State-the-art of the role of Radiotherapy in NSCLC

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

ESMO Preceptorship on NSCLC
Singapore December 2015

Cécile Le Péchoux
Radiation Oncology Department
Standard treatment for early lung cancer

- Around 20% of patients diagnosed with NSCLC have a localized, technically resectable, early stage disease.
- Surgical resection with lobectomy and lymph node sampling is the standard of care in medically fit patients.
- But because of comorbidities, about 25% of these patients do not have standard surgical treatment.
NSCLC T1,T2N0 in XXth century

- Without treatment, nearly 50% of patients die rapidly from progressive disease.
- Alternative approach used to be Conventional RT in inoperable patients:
  - Poor results CRT/surgery but different population +++
  - Survival rates ranging from 20% to 30%
  - Poor local control rates
    - LRR= 6–70%. DRR= 25%
- But more recently…

Great change of outcome with Stereotactic Ablative Radiotherapy or SABR

- Over the last decade, use of lung stereotactic body radiation therapy (SBRT) has increased dramatically
- SBRT is characterized by
  - delivery of high-dose radiation
  - in few fractions (1-10, mostly 3-5) with a high degree of precision
  - steep dose gradients that minimize the dose to normal tissues
- Local control rate: over 90% at 3 yrs in peripheral T, comparable to results obtained with surgery
SURVIVAL AND QUALITY OF LIFE AFTER STEREOTACTIC OR 3D-CONFORMAL RADIOTHERAPY FOR INOPERABLE EARLY-STAGE LUNG CANCER

**Graphs:**
- **(a)** Global Quality of Life
- **(b)** Physical Functioning
- **(c)** Dyspnea

**Legend:**
- Solid line = SABR
- Dashed line = 3D-CRT

**Number at Risk:**

<table>
<thead>
<tr>
<th></th>
<th>SABR 200</th>
<th>3D-CRT 27</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>123</td>
<td>21</td>
</tr>
<tr>
<td>12</td>
<td>42</td>
<td>13</td>
</tr>
</tbody>
</table>

**Statistical Significance:**
P = 0.02
SRT: high dose in small volume

Thus allowing for:

- Steep dose-gradients
- Hypofractionation (3-5x)
- High biological effective dose

40% isodose = BED 60 Gy
60% isodose = BED 112.5 Gy
80% isodose = BED 180 Gy
100% isodose = BED 262 Gy

Complex beam arrangements to conform high-dose regions to the tumor and create steep dose gradients around the target volume (RT or IMRT)

Kindly provided by Pr S. Senan
## SRT in lung cancer: Results

<table>
<thead>
<tr>
<th>Author</th>
<th>N pts</th>
<th>DT(Gy)/D/jour</th>
<th>Reference point</th>
<th>LC (%)</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timmerman 2010</td>
<td>59</td>
<td>44T1 et 15</td>
<td>Edge of PTV</td>
<td>3Yr 90%</td>
<td>MS: 48 m</td>
</tr>
<tr>
<td>Baumann 2009</td>
<td>57</td>
<td>T1-T2</td>
<td>15X3 Gy</td>
<td>3YrLC:92%</td>
<td>3y0S:60%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>67% isodose</td>
<td>LRel:7%</td>
<td>3yrCSS:88%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR:5%</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>DM 16%</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>DM:25%</td>
<td>3yOS:52%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LFR:3%</td>
<td>3yrCSS:66%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RFR:9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>138</td>
<td>30-48 Gy in</td>
<td>65% isodose</td>
<td>LFail R:12%</td>
<td>34 m</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-4 fr</td>
<td></td>
<td>DM:25%</td>
<td>2y0S:64%</td>
</tr>
<tr>
<td></td>
<td>208</td>
<td>3X20…8X7,5</td>
<td>80% isodose</td>
<td>34 m</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LFR:3%</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RFR:9%</td>
<td></td>
</tr>
<tr>
<td>Haasbeck 2010</td>
<td>203</td>
<td>15-15.4</td>
<td>80% isodose</td>
<td>3yLC:89%</td>
<td>3yOS:45%</td>
</tr>
</tbody>
</table>

- **3 yr LC rate 90%**
- **Mortality Rate in periph Tumors: 0 %**
- **Morbidity Rate: <10%**

Timmerman *JAMA* 2010, Baumann *JCO* 09, Acta Onco 06; Lagerwaald *IJROBP* 08; Haasbeck *Cancer* 2010
Stage I

Stereotactic radiotherapy has become the new standard of care in inoperable patients due to co-morbidities and age.

Vansteenkiste et al, ESMO lung guidelines 2014
Outcomes inoperable Pts ≥70 y stage I NSCLC National Cancer Data Base No treatment vs SRT
ESMO lung cancer guidelines 2014

- SABR for early-stage peripheral lung tumours is associated with low toxicity in patients with COPD and the elderly [III, A].

Vansteenkiste et al, Ann Onc 2014

Palma et al, 2012; Henderson 2008; Stephans 2009; Magdeleinat 2005; Lau 2010; Stanic 2014; Widder IJROBP 2011; Haasbeck 2010
Optimal dose and fractionation?

- No standard dose
- More common regimens
  - For stage I: 3X18-20 Gy, 3X15 Gy 4X12 Gy
- Risk adapted SRT needed according to size, location/OAR especially in mediastinum
  - For central tumors: 8X7,5 Gy, 8X7 Gy, 10X5 Gy
- Better to use dose calculation algorithms type B
- Use of modulated beams possible (VMAT)
Optimal dose?
SRT for stage I NSCLC: a Japanese multi-institutional study
(Onishi et al ASCO 06, Abstract 7045)

- 300 pts (193 T1N0, 107 T2N0; 190 inop et 110 operable) treated from 1993-2003
- Results: Median FU: 38 months

<table>
<thead>
<tr>
<th></th>
<th>BED≥100Gy</th>
<th>BED&lt;100Gy</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Control at 5 yrs</td>
<td>86%</td>
<td>67%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5-yr-S\text{al} Rate</td>
<td>65%</td>
<td>37%</td>
<td></td>
</tr>
<tr>
<td>5-yr-S\text{al} Rate Operable pts</td>
<td>74%</td>
<td>37%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>3-yr-Local progression-free-S\text{al} Rate</td>
<td>St IA 81%</td>
<td>St IB 67%</td>
<td></td>
</tr>
</tbody>
</table>
ESMO lung cancer guidelines 2014

- The dose should be to a biologically equivalent tumour dose of ≥100 Gy, prescribed to the encompassing isodose [III, A].
- More and more centers are using Volumetric Modulated Arc Therapy (VMAT, RapidARC..) using complete or partial arcs allowing treatment to be delivered in <15 min.

Vansteenkiste et al, Ann Onc 2014
Extending SBRT to larger T:
Results according to Tumor size

- Local control at 3 years: ~90%
- Increased local failure in larger Tumours frequently but not always
- Some authors suggest higher doses for larger T
- Less evidence of SRT for T over 5 cm
- Higher risk also of regional / distant recurrence

Timmerman JAMA 2010, Baumann JCO 09, Acta Onco 06; Chi systematic review 2010
SABR: Results according to Tumor size

- 57 pts with T1N0 (70%) or T2N0
- Dose=45 Gy (15 Gy×3)
- BED periph: 112
- Estimated risk of failures: 41% (T2) vs 18% (T1)
Results in operable patients according to T size

Rate of
- Local recurrences 9%
- Nodal recurrences 15%
- Distant recurrences 22%

5-yr LPFS
- IA (n=64) 92%
- IB (n=23) 73%

5-yr OS
- IA (n=64) 72%
- IB (n=23) 63%

Onishi et al 2010
The Impact of Tumor Size on Outcomes After Stereotactic Body Radiation Therapy for Medically Inoperable Early-Stage Non-Small Cell Lung Cancer

- 185 pts with 133 T1 and 52 T2
- 82% biopsy proven NSCLC
- Dose: T1: 48 Gy/4fr, Larger T: 54 to 60 Gy/3 fr
  T adjacent to mediastinum: 60 Gy/8 fr or 50 Gy/10 fr
- T size not related to local failure (LC of 94.5%) but
  Importance of BED for local control
  > BED <100 Gy → LFR of 16.7%
  > If BED >100 Gy → LFR of 2.3%
- GTV larger than 100 cm3 or T >5.7 cm are at higher risk of regional and distant failure

Alibhai et al, MGH experience IJROBP 2013
Another Challenge: SABR for central tumours?

- Drawback in central lesions because of increased toxicity (Timmermann JCO 2006)
- 70 pts receiving 60-66 Gy/3fr
- 2-yr local control 95%
- Peripheral tumors
  2-year free from severe toxicity : 83%
- Central tumors:
  2-year freedom from severe toxicity: 54%
- Need for prolonged FU

Severe bronchial stenosis and fistula may occur >2 yrs when large bronchi have received >80 Gy

Timmerman JCO 2006, Miller 2005
Concept of risk adapted SRT

Lageerwald et al, IJROBP 2008

- 206 pts T1T2N0M0
- Fractionation schemes used (T1: 3 X 20 Gy, T1 with large contact to chest wall and T2: 5 X 12 Gy, and 8 X 7.5 Gy for central tumors) determined by
  - T stage
  - Risk of normal tissue toxicity
- Local failure: 7 patients (3%).
- Severe late toxicity: less than 3% of patients (6 pts with ≥Gr 3Pitis, 4 rib fractures)

Several articles published now on Constraints on chest wall
Andolino 2010, Bongers 2011, Petterson 2009, Nambu 2013, Spring Kong RTOG atlas
Outcomes of stereotactic ablative radiotherapy for central lung tumours: A systematic review

Sashendra Senthin, Cornelis J.A. Haasbeek, Ben J. Slotman, Suresh Senan

- 315/563 patients with central T had early-stage NSCLC.
- Heterogeneity in the planning and dose prescription
- Local control rates = 85% if prescribed BED ≥100 Gy.
- Treatment-related mortality = 2.7%
- Grade 3 or 4 toxicities more frequent, but in less than 9% of patients.
- Conclusions: SABR achieves high local control with limited toxicity when appropriate fractionation schedules are used for central tumours.
Patterns of recurrence after SABR: VU experience

Actuarial rates at 2 and 5 years

- 676 pts 2003-2011
- Median FU: 33 mo
- Median time to LR: 14.9 months
- Median time to RR: 13.1 months
- Median time to DR: 9.6 months
- 2nd primaries: 6%

Senthi et al, Lancet Oncol 2012
STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR OPERABLE STAGE I NON–SMALL-CELL LUNG CANCER: CAN SBRT BE COMPARABLE TO SURGERY?


Outcomes After Stereotactic Lung Radiotherapy or Wedge Resection for Stage I Non–Small-Cell Lung Cancer

Inga S. Grills, Victor S. Mangona, Robert Welsh, Cary Chmielewski, Erika McInerney, Shannon Martin, Jennifer Wloch, Hong Ye, and Larry L. Kestin

Onishi IJROBP 2010, Grills JCO 2010
Comparison SRT-Surgery

Systematic review

Stereotactic radiotherapy (SABR) for the treatment of primary non-small cell lung cancer; Systematic review and comparison with a surgical cohort

Francesca Soldà\textsuperscript{a}, Mark Lodge\textsuperscript{b}, Sue Ashley\textsuperscript{c}, Alastair Whittington\textsuperscript{d}, Peter Goldstraw\textsuperscript{e}, Michael Brada\textsuperscript{f,*}

\textsuperscript{a} Harley Street at University College Hospital, London, UK; \textsuperscript{b} INCTR UK, Oxford, UK; \textsuperscript{c} Keswick, Cumbria, UK; \textsuperscript{d} SE London Cancer Network, Guy’s Hospital, London, UK; \textsuperscript{e} Academic Department of Thoracic Surgery, Royal Brompton Hospital, London, UK; \textsuperscript{f} Leaders in Oncology Care, London, UK

- 3201 patients stage I NSCLC treated with SABR
  - 2-yr OS was 70\% (95\% CI: 67–72\%)
  - 2 yr local control = 91\% (95\% CI: 90–93\%).
  - No survival or local PFS difference with different RT technologies used for SABR

- 2038 stage I patients treated with surgery
  - 2yr-OS 68\% (95\% CI: 66–70)
SABR in operable patients?

Attempts of randomized trials have failed (ROSEL, STARS, ACOSOG/RTOG)
Several projects planned to meet this challenge...

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

SABR vs lobectomy in operable stage I pts: pooled analysis of 2 randomized trials

Chang et al, Lancet Oncol 2015

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>SABR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>27 pts</td>
<td>31 pts</td>
</tr>
<tr>
<td>3 yr-OS</td>
<td>79%</td>
<td>95%</td>
</tr>
<tr>
<td>3 yr RFS</td>
<td>80%</td>
<td>86%</td>
</tr>
<tr>
<td></td>
<td>1 RR, 2 DM</td>
<td>1 LR, 4 RR, 2</td>
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<tr>
<td>Gr3/4 AE</td>
<td>44%</td>
<td>10% (all gr3)</td>
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<tr>
<td></td>
<td>15% dyspnea</td>
<td>10% Chest pain</td>
</tr>
<tr>
<td></td>
<td>15% Chest pain</td>
<td>3% rib fracture</td>
</tr>
<tr>
<td></td>
<td>7% lung infect</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1 death</td>
<td>0</td>
</tr>
<tr>
<td>Gr 5 AE</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Chest pain</td>
<td>Chest pain, 6%</td>
</tr>
<tr>
<td></td>
<td>dyspnea</td>
<td>dyspnea, 3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>rib fracture</td>
</tr>
<tr>
<td>Median FU</td>
<td>35.4</td>
<td>40.2</td>
</tr>
</tbody>
</table>

Figure 2: Overall survival (A) and recurrence-free survival (B)

Chang et al, Lancet Oncol 2015
Screening programs

- Prevalence of lung cancer = 1 to 2.8%
- % stage I = 54 to 85%
- 20.0% decreased mortality from LC in the low-dose CT group / Rx group.
- In Stage I tumors, ~40% of patients will die of lung cancer and benefit from radical treatment

National Lung Screening Trial, NEJM 2011 2013;
Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial JAMA 2011,
Palma 2010; Varlotto 2014
M GM, traité pour un carcinome épidermoïde T2aN0M0 en Juillet 2013 60 Gy en 5 séances de 12 Gy

Suivi en Septembre puis Novembre 2013
M F, BPCO severe, inoperable, ayant carcinome épidermoïde du lobe supérieur gauche classé T1b N0 M0. Récusé pour RFA par TDB en raison de proximité au plexus brachial, et traité par SABR à la dose de 60 Gy (8 x 7,5 Gy) en juin 2012.
Challenge: Is it local recurrence or radiation induced lung injury??

- On-going studies
- Importance of early detection so as to discuss salvage surgery (in operable pts)
- PET may help SUV max >5

Dahele 2011; Mattonen 2013
Future for RT in early NSCLC

- Need to pursue prospective studies
- Individualized RT treatment according to radiosensitivity profile.
- As pts undergoing SRT may be more fit in the future:
  - More extensive mediastinal and hilar work-up
  - Importance of long term follow-up
  - Role of adjuvant treatments in operable pts
Local Treatment: Surgery or/and RT

CT Yes pre-op or post-op!

Surgery the standard in early stage NSCLC!!

But for st III?

Adenocarcinoma cT2N2 (médiastino+)

Large Cell Carcinoma cT2N2 (médiastino+)
Stage III: importance of pluridisciplinary approach.

- Very heterogeneous population
- Several treatment available options in 2015
  - TNM importance of nodal involvement
  - Age, PS and Co-morbidities

Importance of PET-CT and brain imaging
Stage III A and selected III B

5-year survival: 20-25% [5-45%]

- Treatment should be decided within a multidisciplinary team UPFRONT
  - Surgery? RT? Both? Tri-modality or Bi-modality? timing of CT?)

- High risk of recurrence (metastatic and local)
  - Distant failure: 30 to 50% Brain 20 to 32%

- Local Failure Rate at 3 years
  - In surgical series (15% to 60%)
  - CTRT: Loco-regional progression rate <30%

Absolute benefit in OS with concomitant CT:

- At 2 years: 5.3%
- At 3 years: 5.7%
- At 5 years: 4.5%

HR = 0.84 [0.74;0.95], p = 0.004

Overall survival sq CTRT vs cc CTRT

Aupérin et al, JCO 2010
Standard of care in stage III inoperable NSCLC in 2015

- Concomitant chemoradiation: standard of care
- Decreased loco-regional progression
- Most studies 2D RT
- Dose: 52-70 Gy 2GyED
- Local Progression
  - Free survival at 3 years 70%

Cumulative incidence of loco-regional progression (5 trials)

Risk of recurrence (%)

Time from randomisation (Years)

<table>
<thead>
<tr>
<th>Absolute reduction in LRP:</th>
<th>At 1 year:</th>
<th>At 2 years:</th>
<th>At 3 years:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- 4.5%</td>
<td>- 5.6%</td>
<td>- 6.0%</td>
</tr>
</tbody>
</table>

HR = 0.77 (95% CI: 0.62-0.95), p = 0.01

So place for improvement!!
Conformal RT and Stage III NSCLC

- Local control is a challenge in locally advanced NSCLC
- How to improve results?
  - Dose escalation, Altered fractionation
  - More precise RT (optimized treatment planning: PET-CT based, 4D CT planning, IGRT)
  - Combination of targeted agents to CTRT?
  - Immunotherapy
Several Dose escalation studies according to Lung tolerance

- **European studies**: NO prolonged Overall Treatment Time
  Maximum tolerated dose (MTD) delivered within 6 weeks
  - Dose escalation safe up to 94.5 Gy /42 fr/6wks if Mean Lung Dose 13.6 Gy or less.

- **RTOG studies**: Prolonged OTT
  Maximum tolerated dose (MTD) delivered > 6 weeks
  - MTD of RT alone $\Rightarrow 83.8$ Gy if $V_{20} < 25$
  - $\Rightarrow 77.4$ Gy if $V_{20}$ between 25-36%.

- **RTOG / Dose escalation CTRT carbo-paclitaxel based studies**

- **Phase II study RTOG 0117 with 74 Gy (MS 26 mo, 1YS=72%)**

Belderbos, 2006, Bradley, 2005; Hayman, 2001; Bradley 2010
Primary objective: To compare the overall survival of patients treated with high-dose versus standard-dose conformal RT with concurrent CT.

Increase of Median Survival from 17.1 months to 24 months (for each factor)

RTOG 0617, NCCTG N0628, CALGB 30609 Conventional vs. High Dose RT

Conventional RT: 60 Gy
- Paclitaxel
- Carboplatin +/- Cetuximab

High Dose RT: 74 Gy
- Paclitaxel
- Carboplatin X 2
- +/- Cetuximab
RTOG 0617: Overall Survival

At 12 mo
- Standard (60 Gy): 81%
- High dose (74 Gy): 69%

At 18 mo
- Standard (60 Gy): 67%
- High dose (74 Gy): 54%

MST: 28.7 months 60 Gy
MST: 19.5 months 74 Gy

HR = 1.56 (1.19, 2.06) p = 0.0007

Patients at Risk
- Standard: 213
- High dose: 206

Months since Randomization

RTOG 9410 CON-QD 1yr survival = 62.1%, MST = 17.0 months

Bradley, ASCO 2013, Lancet Oncol 2015
Local Progression Rate

<table>
<thead>
<tr>
<th>Failure</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>213</td>
</tr>
<tr>
<td>81</td>
<td>206</td>
</tr>
<tr>
<td>9, 1.89</td>
<td>p=0.0319</td>
</tr>
</tbody>
</table>

18-Month Local Progression Rate

25.1% 60 Gy
34.3% 74 Gy

HR=0.77 (95% CI: 0.62-0.95), p=0.01

 Absolute reduction in LRP:
At 1 year: -4.5%
At 2 years: -5.6%
At 3 years: -6.0%

Auperin et al, JCO 2010

Cumulative incidence of loco-regional progression (5 trials)

Bradley, ASCO 2013, Lancet Oncol 2015
Conclusions RTOG 0617

- The high dose arm experienced higher local failure rates.
- Possible explanations for poorer survival on high dose arms
  - more treatment-related deaths in the high-dose chemoradiotherapy and cetuximab groups (74 Gy vs 60 Gy: 8 vs 3 pts; cetuximab comparison: 10 vs 5 pts)
  - Confounding factors: Cetuximab
  - increased heart dose
  - extended therapy duration
  - combination of these factors
Dose intensification: accelerated and/or hyperfractionated RT

- Accelerated repopulation of tumour stem cells, 21-28 days after the start of radiation treatment → radiobiological rationale for accelerated treatments
- Acceleration of RT leading to reduced Overall Treatment Time (<2 wks-5 wks) compared to 6 wks could lead to improved local control ???
- Hyperfractionated RT can reduce long-term normal-tissue morbidity

Modified radiotherapy, overall survival
Conventional radiotherapy, overall survival
Modified radiotherapy, progression-free survival
Conventional radiotherapy, progression-free survival

Survival (%)

Time from randomisation (Years)

In favor of modified RT | Absolute benefit OS | Absolute benefit PFS
---|---|---
At 3 yrs | 3.8% | 1.4%
At 5 yrs | 2.5% | -0.2%
HR, p | 0.88, p=0.009 | 0.94, p=0.19

Mauguen et al, JCO 2011
Better Conformal Radiotherapy

- Technical refinements such as intensity modulated radiotherapy (IMRT) may further decrease:
  - incidence and severity of side effects
  - allow increased individualised radiotherapy doses
Historical comparison: 318 pts treated with 3DRTC (49% had PET) vs 91 pts 4DCT planning and IMRT (82% had PET)

Similar TD, similar CT regimen but difference of FU
SEER database study: 3D RT or IMRT vs 2D RT (13,292 pts treated 2003-2005)

- Importance of loco-regional control in pts with stage III
- This encourages use of high tech RT in stage III LC

<table>
<thead>
<tr>
<th>CRT+</th>
<th>CRT-</th>
</tr>
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<tbody>
<tr>
<td>3yrS</td>
<td>22%</td>
</tr>
<tr>
<td>5yrS</td>
<td>14%</td>
</tr>
</tbody>
</table>

Sher et al, Cancer 2014
Trial investigating the concept of individual radiation dose redistribution within the tumour based on FDG-PET uptake

Several ongoing trials exploring PET driven dose escalation and intensification
RTOG 1106 Trial
PET Boost Trial
RTEP7

Courtesy from JJ Sonke, D De Ruysscher et al
Platinum based CT (CDDP-VNB, CDDP-VP16, Carbo-Taxol) 2-4 cycles and RT 60-66 Gy is the standard in combined CTRT

- Why not add Targeted agents to CTRT?
  No benefit in a non selected population (Kelly JCO 2008)

- Role of consolidation or induction CT?
  No role (Vokes JCO 2007, Hanna 2008)

- New CDDP based regimen combined to RT such as Pemetrexed-CDDP
Better CT combined to 3DRT?

**PROCLAIM: Study Design**

**Concurrent Phase**
- Pemetrexed: 500 mg/m², Cisplatin: 75 mg/m², q3w
- TRT: 66 Gy, 2 Gy/fx daily
  - 3 CYCLES

**Recovery Period** (3–5 wks)

**Consolidation Phase**
- Pemetrexed: 500 mg/m², q3w
  - 4 CYCLES
- PR/CR/SD per RECIST

**Arm A**
- Previously untreated stage IIIA–IIIB* nonsquamous NSCLC PS 0/1
- Etoposide: 50 mg/m² D1–5, q4w
- Cisplatin: 50 mg/m² D1, 8, q4w
- TRT: 66 Gy, 2 Gy/fx daily
  - 2 CYCLES
- Investigator’s choice:
  - Etoposide-Cisplatin: (same dosing/schedule)
  - Vinorelbine-Cisplatin:
    - Vin: 30 mg/m² iv, D1, 8, q3w
    - Cis: 75 mg/m² D1, q3w
  - Paclitaxel-Carboplatin:
    - Pac: 200 mg/m² iv, q3w
    - Car: AUC=6 iv, q3w
  - 2 CYCLES

**Arm B**
- R'

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*Stratified for: ECOG PS (0 vs 1); PET scan staging (yes vs no); gender; and disease stage (IIIA vs IIIB).

†AJCC Cancer Staging Manual (ed 6), 2002. ‡Folic acid, vitamin B₁₂, and dexamethasone administered in Arm A. TRT=thoracic radiotherapy.

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Presented at: ASCO Annual Meeting 2015

Courtesy of Pr Senan ASCO 2015
Randomized study PemCis based CTRT vs EP CTRT

PROCLAIM: Primary Endpoint, OS

- CDDP-Pemetrexed may be an option in non-sq NSCLC

HR (95% CI): 0.98 (0.79, 1.20)
Log-rank p=0.831
Median OS (95% CI), mos
Pem-Cis: 26.8 (20.4, 30.9)
Eto-Cis: 25.0 (22.2, 29.8)

Median follow-up times (mos [range])
- All patients: 22.2 (0.1–66.6)
  Eto-Cis, 22.6 (0.0–71.4)
- Patients alive: Pem-Cis, 32.9 (0.1–66.6)
  Eto-Cis, 35.7 (0.0–71.4)

Total events: 357
- Pem-Cis: 177 events/301 patients
- Eto-Cis: 180 events/297 patients

Courtesy of Pr Senan ASCO 2015
Need for additional systemic treatment

- Targeted agents combined with CTRT? Ongoing studies in EGFR, ALK selected pop
- Other targeted agent difficult to associate!!

More is not always better!
### Immunotherapy and Stage III unresectable NSCLC (START phase III randomised trial)

- 1513 patients included (1006 to tecemotide and 507 to placebo) from Feb 2007 to Nov 2011

<table>
<thead>
<tr>
<th></th>
<th>Placebo 410 pts analysed</th>
<th>Tecemotide 829 pts</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>22.3 mo</td>
<td>25.6 mo</td>
<td>0.123</td>
</tr>
<tr>
<td>Previous cc CTRT (65%)</td>
<td>20.6 months</td>
<td>30.8 months</td>
<td>0.016</td>
</tr>
<tr>
<td>Previous sq CTRT (35%)</td>
<td>24.6 months</td>
<td>19.4 months</td>
<td>0.38</td>
</tr>
<tr>
<td>Serious AE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>14 (3%)</td>
<td>30 (3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13 (3%)</td>
<td>29 (3%)</td>
<td></td>
</tr>
</tbody>
</table>

**Butts Lancet Oncol 2014**
Ongoing trials with immunotherapy

Schema – Phase III
RTOG Foundation

- Stage III NSCLC
- No prior Tx
- ECOG 0-1
- Any histology
- No known sensitizing EGFR mutation or ALK rearrangement
- Availability of 10-15 slides archival tissue

- Thoracic RT to 60 Gy
  CDDP 50 mg/m² Days 1, 8, 29, 36
  IP16 50 mg/m² Days 1-5, 29-33

- Nivolumab every 2 weeks until disease progression or unacceptable toxicity or a total of 1 year
- Placebo every 2 weeks until disease progression or unacceptable toxicity or a total of 1 year

3-8 wks

Medimmune PACIFIC Trial

- Stage III NSCLC
  - Unresectable
  - Tx-naive
  - ECOG 0-1
  - Any histology

- Chemoradiation w/ 2 cycles of Platinum-based Tx

- Register
- Randomize

- MEDI 4736 until disease progression or unacceptable toxicity or a total of 1 year

- Placebo until disease progression or unacceptable toxicity or a total of 1 year

N=702
6/14-6/17
1* Obj: OS
2* Obj: PFS
4-8 wks
Adjuvant Radiotherapy in the post-operative setting

No recent phase III Trials evaluating PORT published
Randomized evidence regarding post-operative radiotherapy in 2015?

- **Post-Operative RadioTherapy Overview**
- 2232 pts in 10 randomized (added Trodella study including stage I pts)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number of Patients</th>
<th>2-year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery alone</td>
<td>1125 pts</td>
<td>58%</td>
</tr>
<tr>
<td>Surgery + PORT</td>
<td>1107 pts</td>
<td>52%</td>
</tr>
</tbody>
</table>

Burdett et al, Lung Cancer 2005, Cochrane Review
Any place for RT after complete resection?

NO according to MA and studies of MA in pN0,N1 (lower risk pts)
Overadded toxicity and/or poor LC:
  Dose > 54 Gy, Daily fraction > 2 Gy
  Large volume RT, no CT-based treatment planning
  Old technique (Cobalt, spinal cord block)
Contributing to OVERMORTALITY
Lessons learned from PORT Meta-analysis
more personalised treatment

- PORT in selected cases: N2

More conformal RT
Resected stage IIIA patients
Local Recurrence Rate

At 3 years

- Without radiotherapy (according to nodal exploration): around 30%
  > 22% - 40%
- With « more modern » RT pre-op or post-op: around 15%
  > 11% (Machtay et al JCO 2001)
  > 13% (Etude ECOG, Keller et al, NEJM 2000)
  > 14.7% (PORT) vs 28.9% (No PORT) (ANITA trial, Douillard IJROBP 2008)
  > SAKK trial comparing pre-operative sequential CTRT versus CT: Local relapse 15% vs 30%

Machtay 2001; Keller 2000; Douillard 2008; Le Pechoux, 2011; Pless 2014
cc CT-RT in resected st II and IIIA NSCLC: NOT a standard

Kaplan Meier estimate of Local Regional Control and Overall Survival

91% at 2 yrs
88% at 5 yrs

72% at 2 yrs
44% at 5 yrs

Kindly provided by Feigenberg et al, ASTRO O6-Abst 114

Keller et al, NEJM 2000
Bradley et al, JCO 2005

<table>
<thead>
<tr>
<th>Time</th>
<th>Ph III ECOG PORT arm 242 pts</th>
<th>ECOG Cc CT-RT 246 pts</th>
<th>RTOG Ph II 88 pts</th>
<th>Feigenberg Ph II 40 pts</th>
<th>Ph III Shen POCRT 69 pts POCT 66 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-yr Sa</td>
<td>52%* (3yr)</td>
<td>50%* (3 yr)</td>
<td>70%</td>
<td>72%</td>
<td></td>
</tr>
<tr>
<td>5-yr Sa</td>
<td>39% (est)</td>
<td>33% (est)</td>
<td>46%</td>
<td>44%</td>
<td>40% POCRT 27% POCT</td>
</tr>
<tr>
<td>MST</td>
<td>38 mo</td>
<td>39 mo</td>
<td>56.3 mo</td>
<td>-</td>
<td>40 mo // 27,5 mo</td>
</tr>
</tbody>
</table>
PORT in N2 Patients

<table>
<thead>
<tr>
<th>N2</th>
<th>RADIOTHERAPY</th>
<th>NO RADIOTHERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=224</td>
<td>No CT</td>
<td>IV VRL+CDDP</td>
</tr>
<tr>
<td>Number of patients</td>
<td>68</td>
<td>48</td>
</tr>
<tr>
<td>MS, mos</td>
<td>22.7</td>
<td>47.4</td>
</tr>
<tr>
<td>1 year survival</td>
<td>73.5 %</td>
<td>97.9 %</td>
</tr>
<tr>
<td>2 year survival</td>
<td>47.6%</td>
<td>76.6%</td>
</tr>
<tr>
<td>5 year survival</td>
<td>21.3%</td>
<td>47.4%</td>
</tr>
<tr>
<td>% deaths</td>
<td>54 (79%)</td>
<td>28 (58 %)</td>
</tr>
</tbody>
</table>

Douillard JY, ASTRO 06 plenary Session, Lancet Oncol 2006
Population-based cohort, Lally et al, JCO 2006

Subgroup analysis according to RT in favour of sequential CT and PORT
One should always be cautious with such analyses
4483 resected pts NSCLC N2
National Cancer Data base Robinson and al, JCO 2015

Pts treated between 2006-2010
Median FU: 22 months
All had adjuvant CT but
Median D: 54 Gy (45-80 Gy)
Date start RT/last CT>45 d: 40.2%
Date start RT/last CT>90 d: 31.2%
Pronostic factors for OS (MVA): age<, F gender, comorbidity, T, PolyCT,
Surgery>lobectomy at RPO

Surg + adj CT + PORT:
Improved survival 4% (p=0.027)

<table>
<thead>
<tr>
<th></th>
<th>No PORT</th>
<th>PORT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>40.7 mo</td>
<td>45.2 mo</td>
<td>0.014</td>
</tr>
<tr>
<td>3-yr Survival</td>
<td>55.2%</td>
<td>59.3%</td>
<td></td>
</tr>
<tr>
<td>5-yr Survival</td>
<td>34.8%</td>
<td>39.3%</td>
<td></td>
</tr>
<tr>
<td>Adj Median OS</td>
<td>40.9 mo</td>
<td>45.2 mo</td>
<td>0.027</td>
</tr>
<tr>
<td>Adj 3-yr Survival</td>
<td>55.7%</td>
<td>59.9%</td>
<td></td>
</tr>
<tr>
<td>Adj 5-yr Survival</td>
<td>34.6</td>
<td>38.4%</td>
<td></td>
</tr>
</tbody>
</table>
Re evaluation of the role of PORT
National Cancer Data base Corso and al, JTO 2015

<table>
<thead>
<tr>
<th>Stage</th>
<th>N</th>
<th>5-yr Survival</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No PORT</td>
<td>PORT</td>
</tr>
<tr>
<td>N0 pts</td>
<td>N=5836 (19,1%)</td>
<td>5387 (20%) 48%</td>
<td>449 (13,1%) 37,7%</td>
</tr>
<tr>
<td>N1 pts</td>
<td>N=17,737 (58,1%)</td>
<td>16,416 (60,5%) 39,4%</td>
<td>1321 (38,5%) 34,8%</td>
</tr>
<tr>
<td>N2 pts</td>
<td>N=6979 (22,8%)</td>
<td>5319 (19,6%) 27,8%</td>
<td>1660 (48,4%) 34,1%</td>
</tr>
</tbody>
</table>
PORT with doses of 45 to 54 Gy seemed significantly associated with improved OS on multivariate analysis.
Many changes since publication of PORT Meta-analysis: selection and treatment of pts

- Better selection (PET, Brain imaging)
- Better Quality of surgery
- (Neo-) adjuvant CT has now become a standard of care in stage II and III pts
- Better radiotherapy
Is RT necessary in completely resected patients with mediastinal involvement? 

Maybe...

Technical advances of radiotherapy may enhance the ability of RT to improve local relapse free survival, DFS and possibly overall survival. BUT this has to be proven....
LUNG ART phase III Trial
(IFCT O5O3-UK group-EORTC 22055-08053)
Trial registry: NCT00410683

Completely resected NSCLC with mediastinal histo or cytologically proven nodal involvement

Main end-point: DFS, 700 pts needed to show a 10% difference in DFS (from 30% to 40%)

Possibility of adjuvant CT
Pre-op and/or Post-op CT

Control
Conformal PORT (54 Gy)

With the support of INCa (French National Cancer Institute)
Cohort of 3395 resected pts NSCLC St II, III
Incomplete Resection : Any Role for PORT??

Survival seems improved in all pts (p<0.04)

Pts treated between 2003-2011
All; R1,R2 surgery
RT: 1207 pts (35.6%)
1892 pts R1 (55.7%)
129 pts R2 (3.8%)
1374 pts R1 or R2

National Cancer Data base Wang and al, JCO 2015
Take Home message

- **Stage I inoperable pts**: SBRT has become new standard of care
- **Population of stage III patients** (high risk of local and distant failure) has changed
  - Better staging (PET CT, brain MRI)
- **In the pre-PET era**, high rate of distant metastases diluted any real effect of local control on overall outcome
- **Operable pts**
  - PORT: no role in pN0 and pN1 after complete resection. For pts with N2 involvement, randomized trial ongoing
  - Different options available integrating chemotherapy, surgery and radiotherapy (40% at 5 years in recent trials)
**Take Home message**

- **Inoperable pts**
  - Concomitant CTRT is still the standard with RT dose 60-66 Gy and platinum based CT (MS 25 mo, 3-ys 40%)
  - Concept of « one size fits all » treatment intensification has reached its limit! RT dose escalation, Targeted agents to unselected population: negative trials
  - Progress in high Tech RT allows optimisation of local control with less toxicity

- **More biologically driven dose escalation trials ongoing, and trials devoted to pts with driving mutations**
Collaborations and prospective studies needed!!!

Thank you for your attention