Adjuvant radiotherapy for completely resected early stage NSCLC

ESMO Preceptorship on lung Cancer
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Disclosures

- Dr Cecile Le Pechoux
  - Participation to Boards or scientific meetings: AstraZeneca, Lilly, PrimeOncology
Local approach in early NSCLC: what is the best treatment for each individual patient??

- **Surgery**
  - Stage I, II and selection of st III

- **Radiotherapy**
  - Stage I, II (inoperable) and III

- **Surgery + Radiotherapy**
  - Usually combined when *higher risk of LR*
  - Concerns mostly stage IIIN2 patients and Pancoast Tumours
    - Pre-op RT with ccCT
    - Post op RT
Stage III: importance of pluridisciplinary approach.

- Very heterogenous population
- Several treatment available options in 2018
  - TNM, importance of nodal involvement
  - Age, PS and Co-morbidities...cardiopulmonary

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

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

- 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 40%)
  > CTRT: Loco-regional progression rate < 30%

- Treatment should be decided within a multidisiplinary team UPFRONT

  > Surgery? RT? Both? Tri-modality or Bi-modality? timing of CT?)

Adjuvant Radiotherapy in the post-operative setting

No recent phase III Trials evaluating PORT published
Randomized evidence regarding post-operative radiotherapy in 2017?

- **Post-Operative RadioTherapy Overview**
- 2232 pts in 10 randomized (added Trodella study including stage I pts)
  - Surgery alone (1125 pts)
  - Surgery + PORT (1107 pts)

  2-year Survival: 58%

- 2-year Survival: 52%

Any place for RT after complete resection?

**NO** according to MA and studies of MA

- Especially in pN0,N1 or pSt I and II (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 should be reevaluated in high risk patients: N2

- More conformal RT

![Graph showing hazard ratio and test for trend](image)

PORT, Lancet 1998
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
Neo adjuvant or adjuvant CT is the standard in resected patients with mediastinal involvement

Timing of adjuvant RT?

Lace MA Pignon et al, JCO 2007; NSCLC MA Collaborative group Lancet 2010
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

Keller et al (ECOG), NEJM 2000
Bradley et al (RTOG), JCO 2005
Shen et al, Radiother Oncol 2014

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

<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></td>
<td>No CT</td>
<td>IV VRL+CDDP</td>
</tr>
<tr>
<td>N=224</td>
<td>68</td>
<td>48</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><strong>47.4%</strong></td>
</tr>
<tr>
<td>% deaths</td>
<td>54 (79%)</td>
<td>28 (58%)</td>
</tr>
</tbody>
</table>

• Subgroup analysis according to RT in favour of sequential CT and PORT
• One should always be cautious with such analyses

ANITA trial: Phase III Adjuvant Vinorelbine and Cisplatin versus Observation

Douillard JY, ASTRO 06 plenary Session, Lancet Oncol 2006
Phase II randomized study Comparing adjuvant CT to CTRT for Completely Resected Unsuspected N2-Positive Non-Small Cell Lung Cancer (Sun et al, JTO 2017)

Completely resected NSCLC (IIIA, mN2)

Informed consent

4-8 weeks after surgery

# Stratification factor
1. single vs multi station N2
2. Pneumonectomy vs non-Pneumonectomy

Primary endpoint: DFS

Statistical hypothesis:
Improve 2-year DFS rate from 50% (CT arm) to 70% (CCRT arm)

SUN et al, Randomized Phase II Trial Comparing Chemoradiotherapy with Chemotherapy for Completely Resected Unsuspected N2-Positive Non-Small Cell Lung Cancer ESMO 2017, JTO 2017
Ccl: no difference in DFS and OS between two treatment arms, so no survival benefit from adjuvant CCRT compared with platinum-based CT alone for completely resected unsuspected N2-positive NSCLC.

However, the role of sequential radiotherapy administered after adjuvant CT is being evaluated, and further study needed to evaluate the optimal radiotherapy approach for completely resected N2-positive NSCLC.
4483 resected pts NSCLC N2
National Cancer Data base Robinson and al, JCO 2015

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

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 et RPO

<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>No PORT</th>
<th>PORT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0 pts</td>
<td>5836 (19.1%)</td>
<td>5387 (20%)</td>
<td>48%</td>
<td>37.7%</td>
<td>0.009</td>
</tr>
<tr>
<td>N1 pts</td>
<td>17,737</td>
<td>16,416 (60.5%)</td>
<td>39.4%</td>
<td>34.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N2 pts</td>
<td>6979 (22.8%)</td>
<td>5319 (19.6%)</td>
<td>27.8%</td>
<td>34.1%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

30,552 Pts st II-III treated 1998-2006
PORT with doses of 45 to 54 Gy seemed significantly associated with improved OS on multivariate analysis
Radiation Therapy is Independently Associated with Worse Survival After R0-Resection for Stage I–II Non-small Cell Lung Cancer: An Analysis of the National Cancer Data Base (2004-2014)

- 197,969 st I–II NSCLC pts → R0 resection and 4613 PORT with median RT D 55Gy
- On adj analysis, ttt at community cancer program, sublobectomy, tumor size (3–7 cm), and pN1/Nx associated with RT.
- PORT group had shorter MedOS (45.8 vs. 77.5 months, p<0.001)

After propensity score matching,
Location of locoregional failure?

- Out of 54 pts/250 who had LRF as first event, 48 (89%) had recurrence within proposed PORT CTV
- **Left-sided NSCLC**, most common LN failure
  - 4R, 7, 4L, 6, 10L, and 5.
- **Right-sided NSCLC**, most common LN failure
  - 2R, 10R, 4R, and 7

From 2005 to 2011, 250 consecutive pts with pT1-3 N2 NSCLC who underwent complete resection but who did not receive PORT were identified. 65% of first failures: Distant. 9% of first failure Supraclavicular. 31.2% of first failures: LRF
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

**CT effect & stage**

<table>
<thead>
<tr>
<th>Category</th>
<th>No. Deaths / No. Entered</th>
<th>Hazard ratio (Chemotherapy / Control)</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA</td>
<td>102 / 347</td>
<td>1.41</td>
<td>[0.96;2.09]</td>
</tr>
<tr>
<td>Stage IB</td>
<td>509 / 1371</td>
<td>0.92</td>
<td>[0.78;1.10]</td>
</tr>
<tr>
<td>Stage II</td>
<td>880 / 1616</td>
<td>0.83</td>
<td>[0.73;0.95]</td>
</tr>
<tr>
<td>Stage III</td>
<td>865 / 1247</td>
<td>0.83</td>
<td>[0.73;0.95]</td>
</tr>
</tbody>
</table>

Chemotherapy better | Control better
Test for trend: p = 0.051

**Lung Adjuvant Cisplatin Evaluation (LACE)**
A Pooled Analysis of 5 Randomized Trials Including 4,584 Patients

LACE Meta-analysis
Kindly provided by JP Pignon et al, ASCO 2006
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)
Trial registry: NCT00410683

Completely resected NSCLC with mediastinal histo or cytologically proven nodal involvement

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

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

Conformal PORT (54 Gy)

With the support of INCa (French National Cancer Institute)
Cohort of 3395 resected pts NSCLC St II, III Incomplete Resection (R1,R2): 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

- No role for PORT in RO resected early lung cancer (MA 1998)
- PORT may have a role in N2 stage III pts
- Stage III patients (high risk of local and distant failure)
  > Importance of 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
- Among Operable pts
  > If N2+, PORT not a standard, but retrospective data, large database studies seem to show PORT may improve OUTCOME. Randomized trial (Lung ART) ongoing
  > Different options available integrating chemotherapy, surgery and radiotherapy (40% at 5 years in recent trials)
- PORT should be delivered to R1R2 patients
Adjuvant Systemic Therapy and Adjuvant Radiation Therapy for Stage I to IIIA Completely Resected Non–Small-Cell Lung Cancers: American Society of Clinical Oncology/Cancer Care Ontario Clinical Practice Guideline Update

*Mark G. Kris, Laurie E. Gaspar, Jamie E. Chaft, Erin B. Kennedy, Christopher G. Azzoli, Peter M. Ellis, Steven H. Lin, Harvey L. Pass, Rahul Seth, Frances A. Shepherd, David R. Spigel, John R. Strawn, Yee C. Ung, and Michael Weyant*

**Recommendation 1.3.** Stages IIAB and IIIA: Adjuvant cisplatin-based chemotherapy is recommended (Type: Evidence based and Panel consensus; Benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong).

**Recommendation 2.2.** Stage IIIA (N2): Adjuvant radiation therapy is not recommended for routine use. A postoperative multimodality evaluation, including a consultation with a radiation oncologist, is recommended to assess benefits and risks of adjuvant radiotherapy for each patient with N2 disease (Type: Evidence based and Panel consensus; Benefits outweigh harms; Evidence quality: Intermediate; Strength of recommendation: Moderate).
Collaborations and prospective studies needed!!

Thank you for your attention

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