# ADJUVANT RADIOTHERAPY FOR LUNG CANCER

40 th 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 IIIN2 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
  - R2resection
  - N2 status

# R0 N0-1 TUMOURS

# AFTER COMPLETE RESECTION

- Randomised evidence?

ELSEVIER

International Journal of Radiation Oncology*Biology*Physics

Volume 6, Issue 8, August 1980, Pages 983-986

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

Paul Van Houtte M.D. †, Pierre Rocmans M.D. ††, Philippe Smets M.D. †††, Jean-Claude Goffin M.D. †, Jacqueline Lustman-maréchal M.D. †, Patric Vanderhoeft M.D. ††, Jacques Henry M.D. †

# VAN HOUTTE ET AL…..
# 1980

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

**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
- T 2 group ($p < 0.05$),
- especially after pneumectomy (16 % versus 43 % )

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

| | Radiotherapy group | Control group |
|---|---|---|
| Lobectomy | 35 | 43 |
| Pneumectomy | 16 | 38 |
| Total | 51 | 81 |
| $T_1$ | 33 | 39 |
| $T_2$ | 15 | 39 |
| $T_3$ | 3 | 3 |
| Total | 51 | 81 |

# CRITICISMS…

TV: Mediastinum

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

ELSEVIER

International Journal of Radiation Oncology*Biology*Physics

Volume 27, Issue 3, 20 October 1993, Pages 525-529

Clinical original contribution

## Postoperative radiotherapy after pneumonectomy: Impact of modern treatment facilities

Patricia Phlips M.D. [1], Pierre Rocmans M.D. [2], Patrick Vanderhoeft M.D. [2], Paul van Houtte M.D., PH.D. [1]

Retrospective Data

5-year survival rate 8% vs 30%

31% of the control surgical group including less advanced tumors

# CT BASED PLAN

- Randomised evidence?

ELSEVIER

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], Pierluigi Granone [b], Salvatore Valente [c], Vincenzo Valentini [a], Mario Balducci [a], Giovanna Mantini [a], Adriana Turriziani [a], Stefano Margaritora [b], Alfredo Cesario [b], Sara Ramella [a], Giuseppe M Corbo [c], Rolando M D'Angelillo [a], Antonella Fontana [a], Domenico Galetta [b], Numa Cellini [a]

# ITALIAN TRIAL/ TRODELLA TRIAL

CT-plan
Linac
TV:
bronchial stump
homolateral hilum

**104 patients**

- pathological stage I

**Local Recurrence**

**LR Low in Stage I. Routine RT is not recommended currently**

**5 year OS**

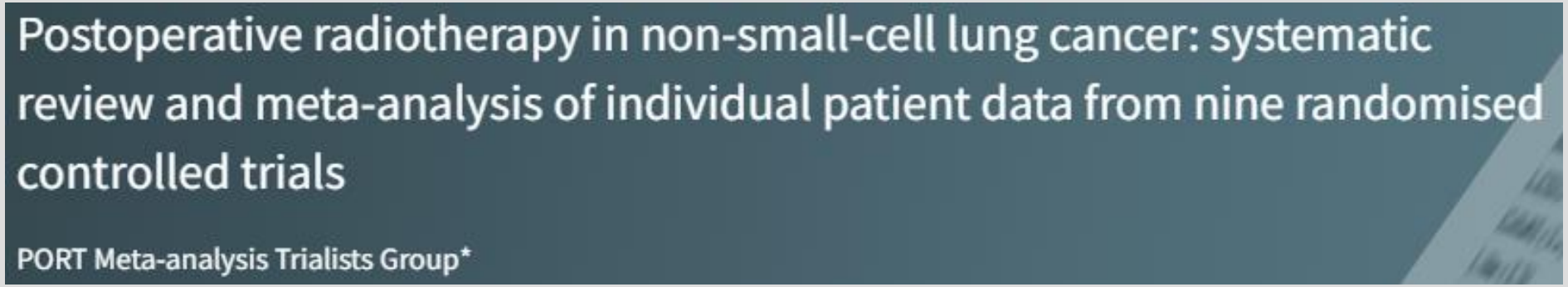
- No significant diff (67% vs 58%)

**Toxicity**

- NS

# R0 RESECTION…CONT

- Metaanalysis?



# PORT META ANALYSIS 1998

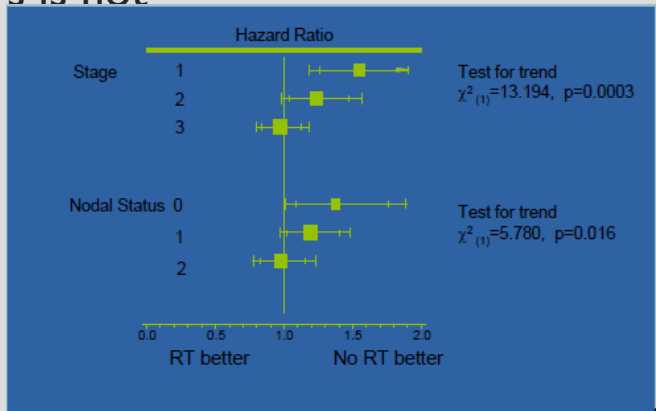
- Significant adverse effect of PORT on survival (hazard ratio 1·21 [95% CI 1·08–1·34])
- 21% relative increase in the risk of death is equivalent to an absolute

**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

JAMA Oncology | Original Investigation

# Effect of Postoperative Radiotherapy for Patients With pIIIA-N2 Non–Small Cell Lung Cancer After Complete Resection and Adjuvant Chemotherapy
## The Phase 3 PORT-C Randomized Clinical Trial

Zhouguang Hui, MD; Yu Men, MD; Chen Hu, PhD; Jingjing Kang, MD; Xin Sun, MD; Nan Bi, MD, PhD; Zongmei Zhou, MD; Jun Liang, MD; Jima Lv, MD; Qinfu Feng, MD; Zefen Xiao, MD; Dongfu Chen, MD; Yan Wang, MD; Junling Li, MD; Jie Wang, MD; Shugeng Gao, MD; Luhua Wang, MD; Jie He, MD

2021

**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% | S |
| 3yr DFS – 40.5% vs 32.7% | NS |
| **Per protocol** 3yr DFS – 42.8% vs 30.6% | S |
| 3yr OS – 78.3% vs 82.8% | NS |

# 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

# PORT-C (CONT.)

- 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

# Postoperative radiotherapy versus no postoperative radiotherapy in patients with completely resected non-small-cell lung cancer and proven mediastinal N2 involvement (Lung ART): an open-label, randomised, phase 3 trial

2022

Cecile Le Pechoux, MD • Nicolas Pourel, MD • Prof Fabrice Barlesi • Delphine Lerouge, MD • Delphine Antoni, MD • Bruno Lamezec, MD • et al. Show all authors

N – 501

Median f/up – 4.8 years

Multicentric study
**pIIIA 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<br>25% vs 46% | S |
| 3yr DFS – 47% vs 44% | NS |
| 3yr OS – 67% vs 69% | NS |
| Gr 3-4 pneumonitis<br>5% vs 0.4% | |
| Grade 3-4 cardiopulmonary toxicity – 11% vs 5% | |

# LUNG ART (CONT.)

- 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

# LUNG ART (CONT.)

- 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

# SEQUENCE OF CT, PORT (CONT.)

- 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

# PREOPERATIVE RT

- 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

| Setting of PORT | Radiation dose |
|---|---|
| Pre-operative | 45 Gy/ 25#s |
| Post-operative (R0 resection) | 50 Gy/ 25#s |
| Post-operative (R1 resection) | 54 – 60 Gy/ 27 – 30 #s |
| Post-operative (R2 resection) | 60 Gy/ 30#s |

# RADIATION TREATMENT VOLUMES

- 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

Published : 2015
Reaffirmed : 2017

- In completey 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

# ASTRO GUIDELINES (CONT.)

- 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

NCCN GUDELINES