ADJUVANT RADIOTHERAPY FOR LUNG CANCER

40th AROI-ICRO SUN PG Teaching Course

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LEARNING POINTS

- Post-operative RT - indications
- Sequence of trimodality therapy
- Pre-operative RT?
- Dose of RT
- Current guidelines
INTRODUCTION

• RT has a potential role in all stages of NSCLC
  • Definitive
  • Palliative

• Role of RT in addition to surgery, however, is not established by survival benefit in Phase III studies
  • Post-operative
  • Pre-operative
LOCAL TREATMENT APPROACHES IN EARLY NSCLC

• Surgery Stage I, II and selected stage III
• Radiotherapy Stage I,II (inoperable) and III
• Surgery + Radiotherapy
  • Usually combined when higher risk of LR > Concerns mostly stage IIIIN2 patients and Pancoast Tumours
    • Pre-op RT with CT
    • Post op RT
POST-OPERATIVE RT
COMPLETE RESECTION (CR) – IASLC DEFINITION

- microscopically free resection margins (R0),
- systematic nodal dissection or lobe-specific systematic nodal dissection,
- lack of extracapsular nodal extension (ENE), and
- negativity for tumour infestation at the highest mediastinal node removed
ADEQUATE INTRAOPERATIVE LYMPH NODE STAGING -EUROPEAN SOCIETY OF THORACIC SURGEONS (ESTS) DEFINITION

Systematic nodal examination including
- at least three intrapulmonary and hilar nodes and
- at least three mediastinal nodal stations depending on the location of the primary tumour
  - Levels 4, 7, 10 for right lung cancers
  - Levels 4, 5, 6, 7, 10 for left lung cancers
ADJUVANT RADIOTHERAPY IN POSTOPERATIVE SETTING

- Scenarios
  - Completely resected
  - R1 resection
  - R2 resection
  - N2 status
R0 N0-I TUMOURS
AFTER COMPLETE RESECTION

- Randomised evidence?

Postoperative radiation therapy in lung cancer: A controlled trial after resection of curative design

Paul Van Houtte M.D. ¹, Pierre Roermans M.D. ², Philippe Smets M.D. ³, Jean-Claude Goffin M.D. ⁴, Jacqueline Lustman-mariéchal M.D. ⁵, Patric Vanderhoeft M.D. ⁶, Jacques Henry M.D. ⁷
175 patients
- complete resection and no lymph node involvement

5-year survival rates
- 24% in the RT arm
- 43% in the control arm

RT unnecessary after R0 resection

squamous cell carcinoma
- RT detrimental
- T2 group (p < 0.05).
- especially after pneumectomy (16% versus 43%)

TV: mediastinum sternal notch to 5 cm below carina.
FS: 15 x 9 cm.
Dose: 60Gy
Machine: Co 3 field

Table 3. Squamous and large cell carcinoma surgical resection and staging

<table>
<thead>
<tr>
<th></th>
<th>Radiotherapy group</th>
<th>Control group</th>
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<tbody>
<tr>
<td>Lobectomy</td>
<td>35</td>
<td>43</td>
</tr>
<tr>
<td>Pneumectomy</td>
<td>16</td>
<td>38</td>
</tr>
<tr>
<td>Total</td>
<td>51</td>
<td>81</td>
</tr>
<tr>
<td>T1</td>
<td>33</td>
<td>19</td>
</tr>
<tr>
<td>T2</td>
<td>15</td>
<td>39</td>
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<tr>
<td>T3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>51</td>
<td>81</td>
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CRITICISMS...

- Dose > 54 Gy
- Daily fraction >2 Gy
- Large volume RT,
- no CT based treatment planning
- Old technique (Cobalt, spinal cord block)
- Contributing to OVERMORTALITY

5-year survival rate 8% vs 30%
31% of the control surgical group including less advanced tumors
CT BASED PLAN

- Randomised evidence?

Radiotherapy and Oncology
Volume 62, Issue 1, January 2002, Pages 11-19

Adjuvant radiotherapy in non-small cell lung cancer with pathological stage I: definitive results of a phase III randomized trial

Lucio Trodella a, R., Pierluigi Granone b, Salvatore Valent e, Vincenzo Valentin i, Mario Balducci a, Giovanna Mantini a, Adriana Turzi zani a, Stefano Manganor a, Alfredo Cesario b, Sara Ramella a, Giuseppe M Corbo b, Rolando M D'Angelillo a, Antonella Fontana a, Domenico Galletta b, Numa Cellini b
### ITALIAN TRIAL/ TRODELLA TRIAL

<table>
<thead>
<tr>
<th>104 patients</th>
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<tr>
<td>• pathological stage I</td>
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<table>
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<tr>
<th>Local Recurrence</th>
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<tbody>
<tr>
<td><strong>LR Low in Stage I. Routine RT is not recommended currently</strong></td>
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<table>
<thead>
<tr>
<th>5 year OS</th>
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<tbody>
<tr>
<td>• No significant diff (67% vs 58%)</td>
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<table>
<thead>
<tr>
<th>Toxicity</th>
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<tbody>
<tr>
<td>• NS</td>
</tr>
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</table>

CT-plan Linac TV: bronchial stump homolateral hilum
• Metaanalysis?

Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials

PORT Meta-analysis Trialists Group*
PORT META ANALYSIS 1998

• Significant adverse effect of PORT on survival (hazard ratio 1.21 [95% CI 1.08–1.34])
• 21% relative increase in the risk of death is equivalent to an absolute
  Adjuvant RT detrimental to patients with early-stage completely resected NSCLC and should not be used routinely for such patients
• The role of postoperative radiotherapy in the treatment of N2 tumours is not clear
  Role of PORT in the treatment of tumors with N2 involvement was unclear
CONCLUSION – PORT IN R0 N0-1

• PORT results in overall survival detriment in completely resected N0-1 NSCLC

• Hence, PORT is not recommended in this setting
EVIDENCE IN STAGE III R0 N2 TUMOURS
**pIIIA N2 NSCLC**

CR → 4 cycles adj CT (platinum doublet)

**Inclusion**
- 18 – 70 years
- ECOG upto 1
- < 10% wt loss before Sx
- FEV1 > 1L

**Exclusion**
- Pneumonectomy
- H/o other cancers
- Neoadj CT
- Uncontrolled active infection

**N** = 364; Per protocol - 310

**Median f/up – 46 months**

**Post operative RT**
- 3D CRT/ IMRT
- 50Gy/25#
  -(N – 184)

**Observation**
- (N – 180)

**PORT vs Observation**
- 3yr LRR – 9.5% vs 18.3%
- 3yr DFS – 40.5% vs 32.7%
- 3yr OS – 42.8% vs 30.6%

**Per protocol**
- 3yr LRR – 9.5% vs 18.3%
- 3yr DFS – 42.8% vs 30.6%
- 3yr OS – 78.3% vs 82.8%

**3yr DFS**
- PORT vs Observation: 40.5% vs 32.7%
- Per protocol: 42.8% vs 30.6%

**3yr OS**
- PORT vs Observation: 78.3% vs 82.8%
- Per protocol: 78.3% vs 82.8%

**3yr LRR**
- PORT vs Observation: 9.5% vs 18.3%
- Per protocol: 9.5% vs 18.3%

**Median f/up**
- PORT: 46 months
- Observation: 46 months
PORT-C (CONT.)

- Limitations:
  - 20% of PORT arm patients did not receive PORT
  - Single centre trial
  - >80% adenocarcinoma
  - Tyrosine kinase inhibitors used – data not given
  - 10% received 3D-CRT
• Conclusion
  • RT affords better locoregional control
  • When RT is given adequately, it may afford better disease free survival
  • Further studies needed to identify optimal patients who benefit from PORT
Multicentric study pIII A N2 NSCLC
CR; neoadj or adj chemo allowed

Inclusion
• >18 years
• ECOG upto 2

Post operative RT
3D CRT/ IMRT
54Gy/25-27# (N – 252)

Observation (N – 249)

PORT vs Observation
3yr Mediastinal relapse
25% vs 46% [S]

3yr DFS – 47% vs 44% [NS]

3yr OS – 67% vs 69% [NS]

Gr 3-4 pneumonitis
5% vs 0.4%

Grade 3-4 cardiopulmonary toxicity – 11% vs 5%
Limitations:

- Around 90% received RT by 3D-CRT
- NACT was acceptable in the protocol → included patients with worse prognosis?
- Use of biologicals – information not available
• Conclusion
  • 3D Conformal PORT cannot be recommended as the standard of care in patients with stage IIIA N2 NSCLC
  • However, it can significantly reduce the risk of mediastinal relapse
OLDER EVIDENCE

- Multiple meta-analyses and retrospective studies spanning from early 1980s – 2020
- Older studies show minimal benefit
  - 2D techniques
  - Sub-par staging methods
  - Non-use of chemotherapy, biologicals
- More recent retrospective evidence including SEER database results show there may be an Overall survival benefit with PORT in Stage III R0 with N2 disease
SEQUENCE OF CT, PORT

- National Cancer Database (NCDB) registry analyses for pN2 NSCLC patients
  - Sequential CT and PORT were associated with superior survival compared with postop CRT

- Randomised ECOG trial
  - PORT vs PORT with conc CT had similar 3yr OS
• Adjuvant chemotherapy offers absolute overall survival improvement of 5-15% by various meta-analyses

• PORT is associated with better local recurrence rates; no OS benefit

• Hence, PORT to be delivered sequentially after CT so as not to interfere with adjuvant CT schedule or cause treatment breaks
PORT AFTER INCOMPLETE RESECTION
PORT AFTER R1/R2 RESECTION

• NCDB-based analysis of 3395 patients showed an improved OS across all nodal stages with PORT in patients with incompletely resected (R1/2) Stage II-III NSCLC
• OS improvement was most pronounced in pN0 disease, with a 5-year OS of 41% vs. 26% with and without PORT, respectively
• There is no level I evidence recommending the use of induction radiation therapy (or chemoradiation therapy) followed by surgery for patients with resectable stage III NSCLC
TARGET VOLUMES & DOSE
## RADIATION DOSE

<table>
<thead>
<tr>
<th>Setting of PORT</th>
<th>Radiation dose</th>
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<tbody>
<tr>
<td>Pre-operative</td>
<td>45 Gy/ 25#s</td>
</tr>
<tr>
<td>Post-operative (R0 resection)</td>
<td>50 Gy/ 25#s</td>
</tr>
<tr>
<td>Post-operative (R1 resection)</td>
<td>54 – 60 Gy/ 27 – 30 #s</td>
</tr>
<tr>
<td>Post-operative (R2 resection)</td>
<td>60 Gy/ 30#s</td>
</tr>
</tbody>
</table>
PORT-CTV must account for the lymph nodes involved according to the surgery and pathology report and should consider preoperative imaging.

In cases of neoadjuvant chemotherapy, initially involved lymph node stations should be included, even in cases of downstaging.
RADIATION TREATMENT VOLUMES (CONT.)

- Volumes should include
  - pathologically involved and resected mediastinal lymph node stations
  - bronchial stump
  - ipsilateral hilum
  - ipsilateral nodal stations 4 and 7
GUIDELINES
ASTRO GUIDELINES

• In completely resected (R0) LA NSCLC with N2 disease, PORT is strongly recommended

• In completely resected (R0) LA NSCLC with N0-1 disease, PORT results in inferior survival and is NOT routinely recommended

• PORT should be delivered sequentially after CT

Published : 2015
Reaffirmed : 2017
• Patients with microscopic residual (R1) primary disease (i.e., positive margins) and or microscopic nodal disease (i.e., extracapsular extension) are strongly recommended for PORT (low quality evidence)

• Patients with gross residual primary or macroscopic nodal disease (R2) are strongly recommended for PORT

• There is no Level I evidence recommending the use of induction RT for resectable Stage III NSCLC