Radiotherapy for NSCLC

Dr Fiona McDonald
Consultant Thoracic Clinical Oncologist
Disclosures

Consulting fees: Astra Zeneca

Speaker fees: Astra Zeneca, Elekta

Research grants: Elekta, MSD, Varian, Accuray
Objectives

SBRT in Early Stage Disease

Radical Treatment for Locally Advanced Disease

Changing role of RT in Advanced Disease
Case: Presentation

71 year old female

Presented with SOBE & minimal haemoptysis

PMH: Hypercholesterolaemia

DH: Atorvastatin

PS: 1

Ex smoker: Prior 40 PYH, stopped 10 years ago
Case: **Investigations**

**CT:** T4 (6.3 cm) N3 (contralateral mediastinal LN) Mo RUL

**PET:** SUV max 19.2

**CT Brain:** No intracranial disease

**Path:** EBUS (stent insertion)
Adenocarcinoma TTF1 + PDL1 70%
EGFR WT No ALK re-arrangement

**LFTs:** FEV1 1.5 77% FVC 2.3 97% TLCO 77%
Case: What treatment would you recommend?

- Neo-adjuvant chemotherapy + surgery
- Sequential radical chemoradiotherapy +/− Durvalumab
- Concurrent radical chemoradiotherapy +/− Durvalumab
- Radical radiotherapy
- Palliative radiotherapy
- Palliative SACT
SABR in Early Stage Disease

Early stage → Locally advanced → Oligo-metastatic → Oligo-recurrent → Oligo-progressive → Advanced
Highly conformal plans
High precision delivery
Hypo-fractionation
High-dose per fraction
Low toxicity

3yr OS following SABR up to 80%
Louie et al  Rad Onc 2015;
### How does SABR compare to surgery?

<table>
<thead>
<tr>
<th>Study</th>
<th>Surgical Study Arm</th>
<th>SBRT Study Arm</th>
<th>Eligibility</th>
<th>Primary Endpoint</th>
<th>Secondary Endpoints</th>
<th>Recruitment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dutch ROSEL Trial (NCT00687986)</td>
<td>Anatomical resection with lymph node dissection</td>
<td>60 Gy in 3# or 60 Gy in 5#</td>
<td>Operable patients, Stage IA disease</td>
<td>5 year local control</td>
<td>Toxicity, OS, quality adjusted life years</td>
<td>22 patients</td>
</tr>
<tr>
<td>U.S. STARS Trial (NCT00840749)</td>
<td>Anatomical resection</td>
<td>60 Gy in 3# or 60 Gy in 4#</td>
<td>Operable patients, Stage IA &amp; IB disease ≤4 cm</td>
<td>3 year OS</td>
<td>Toxicity, progression-free, disease-specific survival</td>
<td>36 patients</td>
</tr>
<tr>
<td>U.S. ACOSOG Trial (NCT01336894)</td>
<td>Sublobar resection +/- brachytherapy</td>
<td>Variable dose in 3#</td>
<td>‘High operable risk’ patients, stage IA disease</td>
<td>5 year OS</td>
<td>Toxicity, disease free survival</td>
<td>13 patients</td>
</tr>
</tbody>
</table>

#### Results

- **58 Operable Patients**
  - T1-2 No Mo <4 cm NSCLC
  - Median F/U 35-40 months
- **No difference in OS**
- **SABR lower G3-4 toxicity**

Chang et al Lancet Oncol 2015;
How does SABR compare to conventional RT?

SPACE: Phase II Trial of RT vs SABR

Trend of improved LC with SABR
Improved toxicity & HRQL with SABR

Nyman et al Rad Onc 2016;
How does SABR compare to conventional RT?

**CHISEL: Phase III Trial of RT vs SABR**

Medically Inoperable or Declined Surgery
Stage 1 Peripheral NSCLC <5 cm (PET staged)

Primary Endpoint: Time to local failure

Randomise (2:1)

- **SABR**
  - 54 Gy 3# or 48 Gy in 4# to covering isodose

- **Conventional RT**
  - 66 Gy 33# or 50 Gy 20#

101 patients recruited

101 patients recruited

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Ball et al Lancet Oncol 2019;
CHISEL: Phase III Trial of RT vs SABR

- Overall Survival
  - HR 0.53 p = 0.027
  - Standard RT vs SABR

- Freedom from local failure
  - HR 0.32 p = 0.008
  - Standard RT vs SABR

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Is SABR safe for central lesions?

IASLC recommended definition of central lesion

GTV within 2 cm zone around bronchial tree, major vessels, heart, oesophagus, spinal cord, phrenic & recurrent laryngeal nerve, brachial plexus
RTOG 0813: Phase I/II Trial of 5# SABR for central early stage NSCLC

T1-2 No Mo ≤5 cm
Phase I trial to establish MTD with 5# SABR
10-12 Gy x 5 in 0.5 Gy increments TITE CRM p(DLT) = 20%
One year cumulative F/U over ≤4 patients prior to each dose level

<table>
<thead>
<tr>
<th>SBRT Dose</th>
<th># pts</th>
<th>Grade 3 n (%)</th>
<th>Grade 4 n (%)</th>
<th>Grade 5* n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10X5</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10.5X5</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>11X5</td>
<td>14</td>
<td>1 (7.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11.5X5</td>
<td>38</td>
<td>4 (10.5)</td>
<td>0</td>
<td>2 (5.3)</td>
</tr>
<tr>
<td>12X5</td>
<td>33</td>
<td>5 (15.2)</td>
<td>1 (3.0)</td>
<td>1 (3.0)</td>
</tr>
</tbody>
</table>

*grade 5 AEs = hemoptysis at a mean 13 mo post SBRT (range 5.5-14mo)
LungTech: Phase II Trial of 8# SABR for central early stage NSCLC

Medically Inoperable Central NSCLC <7 cm

Primary Endpoint: Freedom from local progression at 3 years

Target Patient Number: 150

PI: Prof Ursula Nestle
NCT01795521

SABR 60 Gy 8#
LUSTRE: Phase III Trial of Conventional RT vs SABR for early stage NSCLC

Medically Inoperable or Declined Surgery
Stage 1 Peripheral or Central NSCLC <5 cm

Randomise (2:1)

Primary Endpoint: Local Control

SABR
48 Gy 4# or 60 Gy 8#

Conventional RT
60 Gy 15#

Planned accrual of 324 patients

PI: Dr Tim Whelan
NCT01968941

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Is SABR safe for ultra-central lesions?

Corradetti et al NEJM 2012; 366: 2327

47 patients
60 Gy in 12#
Median F/U 29 mths
Median OS 16 mths
15% Fatal pulmonary haemorrhage

Tekatli et al JTO 2016; 11: 1081-9
SUNSET: Phase I Trial of Conventional RT vs SABR for early stage NSCLC

Ultra-central tumor location:
PTV(≤ 6 cm), touching or overlapping the central bronchial tree, esophagus, pulmonary vein, or pulmonary artery

Primary Endpoint: MTD G3-5 toxicity rate ≤30%

Planned accrual of 30 patients

<table>
<thead>
<tr>
<th>DOSE LEVELS</th>
<th>Level -1</th>
<th>Level 0</th>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose per fraction:</td>
<td>4 Gy</td>
<td>6 Gy</td>
<td>7.5 Gy</td>
<td>10 Gy</td>
<td>12 Gy</td>
</tr>
<tr>
<td>Number of fractions:</td>
<td>15</td>
<td>10</td>
<td>8</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Total Dose:</td>
<td>60 Gy</td>
<td>60 Gy</td>
<td>60 Gy</td>
<td>60 Gy</td>
<td>60 Gy</td>
</tr>
</tbody>
</table>

PI: Meredith Giuliani
How does SABR compare to no treatment?

Population-based time-trend analysis: Impact of SABR

- Wide spread availability of SABR
- Absolute RT use increase
- Decline in the proportion of untreated elderly patient
- Improvement in OS

Palma et al. JCO 2010; 28: 5153
Radical Treatment for Locally Advanced Disease

Early stage → Locally advanced → Oligo-metastatic → Oligo-recurrent → Oligo-progressive → Advanced

Life demands excellence
The Royal Marsden

The Challenge .......

Baseline patient factors:
Performance status, co-morbidities, weight loss

Tumour factors:
Histological subtype, genetic/mutational status & intra-tumour heterogeneity. Disease stage, primary tumour volume & location, extent of nodal involvement

Organ at risk factors:
Lung function and cardiac function, Proximity of target to OARs
**Meta-Analysis of Concomitant vs Sequential CRT in LA NSCLC**

- **3 yr OS benefit**: 5.7%
- **3 yr LR PFS benefit**: 6%
- Increased ≥G3 oesophageal toxicity 4 to 18%

Auperin et al JCO 2010;
Meta-Analysis of Accelerated RT in LA NSCLC

5 yr OS benefit 2.5%
## Why cisplatin backbone in cCTRT setting?

<table>
<thead>
<tr>
<th>Trial</th>
<th>Accrual Period</th>
<th>No. of Randomly Assigned Patients</th>
<th>Patients Alive</th>
<th>Median Follow-Up (years)</th>
<th>Concomitant Chemoradiotherapy</th>
<th>Sequential Chemoradiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 9631</td>
<td>1988-1999</td>
<td>91</td>
<td>7</td>
<td>9.2</td>
<td>Cb 100 mg/m²/wk × 6 wk</td>
<td>Start on day 50 after induction CT: 60 Gy, 30 f, 6 wk; RT started in 80% of patients</td>
</tr>
<tr>
<td>WJ/LCG15</td>
<td>1992-1994</td>
<td>314</td>
<td>41</td>
<td>4.9</td>
<td>Cisplatin 80 mg/m² days 1, 29, Vd 3 mg/m² days 1, 8, 29, 36, Mi 8 mg/m² days 1, 29</td>
<td>Induction CT: cisplatin 80 mg/m² days 1, 29, Vd 3 mg/m² days 1, 8, 29, 36, Mi 8 mg/m² days 1, 29</td>
</tr>
<tr>
<td>RTOG 9410</td>
<td>1994-1998</td>
<td>407</td>
<td>38</td>
<td>6.4</td>
<td>Cisplatin 100 mg/m² days 1, 29, Vb 5 mg/m² weekly × 5 wk</td>
<td>Induction CT: cisplatin 100 mg/m² days 1, 29, Vb 5 mg/m² weekly × 5 wk</td>
</tr>
<tr>
<td>GMMA Ankara</td>
<td>1995-1996</td>
<td>30</td>
<td>0</td>
<td>8.0</td>
<td>Cisplatin 6 mg/m² daily</td>
<td>Induction CT: cisplatin 40 mg/m², Et 200 mg/m², if 200 mg/m² days 1, 3, 5, 29, 31, 33</td>
</tr>
<tr>
<td>GLO-GoPC NPC 95-01</td>
<td>1996-2000</td>
<td>206</td>
<td>22</td>
<td>8.0</td>
<td>Cisplatin 20 mg/m² days 1-5, 29-33, Et 50 mg/m² days 1-5, 29-33; consolidation CT: cisplatin 80 mg/m² days 78, 106, Vn 30 mg/m²/wk days 78-127</td>
<td>Induction CT: cisplatin 120 mg/m² days 1, 29, 67, Vn 30 mg/m²/wk days 1-78</td>
</tr>
<tr>
<td>EORTC 08972</td>
<td>1999-2003</td>
<td>158</td>
<td>29</td>
<td>4.2</td>
<td>Cisplatin 6 mg/m² daily</td>
<td>Induction CT: cisplatin 75 mg/m² days 2, 23, gemcitabine 1,250 mg/m² days 1, 8, 22, 29</td>
</tr>
</tbody>
</table>

Cisplatin doublet can be combined at full dose with RT

Auperin et al J Clin Oncol 2010
Systemic doublet choice in cCTRT setting?

- Cisplatin - etoposide
- Cisplatin - vinorelbine
- Carboplatin - paclitaxel (US)
- Cisplatin daily (NKI)

Evidence to support one regime over another?

Meta-analysis 79 studies
3090 patients from 31 CE studies / 3728 patients from 48 CP studies

3 Year OS

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>CE</th>
<th>CP</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis</td>
<td>9%</td>
<td>7%</td>
<td>0.17</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>20%</td>
<td>15%</td>
<td>0.18</td>
</tr>
<tr>
<td>N/V</td>
<td>20%</td>
<td>9%</td>
<td>0.018</td>
</tr>
<tr>
<td>Anemia</td>
<td>16%</td>
<td>8%</td>
<td>0.06</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>14%</td>
<td>6%</td>
<td>0.001</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>54%</td>
<td>23%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Stauer et al JAMA Oncol 2016;
RTOG 0617: Phase III in Stage III NSCLC
60 Gy vs 74 Gy +/- Cetuximab

Overall Survival (percent)

Median OS
20 vs 29 months

Heart doses correlated with survival

Bradley et al Lancet Oncol 2015;
**PROCLAIM: Pemetrexed in Non-Squamous**

555 patients treated

No difference OS median 27 vs 25 mths

Trend towards OS for IIIb & PTV >700 ml

Trend towards PFS

Significantly fewer ≥G3 drug-related AE

Senan et al JCO 2016; 34: 953
‘Better than Expected’ Survival due to Additional Technical Advances?

RTOG 0617 60 Gy Cohort
MS 29 months 2 year OS 57%
91% PET staged / 46% IMRT

PROCLAIM
MS 27 months 2 year OS 52%
81% PET staged

NKI
Daily low dose Cisplatin 6 mg/m²
66 Gy 24 # 2.75 Gy/#
MS 36 months 2 year OS 61%
100% PET Staged / 76% IMRT

Dieleman et al IJROBP 2018;
Induction or consolidation chemotherapy?

Ahn et al JCO 2015;

Vokes et al JCO 2007;
Integration of TKIs?

RTOG1306: cCRT +/- Induction TKI

Primary Endpoint: PFS

ITT Group

Disease Free Survival

HR 0.90

HR 0.61

Mut + Group

Kelly et al JCO 2015

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PACIFIC: Phase III Trial of Adjuvant Duvalumab after cCRT in LA NSCLC

Stage III NSCLC
Concomitant CRT with at least 2 cycles of platinum based systemic therapy

Adjuvant
Anti PD-1
Duvalumab up to 12 mths

Placebo up to 12 mths

2 year OS
Durvalumab
66%
Placebo
56%

Halving of incidence on new CNS disease
6% vs 12%

Low rates of grade ≥3 pneumonitis / pneumonia 7.8% vs 5.6%
~ 45% each arm Stage IIIB disease

Antonia et al NEJM 2018;
# PACIFIC: PFS & OS by Subgroup

<table>
<thead>
<tr>
<th></th>
<th>PFS HR (95% CI)</th>
<th>OS HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age at randomization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65 years</td>
<td></td>
<td></td>
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<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Disease stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IIIB</td>
<td></td>
<td></td>
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<tr>
<td><strong>Tumor histologic type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
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<td></td>
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<tr>
<td>Non-squamous</td>
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<tr>
<td><strong>Prior definitive CT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carboplatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Best response to prior treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>NA*</td>
<td>NA*</td>
</tr>
<tr>
<td>PR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
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<tr>
<td><strong>EGFR status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td></td>
<td>NA*</td>
</tr>
<tr>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
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</tbody>
</table>

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The Royal Marsden

PACIFIC: PFS & OS by PDL1 Status

- 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
## PACIFIC: Safety

<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</td>
<td>161 (33.9)</td>
<td>58 (24.8)</td>
</tr>
<tr>
<td>pneumonitis, n (%)</td>
<td></td>
<td></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>

AE, adverse event.
Back to the Case: Treatment

Concurrent radical chemoradiotherapy & adjuvant Durvalumab

- Cisplatin & Pemetrexed 3 cycles
- 4D CT motion management
- VMAT single arc
- Lung V20 33% MLD 18 Gy
- Daily CBCT image verification
- 64 Gy 32# concurrent with cycles 2
- 11.04.18
- Grade 2 oesophagitis
- Adjuvant Durvalumab D1 C1 13.06.18
Case: Outcome

June 2018
Post 1st Durvalumab
3 week in patient admission

Day 1 Cycle 2 Durvalumab
13.08.18

Oct 2018
Post 7\textsuperscript{th} Durvalumab

Jan 2019
Post 12th Durvalumab
Trimodality Treatment: ESMO Consensus Guidelines

IMAGING: CT-SCAN
- No enlarged LNs and peripheral tumour
  - Not required if negative LNs on PET
- No enlarged N2 nodes but central tumour or hilar LNs
  - Enlarged discrete N2 LNs
- Extensive mediastinal N2 infiltration

INVASIVE LN RESULT
- Surgery: unforeseen N2
- Potentially resectable N2
- Not required
- Unresectable N2

CATEGORY OF N2
- N0-N1
- N2
- N3

THERAPEUTIC APPROACH
- Adjuvant chemotherapy (radiotherapy)
- Dedicated multidisciplinary assessment
- Surgical multimodality treatment
- Non-surgical multimodality treatment

Eberhardt et al Ann Oncol 2015;
Patients with positive resection margin or extra-capsular spread were excluded

Le Pechoux et al Oncologist 2011;
The changing role of RT in Advanced Disease
Traditional Standard of Care?
When I started oncology training ....

<table>
<thead>
<tr>
<th>Palliative RT</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td></td>
</tr>
<tr>
<td>Alleviation of pain</td>
<td>Bone metastasis</td>
</tr>
<tr>
<td>Shrinkage of symptomatic mass</td>
<td>Fungating subcutaneous metastasis</td>
</tr>
<tr>
<td>Control of bleeding</td>
<td>Tumour invading pulmonary artery causing haemoptysis</td>
</tr>
<tr>
<td>Relief of obstruction / compression</td>
<td>Tumour around main bronchus / SVC Disease causing MSCC Brain metastases</td>
</tr>
</tbody>
</table>

Median OS 7.9 months

Overall Survival

Time (Months)

Schiller et al NEJM 2002;
WBRT for brain metastases?

A NEW PROGNOSTIC INDEX AND COMPARISON TO THREE OTHER INDICES FOR PATIENTS WITH BRAIN METASTASES: AN ANALYSIS OF 1,960 PATIENTS IN THE RTOG DATABASE

<table>
<thead>
<tr>
<th>Graded Prognostic Assessment</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt;60</td>
<td>50-59</td>
<td>&lt;50</td>
</tr>
<tr>
<td>KPS</td>
<td>&lt;70</td>
<td>70-80</td>
<td>90-100</td>
</tr>
<tr>
<td>Number of cranial mets</td>
<td>&gt;3</td>
<td>2-3</td>
<td>1</td>
</tr>
<tr>
<td>Extra-cranial mets</td>
<td>Present</td>
<td>Absent</td>
<td></td>
</tr>
</tbody>
</table>

Sperduto et al IJROBP 2009; 70: 510
QUARTZ: WBRT vs Optimal Supportive Care

Median OS P=0.52
WBRT 9.3 weeks
OSC 8.1 weeks

Mean QALY
WBRT 43 days
OSC 41 days

Mulvenna et al Lancet 2016
‘Radical’ RT has been SOC for years …..

RTOG 9508 Phase III Trial WBRT +/- SRS boost

Significant survival advantage in patients with single metastasis 6.5 vs 4.9 months p=0.04

333 Patients 64% Primary Lung Cancer

Adjuvant WBRT for 1-3 brain metastases?

Adjuvant Whole-Brain Radiotherapy Versus Observation After Radiosurgery or Surgical Resection of One to Three Cerebral Metastases: Results of the EORTC 22952-26001 Study

- 359 patients
- 1-3 BM, WHO PS 0-2, controlled extra-cranial disease
- Neurosurgery or SRS randomised, WBRT 30 Gy 10 # vs observation
- Significant decrease in relapse intra-cranially with WBRT
- Significant decrease in neurological deaths (28% WBRT vs 44% obs)
- No difference in duration of functional independence
- No difference in OS (10.9 mths WBRT vs 10.7 mths obs)

Subsequent HR QOL data
- Significant and clinically relevant decrease in HR QOL with WBRT
- Recommend close monitoring with MRI rather than WBRT

Kocher et al JCO 2011 & 2013;
What about Extra-cranial Oligo-Metastatic Disease?

- **Synchronous**
  - Untreated Distant Metastasis
  - Untreated Primary Lesion

A clinical scenario in which oligometastatic disease is detected at the time of diagnosis of the primary tumour

- **Metachronous Oligo-Recurrent**
  - Untreated Distant Metastasis
  - Treated Primary Lesion

A clinical scenario in which the development of oligometastatic disease after treatment of the primary tumour

Oli-GOMEZ Trial

SABR-COMET Trial
Oli-GOMEZ: Phase II Trial of LCT & SOC vs SOC in synchronous oligo-metastatic NSCLC

First-line treatment for oligometastatic stage IV NSCLC (1-3 metastases)

Acceptable regimens:
- ≥4 cycles of platinum-based doublet+/+BV
- Osimertinib and crizotinib are acceptable for patients with EGFR mutations and EML4-ALK fusions, respectively.
- CNS metastases can be treated prior to enrollment

No local consolidation therapy (LCT) arm**

Physician choice for standard maintenance or surveillance*

PD

Non-PD
Enroll, randomize

LCT arm

Local consolidation (surgery and/or radiation to primary and metastases)

Physician choice for standard maintenance or surveillance*

PD

Eligibility
- 1-3 mets after completion of first-line treatment
- Non-PD
- PS 0-2
- Candidate for local therapy

Covariates
- Number of mets (1 vs. 2-3)
- Response to first-line chemo (SD vs. PR/CR)
- N0/N1 vs. N2/N3
- CNS Mets (yes/no)
- EGFR/EML4ALK status

Gomez et al Lancet Oncol 2016; 17(12):1672-1682
Oli-GOMEZ: ASTRO 2018 Update

mPFS 14.4 vs 4.4 mths in favour of local therapy p=0.02

mOS 41.2 vs 17.0 mths in favour of local therapy HR=0.40 P=0.017

No additional ≥Grade 3 AEs in either arm
**SABR-COMET:** Phase II Trial of SABR & SOC compared to SOC in metachronous oligo-metastatic disease

**Primary Endpoint:**
- Overall Survival

**Secondary Endpoints:**
- Progression-free survival
- Toxicity
- Quality of life
- Lesional control rate

**Inclusion Criteria:**
Controlled primary defined as ≥3 mths since original tumor treated definitively, with no progression at primary site

Up to 5 hematogenous metastases (maximum 3 in any single organ)

All sites of disease safely treatable
SABR-COMET: Phase II Trial of SABR & SOC compared to SOC in metachronous oligo-metastatic disease

mPFS 12 vs 6 mths in favour of local therapy p=0.001

mOS 41 vs 28 mths in favour of local therapy p=0.09
Oligo-Persistent & Oligo-Progressive Disease

At least 15% pattern of disease probably suitable for SBRT

Yoshida et al Lung Ca 2015; Al-Halabi et al JTO 2015;
HALT: Phase II Trial of SBRT & TKI for Oligo-Progressive Oncogene Addicted Lung Tumours

Advanced NSCLC
EGFR / ALK + with response to TKI

Progression

TKI

Oligo-Progression
Randomise (2:1)

Target: 110 patients

SBRT & continue TKI

Primary Endpoint:
Progression Free Survival

Widespread Progression

Continue TKI

Primary Endpoint:
Progression Free Survival

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Clinical Practice Guidelines

Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

P. E. Postmus¹, K. M. Kerr², M. Oudkerk³, S. Senan⁴, D. A. Waller⁵, J. Vansteenkiste⁶, C. Escrivel⁷ & S. Peters⁷,
on behalf of the ESMO Guidelines Committee

Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

D. Planchard¹, S. Popat², K. Kerr³, S. Novello⁴, E. F. Smit⁵, C. Faivre-Finn⁶, T. S. Mok⁷, M. Reck⁸,
P. E. Van Schil⁹, M. D. Hellmann¹⁰ & S. Peters¹¹, on behalf of the ESMO Guidelines Committee

ESTRO ACROP guideline

ESTRO ACROP guidelines for target volume definition in the treatment of locally advanced non-small cell lung cancer

Ursula Nestle⁴, Dirk De Ruyscher⁵, Umberto Ricardi⁶, Xavier Geets⁷, Jose Belderbos⁸, Christoph Pöttgen⁹, Rafał Dziadziuszko⁵, Stephanie Peeters⁴, Yolande Lievens⁷, Coen Hurkmans⁸, Ben Slotman⁴, Sara Ramella⁹, Corinne Faivre-Finn⁷, Fiona McDonald⁷, Farkhad Manapov⁸, Paul Martin Putora⁴, Cécile LePéchoux⁴, Paul Van Houtte¹¹
Clinical Practice Guidelines

**MEDIASTINAL BIOPSY FINDINGS**

<table>
<thead>
<tr>
<th>T1-3, N0-1 (including T3 with multiple nodules in same lobe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable(^k,n)</td>
</tr>
<tr>
<td>Medically inoperable</td>
</tr>
</tbody>
</table>

**INITIAL TREATMENT**

- Surgical resection\(^k\) + mediastinal lymph node dissection or systematic lymph node sampling
- See Treatment according to clinical stage (NSCL-2)

**ADJUVANT TREATMENT**

- See Adjuvant Treatment (NSCL-3)

**T1-2, T3 (other than invasive), N2 nodes positive, M0**

- Definitive concurrent chemoradiation\(^l,d\) (category 1)
  - or
  - Induction chemotherapy\(^o,w\) ± RT\(^l\)

- No apparent progression
  - Local
    - RT\(^l\) (if not given) ± chemotherapy\(^o\)
  - Systemic
    - See Treatment for Metastasis limited sites (NSCL-13) or distant disease (NSCL-16)

**T3 (invasion), N2 nodes positive, M0**

- Definitive concurrent chemoradiation\(^l,q\)

**ADJUVANT TREATMENT**

- Durvalumab\(^q\) → Surveillance (NSCL-15)

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Take home messages

SBRT important option for peripheral ES NSCLC lesions

**CAUTION** with SBRT for ‘central’ & ‘ultracentral’ lesions

cCRT is treatment of choice for LA

Adjuvant IO should be considered for PDL1 ≥1%

‘Radical’ RT has an increasing role in advanced NSCLC
Thank you

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