NSCLC (OITROLC)</td>
</tr>
<tr>
<td>NCT02316002</td>
<td>USA</td>
<td>2</td>
<td>42</td>
<td>Phase II Study of Pembrolizumab After Curative Intent Treatment for Oligometastatic NSCLC</td>
</tr>
<tr>
<td>NCT02417662</td>
<td>UK</td>
<td>3</td>
<td>340</td>
<td>Stereotactic Ablative Radiotherapy for Oligometastatic NSCLC (SARON)</td>
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<tr>
<td>NCT03119519</td>
<td>China</td>
<td>5-2</td>
<td>590-148</td>
<td>Local Definitive-Non-Salvage Radiotherapy in Synchronous Oligometastatic NSCLC</td>
</tr>
<tr>
<td>NCT03275597</td>
<td>USA</td>
<td>Ib</td>
<td>21</td>
<td>Phase Ib study of S0RT in oligometastatic NSCLC with dual immune checkpoint inhibition</td>
</tr>
</tbody>
</table>
Metachronous oligometas
Stereotactic ablative radiotherapy for comprehensive treatment of oligometastatic tumors (SABR-COMET): Study protocol for a randomized phase II trial

David A Palma1*, Cornelis J A Haasbeek2, George B Rodrigues1, Max Dahele2, Michael Lock1, Brian Yaremko1, Robert Olson3, Mitchell Liu3, Jason Panarotto4, Gwendolyn H M J Griffioen2, Stewart Gaede1, Ben Slotman2 and Suresh Senan3

- Phase II trial. All main tumour types
- 99 patients accrued
- At least 3 months since treatment of primary tumour
- OS 41m vs 28m favouring SABR
- 5yr OS 46% Vs 24%, and 16% had NED at 5 years
- Only 18 lung cancer patients
- More trials needed!
SABR-COMET 10 – up to 10 “oligometas”!
Patients on follow up following radical treatment with ≤ 3 extracranial oligometastases all suitable for SBRT and non-small cell lung, breast or prostate primary cancer fulfilling eligibility criteria.

**Randomisation (1:1)**

**Standard care (SOC)**
- SOC to be defined prior to randomisation
- May include further chemotherapy, hormone therapy, palliative radiotherapy or observation at investigator discretion

**SBRT + Standard care (SOC)**
- SBRT dose and fractionation dependent on site of metastasis and proximity to normal tissues
- SBRT to be performed by SOG as defined prior to randomisation. SOC may include further chemotherapy, hormone therapy or observation at investigator discretion

**Follow-up**
All patients will be reviewed every 3 months with a clinical examination and tumour markers (where applicable) during years 1 and 2, and 6 monthly thereafter to five years. Staging and follow up imaging protocols will be tumour type dependent.

- **Breast:** imaging is 3 monthly CT scans for years 1 and 2, and 6 monthly thereafter to 5 years.
- **Lung:** imaging is 3 monthly CT scans for years 1 and 2, 6 monthly to year 3 and then annually to year 5.
- **Prostate:** imaging in the form of a CT scan will be performed at 6, 12 and 24 months with imaging triggered by appropriate PSA rises. A rising PSA defined as 2 successive PSA rises from nadir, measured a minimum of 4 weeks apart. If the overall PSA rise has a doubling time of ≤ 3 months or the PSA level has doubled the original PSA value at time entry or if clinically indicated, then restaging should be considered.
- All patients will have a toxicity assessment at each clinic visit and patient reported quality of life (QOL) assessment at 3, 6, 12, 18 and 24 months.
- **Footnotes:**
  - CT scans may be replaced by FDG PET-CT scan or whole body dwMR if locally available.
  - CT scans may be replaced by Choline PET/CT scan or whole body dwMR if locally available.

---

<table>
<thead>
<tr>
<th>Trial number</th>
<th>country</th>
<th>phase</th>
<th>N</th>
<th>title</th>
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<tr>
<td>NCT02975609</td>
<td>China</td>
<td>2</td>
<td>300</td>
<td>Phase II Trial of SBRT Compared With Conventional Radiotherapy for Oligometastatic NSCLC</td>
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<tr>
<td>NCT02759783</td>
<td>UK</td>
<td>II/III</td>
<td>206</td>
<td>A Randomised Trial of Conventional Care Versus SBRT for Extracranial Oligometastases (CORE)</td>
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<tr>
<td>NCT03137771</td>
<td>USA (RTOG)</td>
<td>II/III</td>
<td>300</td>
<td>Maintenance Systemic Therapy Versus Consolidative SBRT Plus Maintenance Systemic Therapy for Limited Metastatic NSCLC</td>
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<tr>
<td>NCT03489616</td>
<td>China</td>
<td>2-5</td>
<td>45</td>
<td>Chemotherapy combination with local radiotherapy and rhGM-CSF for oligometastatic NSCLC</td>
</tr>
<tr>
<td>NCT01796288</td>
<td>China</td>
<td>2</td>
<td>200</td>
<td>The Value of Radiotherapy in the Oligometastatic NSCLC With Clinical Benefits From Erlotinib as Second-line Treatment (ROLE)</td>
</tr>
<tr>
<td>NCT02893332</td>
<td>China</td>
<td>3</td>
<td>200</td>
<td>SBRT in Newly Diagnosed Advanced Staged Lung Adenocarcinoma (SINDAS) EGFR mt</td>
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<tr>
<td>NCT02314364</td>
<td>USA</td>
<td>II</td>
<td>30</td>
<td>A Trial of Integrating SBRT With Targeted Therapy in Stage IV Oncogene-driven NSCLC</td>
</tr>
<tr>
<td>NCT03410043</td>
<td>USA</td>
<td>II</td>
<td>143</td>
<td>Trial of Local Consolidation Therapy After Osimertinib for Patients With EGFR Mutant Metastatic NSCLC</td>
</tr>
</tbody>
</table>
Oligoprogresive
HALT
Ablative Local Therapy for Oligo-Progressive Disease in Oncogene-Addicted Lung Tumours

Primary Endpoint: Progression Free Survival

Target: 120 patients

OLIGOPROGRESSIVE

<table>
<thead>
<tr>
<th>Trial number</th>
<th>country</th>
<th>phase</th>
<th>N</th>
<th>title</th>
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<tbody>
<tr>
<td>NCT02756793</td>
<td>Canada</td>
<td>II</td>
<td>54</td>
<td>Stereotactic Radiotherapy for Oligo-Progressive NSCLC (STOP-NCTC)</td>
</tr>
<tr>
<td>NCT03256981</td>
<td>UK</td>
<td>II/III</td>
<td>110</td>
<td>Stereotactic Body Radiotherapy for the Treatment of OPD (HALT) EGFR+</td>
</tr>
<tr>
<td>NCT03557411</td>
<td>China</td>
<td>II</td>
<td>42</td>
<td>A trial of SHR-1210 (anti PD-1) in combination with hypofraction Radiotherapy in patients with NSCLC</td>
</tr>
<tr>
<td>NCT02759783</td>
<td>UK</td>
<td>II/III</td>
<td>300</td>
<td>A Randomised Trial of Conventional Care Versus SBRT for Extracranial Oligometastases</td>
</tr>
<tr>
<td>NCT03137771</td>
<td>USA (RTOG)</td>
<td>II/III</td>
<td>300</td>
<td>Maintenance Systemic Therapy Versus Consolidative SBRT Plus Maintenance Systemic Therapy for Limited Metastatic NSCLC</td>
</tr>
</tbody>
</table>
i-SABR
IO stimulation in SPITFIRE trial
NSCLC and brain metastases

- QUARTZ trial examined the role of whole-brain RT (WBRT) plus optimal supportive care in patients with NSCLC and multiple brain metastases.
- No improvement in survival or quality adjusted life years with the addition of WBRT.
- However, it may still be beneficial for some patients with better prognosis, such as those with driver mutations or controlled extra-cranial disease.
- Hippocampal sparing reduces cognitive decline, but few benefit because prognosis is so poor.
- SRS or surgical resection is recommended for single brain. WBRT or SRS recommended after surgery (ESMO 2018 guidelines).
- Limited multiple brain metastases (eg upto to 5) may be suitable for SRS if RPA group I-II, +/- WBRT.
Radiosurgery for brain metastases

- Consider radiosurgery if:
  - Good PS 0-1, or KPS ≥ 70
  - Controlled extra-cranial disease
  - 1-3 metastases (< 3cm size)
Small Cell Lung Cancer
Limited stage SCLC

- CONVERT trial compared twice-daily RT (45 Gy in 30 fractions) to a higher RT dose delivered once daily (66 Gy in 33 fractions)
- OS did not differ between the two groups; however, the survival achieved in both groups was higher and toxicity much lower (>50% reduction) than previously reported.
- Stage I-II had 5yr OS of 50%, Stage IIIA/B - 28%
- As this trial was designed to show superiority of once-daily RT and was not powered to show equivalence, the implication is that twice-daily RT should remain the standard of care.
- Unfortunately twice daily RT not practical in many centres
- Not all patients suitable for concurrent CRT
SCLC – LD. Post chemo consolidation thoracic RT VMAT plan
PCI – SCLC (LD)

**Table 2. Characteristics of the 987 Patients with Small-Cell Lung Cancer in Complete Remission.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group Treated with Prophylactic Cranial Irradiation (N = 528)</th>
<th>Control Group (N = 459)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, no. (%), Age (median and range)</td>
<td>69 (77)</td>
<td>68 (76)</td>
</tr>
<tr>
<td>Age, range (yr)</td>
<td>64-80</td>
<td>64-79</td>
</tr>
<tr>
<td>55-64 yr, no. (%), LVEF, mmHg (median and range)</td>
<td>177 (14)</td>
<td>178 (14)</td>
</tr>
<tr>
<td>LVEF, mmHg (median and range)</td>
<td>55 (41)</td>
<td>55 (40)</td>
</tr>
<tr>
<td>Extensive Initial Disease</td>
<td>12%</td>
<td>17%</td>
</tr>
</tbody>
</table>

5.4% improvement in 3y OS

54% reduction in risk of brain metastases


Lung cancer: Building hope in challenging times
SCLC – Extensive stage
PCI: ED-SCLC

1 year: 27.1% vs. 13.3%
HR: 0.68 (0.52-0.88)  p=0.003
Risk of brain relapse more than halved

PCI: ED-SCLC

Figure 1. Cumulative Incidence of Symptomatic Brain Metastases.
The difference in the cumulative incidence of brain metastases between the irradiation group and the control group was significant (P<0.001, by Gray’s method).


Lung cancer: Building hope in challenging times
Addition of Thoracic RT in ED – CREST trial

Overall and Progression-Free Survival

Overall survival
HR = 0.84 (95% CI 0.69-1.01) p=0.066
12 m: 33% vs. 28%
24 m: 13% vs. 3% (p=0.004)

Progression-free survival 6 mos
24% (95% CI 19-30) vs 20% (95% CI 16-26) p=0.001

Progression was less likely in the RT group
HR = 0.73 (95% CI 0.61-0.87) p=0.001

Slotman et al. Lancet 2015; 385: 36-42
Overall survival

With residual intrathoracic disease

Overall result  176/215  197/219  0.81  (0.66 – 1.00)
P < 0.05

Without residual intrathoracic disease

Overall result  25/32  27/29  1.02  (0.59 – 1.77)
N.S.

Slotman et al. Lancet 2015; 385: 36–42
Recurrences occurred later and were more often in extra-thoracic and extra-cranial sites.
Summary of TRT in ED SCLC

Thoracic radiotherapy (30Gy in 10fx)
- Improves overall survival
- Improves progression-free survival
- Improves intrathoracic control
- TRT should be offered in addition to PCI to patients with a response but residual intrathoracic disease after chemotherapy
Mesothelioma
PIT Trial in Mesothelioma
Prophylactic Irradiation of Tracts

- UK wide trial, 375 patients randomised
- Chest wall mets at 6/12
  - 6/186 (3.2%) PIT Vs 10/189 (5.3%) no PIT
- Chest wall mets at 12/12
  - 15/186 (8.1%) Vs 19/181 (10.1%)

Conclusion
“There is no role for PIT in MM”
SYSTEMS-2: A randomised phase II study of radiotherapy dose escalation for pain control in malignant pleural mesothelioma

M. Ashton a,b, N. O’Rourke b, N. Macleod b, B. Laird c, J. Stobo d, C. Kelly d, L. Alexander d, K. Franks e, K. Moore b, S. Currie b, R. Valentine b, A.J. Chalmers a,b

a Institute of Cancer Sciences, University of Glasgow, UK
b Beatson West of Scotland Cancer Centre, Glasgow, UK
c Edinburgh Cancer Centre, UK
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ARTICLE INFO

Article history:
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ABSTRACT

SYSTEMS-2 is a randomised study of radiotherapy dose escalation for pain control in 112 patients with malignant pleural mesothelioma (MPM). Standard palliative (20 Gy/5V) or dose escalated treatment (36 Gy/6V) will be delivered using advanced radiotherapy techniques and pain responses will be compared at week 5. Data will guide optimal palliative radiotherapy in MPM.

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Fig. 1. Wire markers denoting the site of pain to aid radiotherapy planning.
Mesothelioma. SMART or not so SMART?
Lung cancer: Building hope in challenging times

IASLC 19th World Conference on Lung Cancer
September 23–26, 2018, Toronto, Canada

424 patients with MPM 2008-2017

123 potential candidates for SMART (29%)

85 eligibility criteria fulfilled (study group)

SMART completed n=85

38 did not meet eligibility
- N2 disease (n=9)
- T4 disease (n=3)
- M1 disease (n=5)
- Synchronous tumor (n=5)
- Previous chemotherapy (n=5)
- Biphasic/sarcomatoid (n=4)
- Other (n=7)

SMART completed (extended group) n=25

Excluded n=13
Toxicities of SMART

- 9 of 62 patients (15%) treated by RT + EPP had grade 4-5 complications

<table>
<thead>
<tr>
<th>Complication types</th>
<th>Total</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with grade 3+ complications, n</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of complication, n°</td>
<td></td>
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Conclusions and take home messages

- Radiotherapy has a role in all stages of disease. Radical and palliative
- Technological developments in radiotherapy have facilitated the developments of new techniques such as SABR/SBRT/SRS. Dose escalation with less side effects
- SABR is the SOC for medically inoperable early stage NSCLC
- Concurrent chemoRT plus durvalumab is the new SOC for stage III NSCLC
- RT in limited and extensive stage SCLC is SOC
- SABR/SBRT in oligo-metastatic disease is very promising and ongoing trials likely change SOC based on phase II trials
- Integration with immunotherapy (i-SABR) very promising
- Ongoing research opportunities are mind-boggling!
- Importance of clever clinical trial designs/platforms
“The pace of cancer immunotherapy clinical studies is such that they have outstripped our progress in understanding the underlying basic science.”

Chen and Mellman Nature 541, 321–330
Potential RT-drug combinations

Fig. 1  RT has great potential to be combined with multiple classes of novel drugs. Reprinted from Nature Reviews Clinical Oncology.11
Thank you
Hairy computer nerds and physicists

Microsoft Corporation, 1978

<table>
<thead>
<tr>
<th>Treatment Planning</th>
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<tr>
<td>Assessment of tumor motion</td>
<td>Large doses per fraction</td>
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<td>Complex beam arrangement</td>
<td>Monitoring of breathing</td>
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<tr>
<td>Advanced planning algorithms</td>
<td>Image-guided targeting</td>
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</table>

“Holy Grail” of radiotherapy

“To deliver a curative radiation dose to the tumour, without causing significant damage to normal tissues”
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