State-of-the-art for Locally Advanced unresectable / inoperable disease NSCLC:
- Post-Operative Radiation Therapy (PORT) in resected N2 NSCLC
- Update on RT/CT for unresectable NSCLC
- Stereotactic RT and IMRT for inoperable NSCLC

Dr Ivan Tham
Head of Department & Senior Consultant
Department of Radiation Oncology
National University Cancer Institute, Singapore
Relevant Disclosures:

Nil
Welcome to Singapore!
Outline

- Stereotactic RT and IMRT for inoperable NSCLC
- Post-Operative Radiation Therapy (PORT) in resected N2 NSCLC
- Update on RT/CT for unresectable NSCLC
Stereotactic RT and IMRT for inoperable NSCLC
Stereotactic Body RT / Stereotactic Ablative Radiotherapy

Key Components

Evidence (single arm)

SBRT vs Conventionally fractionated RT?

Peripheral vs Central?

SBRT vs surgery?

Toxicities of local treatment

Lung changes following SBRT
Key Components of an SBRT/SABR Programme

- Multi-disciplinary management
- Respiratory motion management
- Multiple angles/modulation
- Image-guidance
- Meticulous quality assurance programme
Prospective data for SBRT for inoperable T1/2N0 NSCLC

RTOG 0236 54 Gy/3F
Medically inoperable n=55

3 y OS 56%
3 y LRC 87%

Toxicity: Gr 3: 18%, Gr 4: 4% Gr 5: 0

JCOG 0403 48 Gy/4F
Medically inoperable n=100

3 y OS 60%
3 y LC 87.3%

Toxicity: Gr 3: 10%, Gr 4: 2%, Gr 5: 0

Timmerman et al. JAMA 2010
Nagata, et al. IJROBP 2015
SBRT vs Conventionally Fractionated RT

SPACE
SBRT 66 Gy/3F vs. CFRT 70 Gy/35F
n=102

1/3 had no histology
47% T2 for SBRT vs 25% for CFRT

SBRT better quality of life, cheaper, more convenient

CHISEL: A randomized phase III trial of SABR vs conventional RT for inoperable stage I NSCLC (TROG 09.02, ALTG 09.05)

Freedom from local failure and overall survival

n = 101

HR 0.29, 95% CI 0.13, 0.66
P = 0.002

HR 0.51, 95% CI 0.29, 0.91
P = 0.020

Ball et al. WCLC 2017
Peripheral vs central (vs “ultra-central”)
<table>
<thead>
<tr>
<th>Size</th>
<th>No. of fractions</th>
<th>Rate of acceptance</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4cm</td>
<td>3</td>
<td>High (85%)</td>
</tr>
<tr>
<td>&gt; 4cm</td>
<td>4 – 8</td>
<td>Intermediate (50%)</td>
</tr>
<tr>
<td>&gt; 4cm</td>
<td>8 – 12 (consider 20-33 fractions)</td>
<td>Low (33%)</td>
</tr>
<tr>
<td>OAR infiltration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>minimal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>extensive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distance to carina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 4cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 4cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2.5cm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Roesch et al. Radiat Oncol 2016
Central lesion SBRT
n = 100
T1/2 or isolated local recurrence
4 or 10 fractions
3y OS 70.5%
Grade 3 toxicity <10%
except brachial plexopathy

Respect dose constraints to normal structures

Representative case of SABR designed to spare esophagus, heart, aorta & spine

Surgery vs RT for operable NSCLC?

Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials


Summary
Background The standard of care for operable, stage I, non-small-cell lung cancer (NSCLC) is lobectomy with mediastinal lymph node dissection or sampling. Stereotactic ablative radiotherapy (SABR) for inoperable stage I NSCLC has shown promising results, but two independent, randomised, phase 3 trials of SABR in patients with operable stage I NSCLC (STARS and ROSEL) closed early due to slow accrual. We aimed to assess overall survival for SABR versus surgery by pooling data from these trials.
- Small numbers overall
- Likely small differences
- Different toxicity profile
- “Not surprising ...”
  - Head & neck cancer
  - Anal cancer
  - Cervical cancer
  - Locally advanced NSCLC

Also closed to accrual
RTOG 1021/ACOSOG Z4099, “A Randomized Phase III Study of Sublobar Resection (+/- Brachytherapy) versus SBRT in High Risk Patients with Stage I NSCLC”

Figure 2: Overall survival (A) and recurrence-free survival (B)
One patient died and five had recurrence in the SABR group compared with six and six patients, respectively, in the surgery group. SABR = stereotactic ablative radiotherapy. HR = hazard ratio.
Outcomes outside of randomised trials

NCDB
3 y OS ~73%

ACOSOG Z0030

JCOG 0403
Operable n = 64
3 y OS ~77%
Nagata, et al. IJROBP 2015
### Toxicity of Local Treatment

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Surgery</th>
<th>SBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 – 15%</td>
<td>Atrial arrhythmia&lt;br&gt;Chest tube in &gt; 7 days</td>
<td>Pneumonitis (any grade)</td>
</tr>
<tr>
<td>5 – 10%</td>
<td>Atelectasis&lt;br&gt;Respiratory failure</td>
<td>Pneumonitis (&gt; grade 2)&lt;br&gt;Oesophagitis (any grade)&lt;br&gt;Chest wall pain</td>
</tr>
<tr>
<td>2 – 5%</td>
<td>Pneumonia&lt;br&gt;Haemorrhage (requiring transfusion)</td>
<td>Dermatitis&lt;br&gt;Rib fracture&lt;br&gt;Fatigue</td>
</tr>
<tr>
<td>&lt;2%</td>
<td>Haemorrhage (requiring re-operation)&lt;br&gt;Myocardial infarction&lt;br&gt;Empyema/chylothorax&lt;br&gt;ARDS&lt;br&gt;Nerve injury&lt;br&gt;Death</td>
<td>Nerve injury&lt;br&gt;Oesophagitis (&gt; grade 2)&lt;br&gt;Death</td>
</tr>
</tbody>
</table>

Shah, et al. Semin Radiat Oncol 2017
Lung Changes Following SBRT

Guckenberger et al Radiother Oncol 2007; 85: 435
Summary: SBRT for early stage NSCLC

- SBRT valid treatment option for early stage NSCLC
- Risk-adjusted fractionation for central lesions
- Typically 3 to 8 fractions
- Caution for “ultra-central” lesions
- Main mode of failure is distant metastases
- Need for long-term follow-up
Post-Operative Radiation Therapy (PORT) in resected N2 NSCLC
Data from the PORT Meta-analysis Trialists Group

Stage and nodal status subgroup analysis for survival

Biological Equivalent Dose

Figure 6: Stage and nodal status subgroup analysis for survival

Lancet, 1998

Munro, Lancet 1998
PORT - Controversies

Local control better, but not OS

OS better, but not randomised

Billiet, Radiother Oncol 2014

Large datasets?

- 2 NCDB cohorts - 2006-2010, 2004-2013
- pN2 + adjuvant chemotherapy


Summary: PORT

Resectable LA-NSCLC

.... In case of complete resection, addition of PORT is not routinely recommended, but may be an option following individual risk assessment [V, C]

Postmus et al., Ann Oncol 2017

Timing

- No Chemotherapy
- 4 – 8 weeks after surgery
- After chemotherapy
- 2 – 6 weeks after last chemotherapy

Method & Dose

- 3D – Conformal RT or Intensity Modulated RT
- 54 Gy in 27 – 30 fractions
Update on RT/CT for unresectable NSCLC
Locally Advanced Unresectable NSCLC

- Life before “Pacific”
- Immunotherapy
- Cardiac Toxicity
- Future of Dose Optimisation
- Beyond Photons
Concurrent Chemotherapy +/- Accelerated RT
RTOG 9410

Stage IIIA/B NSCLC
  - Unresectable

Sequential chemo then RT
- Arm 1

Conventional CRT
- Arm 2

Accelerated CRT
- Arm 3

5 year overall survival
- 10%
- 16%
- 13%

Conventional fractionation: 63 Gy/ 34 fractions/ 7 weeks
Accelerated fractionation: 69.6 Gy/ 58 fractions/ 6 wks

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary treatment</th>
<th>Biomarker</th>
<th>Intervention</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAGRIT</td>
<td>Surgery</td>
<td>MAGE-A3</td>
<td>MAGE-A3 immunotherapeutic</td>
<td>Negative</td>
</tr>
<tr>
<td>STOP</td>
<td>CT +/- RT</td>
<td>-</td>
<td>Belagenpumatucel-L</td>
<td>Overall negative (but positive signal for those with RT in &lt;6 mths)</td>
</tr>
<tr>
<td>START</td>
<td>CT+RT</td>
<td>-</td>
<td>Tacemotide</td>
<td>Overall negative (but positive signal for CCRT)</td>
</tr>
<tr>
<td>PACIFIC</td>
<td>CCRT</td>
<td>-</td>
<td>Durvalumab</td>
<td>Positive (interim)</td>
</tr>
</tbody>
</table>

**Adjuvant/Consolidation Immunotherapy for Locally Advanced NSCLC**

![Progression-free Survival in the Intention-to-Treat Population](image)

*Figure 1. Progression-free Survival in the Intention-to-Treat Population.*

Shown are Kaplan-Meier curves for progression-free survival (PFS), defined according to the Response Evaluation Criteria in Solid Tumors, version 1.1, and assessed by means of blinded independent central review. Tick marks indicate censored observations, and vertical lines indicate the times of landmark PFS analyses. The intention-to-treat population included all patients who underwent randomization.
Radiation-Induced Immune Modulation

TABLE 1. Mechanisms of Radiation-Induced Immune Modulation

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor debulking and releasing tumor antigens</td>
<td>Chakraborty et al.</td>
</tr>
<tr>
<td>Not systemically immunosuppressive</td>
<td>Formenti et al.</td>
</tr>
<tr>
<td>Up-regulation of immunogenic cell surface markers</td>
<td>Fas</td>
</tr>
<tr>
<td>ICAM-1, MHC-1</td>
<td>Chakraborty et al.</td>
</tr>
<tr>
<td>Secretion of danger signals and cytokines</td>
<td>Lugade et al.</td>
</tr>
<tr>
<td>IFN-γ, TNFα</td>
<td>Formenti et al.</td>
</tr>
<tr>
<td>IL-1β</td>
<td>Formenti et al.</td>
</tr>
<tr>
<td>Induction of immunogenic cell death</td>
<td>Obeid et al.</td>
</tr>
<tr>
<td>Calreticulin</td>
<td>Apetoh et al.</td>
</tr>
<tr>
<td>HMGB1</td>
<td>Ganss et al.</td>
</tr>
<tr>
<td>Increased homing of immune cells to tumors</td>
<td>Matsumura et al.</td>
</tr>
<tr>
<td>Normalization of tumor vasculature</td>
<td>Lugade et al.</td>
</tr>
<tr>
<td>Secretion of chemo-attractants (excl16)</td>
<td>Klug et al.</td>
</tr>
<tr>
<td>Endothelial expression of VCAM-1</td>
<td>Stromme et al.</td>
</tr>
<tr>
<td>Improved T-cell homing to tumors</td>
<td>Apetoh et al.</td>
</tr>
<tr>
<td>Improved antigen presentation by APC’s</td>
<td>Wu et al.</td>
</tr>
<tr>
<td>Irradiated tumors prime dendritic cells</td>
<td>Klug et al.</td>
</tr>
<tr>
<td>Improved antigen presentation via TLR-4</td>
<td>Dovedi et al.</td>
</tr>
<tr>
<td>Depletion of immunosuppressive cells</td>
<td></td>
</tr>
<tr>
<td>Shifting TAM polarization to M1</td>
<td></td>
</tr>
<tr>
<td>Up-regulation of cell surface PD-L1</td>
<td></td>
</tr>
</tbody>
</table>

Finkelstein et al, Clin Dev Immunol 2011
Sharabi et al, Lancet Oncol 2015
Daly ME et al, J Thorac Oncol 2015

Figure 1: Radiation induces changes to the tumour cell immunophenotype
Radiation-induced DNA and membranous damage, and cytoplasmic reactive oxygen species (ROS) activate many transcription factors and signalling pathways that modulate the immunophenotype and immunogenicity of tumour cells. Modified from Finkelstein and colleagues. }

[Diagram of radiation-induced immune modulation]
What’s next?

RTOG 3505

- Stage III unresectable NSCLC
- Step 1 Registration
  - Tissue submission for PD-L1 assessment*
- Thoracic RT 60 Gy
  - Cisplatin 50mg/m² Days 1, 8, 29, 36
  - Etoposide 50mg/m² Days 1-5, 29-33
- Step 2 Registration**
  - Stratification: ECOG 0 vs. 1; squamous vs. non-squamous; PD-L1 status (≥1%, <1%, not evaluable/undetermined)
- Randomization

- Nivolumab 240mg infused over 30 min q2 weeks for 1 year
- Placebo 240mg infused over 30 min q2 weeks for 1 year

* Verification that archived tissue block is available for submission as the completed submission will be required at least 5 weeks prior to Step 2 Registration
** Assessment for progression after chemoRT; if evidence of distant metastases or local disease progression, will not be randomized


- Strong arguments biologically & mechanistically to combine RT with new immunotherapy drugs
- Possibility of toxicity interactions between new immunotherapy drugs & RT (e.g. pneumonitis/pneumonia)

“Immunoradiotherapy” is here to stay
Unexpected Results of the RTOG 0617

Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study


## Long-term results of RTOG 0617: Multivariable Cox Model for Overall Survival

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Comparison</th>
<th>Dead/Total RL</th>
<th>Dead/Total Group 2</th>
<th>HR (95% CI)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation Level</td>
<td>Standard Dose (RL) vs. High Dose</td>
<td>132/196</td>
<td>14/188</td>
<td>1.30 (1.02, 1.66)</td>
<td>0.0315</td>
</tr>
<tr>
<td>Tumor Location</td>
<td>LLL or central node (RL) vs. Neither LLL nor central node</td>
<td>172/226</td>
<td>107/158</td>
<td>0.86 (0.67, 1.11)</td>
<td>0.2395</td>
</tr>
<tr>
<td>Institution Accrual Volume</td>
<td>1-3 patients (RL) vs. ≥ 4 patients</td>
<td>122/149</td>
<td>157/235</td>
<td>0.74 (0.58, 0.95)</td>
<td>0.0170</td>
</tr>
<tr>
<td>Maximum related esophagitis/ dysphagia grade</td>
<td>Maximum grade &lt; 3 (RL) vs. Maximum grade ≥ 3</td>
<td>230/328</td>
<td>49/56</td>
<td>1.54 (1.12, 2.12)</td>
<td>0.0079</td>
</tr>
<tr>
<td>Volume of PTV (log-transformed)</td>
<td>Continuous</td>
<td>279/384</td>
<td></td>
<td>1.323 (1.041, 1.680)</td>
<td>0.0219</td>
</tr>
<tr>
<td>Heart V5</td>
<td>Continuous</td>
<td>279/384</td>
<td></td>
<td>1.008 (1.002, 1.013)</td>
<td>0.0051</td>
</tr>
</tbody>
</table>

*RL(reference level, HR=hazard ratio, CI=confidence interval, LLL=lower left lobe
*p-value
* HR = hazard ratio, CI = confidence interval, LLL = lower left lobe
Heart V5 based on heart contour performed centrally at NRG (Gore, ASTRO 2016)

Bradley et al. ASTRO 2017
## RESULTS

**Effect of IMRT on heart doses**

<table>
<thead>
<tr>
<th>Heart Doses</th>
<th>3D-CRT</th>
<th>IMRT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>V20</td>
<td>23.5%</td>
<td>19.3%</td>
<td>0.049</td>
</tr>
<tr>
<td>V40</td>
<td>11.4%</td>
<td>6.8%</td>
<td>0.003</td>
</tr>
<tr>
<td>V60</td>
<td>2.4%</td>
<td>1.4%</td>
<td>0.045</td>
</tr>
</tbody>
</table>

### Overall survival univariate analysis

<table>
<thead>
<tr>
<th>Co-variates</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart V20</td>
<td>1.008</td>
<td>1.004, 1.013</td>
<td>0.0005</td>
</tr>
<tr>
<td>Heart V40</td>
<td>1.013</td>
<td>1.006, 1.021</td>
<td>0.0005</td>
</tr>
<tr>
<td>Heart V60</td>
<td>1.023</td>
<td>1.007, 1.039</td>
<td>0.0051</td>
</tr>
</tbody>
</table>

### Overall survival multivariate analysis

<table>
<thead>
<tr>
<th>Co-variates</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart V40</td>
<td>1.013</td>
<td>1.005, 1.02</td>
<td>0.0008</td>
</tr>
</tbody>
</table>

**V_{20} heart** = 
Volume of heart receiving >20 Gy
Outcomes Outside of Controlled Trials
Mortality 180 days after RT

<table>
<thead>
<tr>
<th>GTV &lt; 100 cm³</th>
<th>GTV ≥ 100 cm³ &amp; FEV1% ≥ 80%*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GTV ≥ 100 cm³ &amp; FEV1% &lt; 80%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

*FEV1% = FEV1/FVC

Pulmonary toxicity is real
... and may be worsened by consolidation immunotherapy

New Strategies for Dose Optimisation - Adaptive RT?

- Reduce lung dose
- Dose escalation (plan)


Adaptive RT with PET/CT

RTOG 1106
- Adaptive planning with mid-point PET/CT
- Dose escalation to 86 Gy
- Respecting normal lung tolerance doses
3DCRT vs IMRT vs Protons (vs Heavy Ions)?

- **3DCRT vs IMRT**
  - Non-randomized evidence suggests IMRT can half Grade 3 radiation pneumonitis rate (from 7.9% to 3.5%)
  - Lung V20 seems more associated with pneumonitis than V5

- **IMRT vs PBT**
  - Randomised data (abstract) showed no difference in “treatment failure” rates
    - Local recurrence
    - Radiation pneumonitis

Chun SG et al. ASTRO 2015
Summary: Unresectable LA-NSCLC

Pre-treatment stratification
- Performance status & weight loss
- Lung function test

Doses
- Radical: 60 – 66 Gy in 2 Gy fractions
- Accelerated strategies can be considered

Technique
- At least 3DCRT
  - IMRT likely to have some benefit
  - Proton therapy not yet “prime time”
- Consider “Adaptive RT” strategies
  - Maintain dose coverage

Consolidation immunotherapy
Thank you!