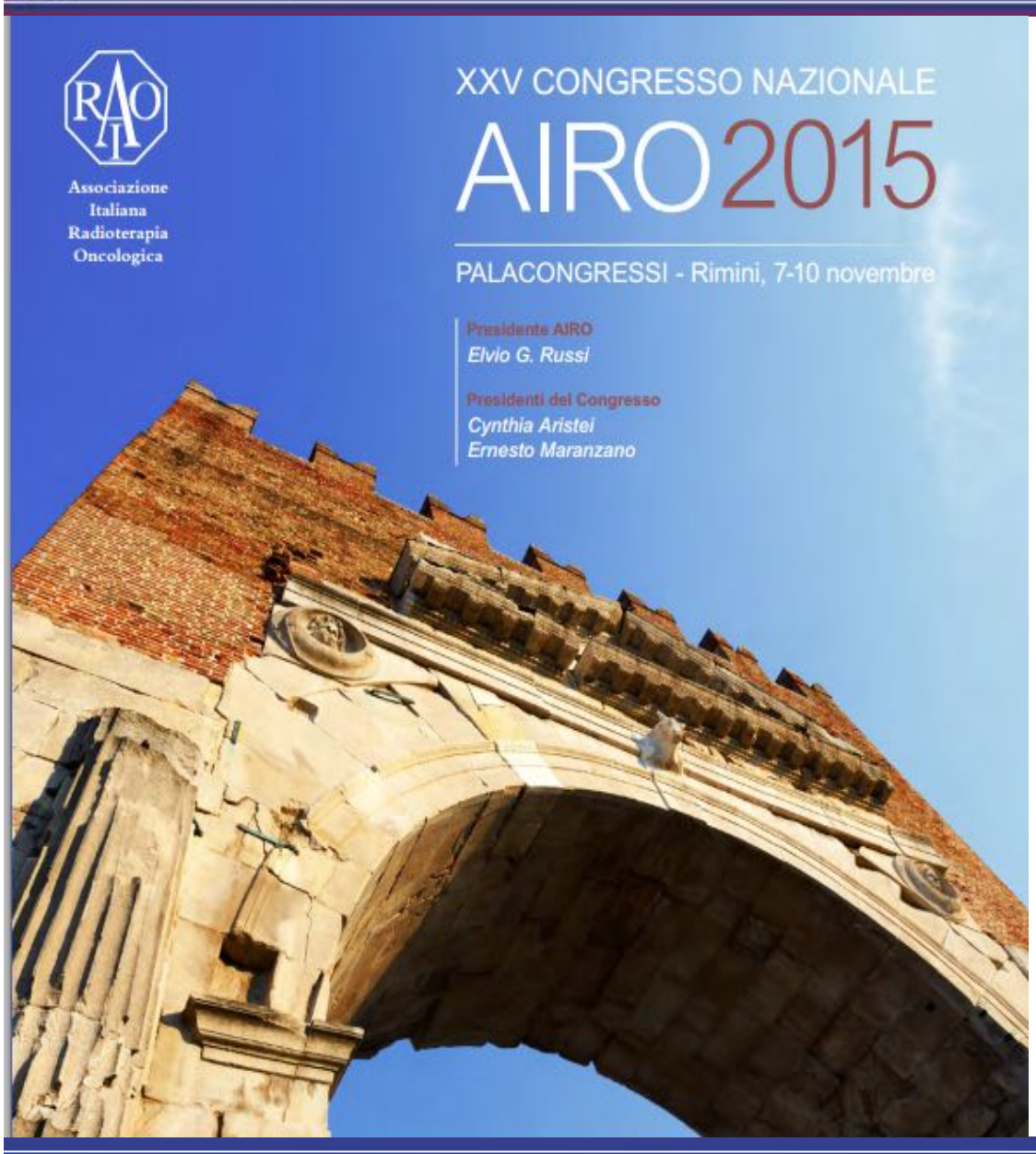

Radioterapia adiuvante nel NSCLC

Dott. Vieri Scotti MD

Radioterapia
AOU Careggi
Firenze

8 novembre 2015

DICHIARAZIONE

Relatore: Vieri SCOTTI

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Consulenza ad aziende con interessi commerciali in campo sanitario **: NIENTE DA DICHIARARE**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Partecipazione ad Advisory Board: **NIENTE DA DICHIARARE**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario:**NIENTE DA DICHIARARE**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario:**NIENTE DA DICHIARARE**

Agenda

Introduction
 Heterogeneity of Stage III Disease
Levels of Evidence and hystorical development of PORT
Adjuvant Radiotherapy in N2 positive disease: what is going on
PORT : Which Volumes?
PORT in R+ patients and after neoadj CT

Agenda

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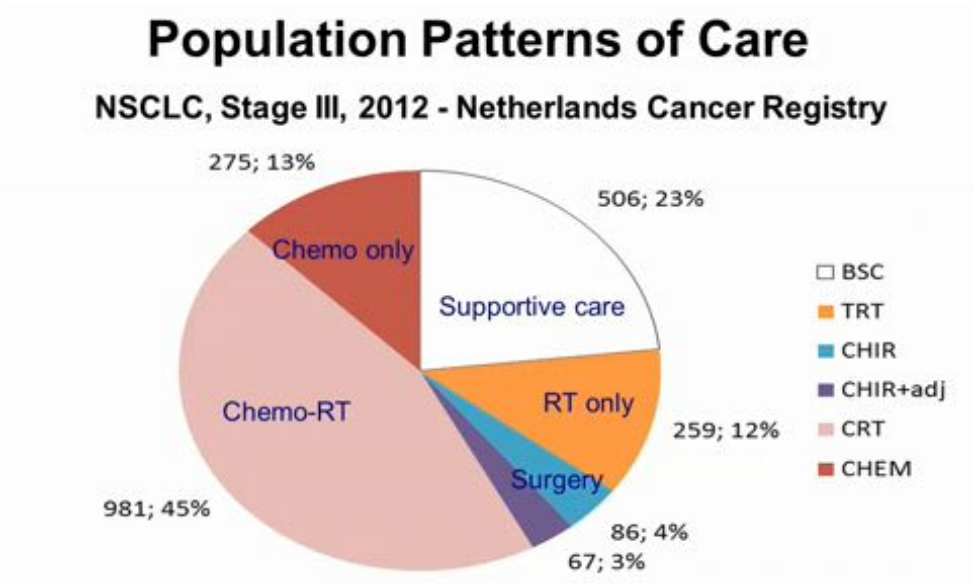
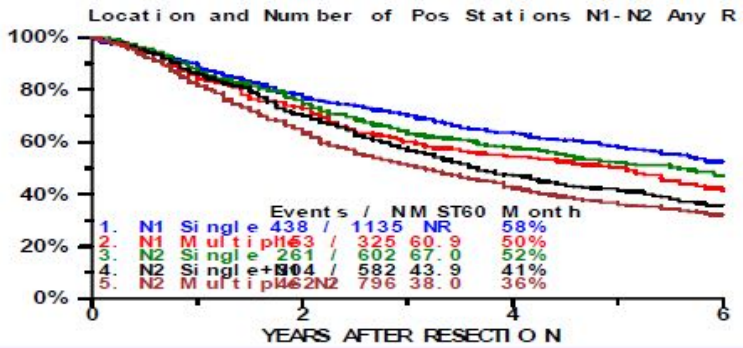


- Stage III includes very different clinical entity
- The mainstain of treatment stays surgery...
  but :
  - 30 - 60 % of LRR
  - 20 - 35% 5 years OS

Pathological – any R



N1 Single = N1a
N1 Multiple = N1b
N2 Single N2 ("skip mets") = N2a1
N2 Single N2 + N1 = N2a2
N2 Multiple N2 = N2b

N1a vs N1b vs N2a1 vs N2a2 vs N2b Comparisons
Adjusted for Histology (adeno vs others), Sex, Age 60+ , R0 Resection, and Region.
(Cox PH regression on All cases)

comparison	HR	P
N1b vs N1a	1.38	0.0005
N2a1 (skip) vs N1b	0.92	0.4331
N2a2 vs N2a1 (skip)	1.37	0.0002
N2b vs N2a2	1.21	0.0117
N2a2 vs N1b	1.26	0.0197

Recommendations

- To keep the present descriptors as they are
- To propose new descriptors for prospective testing:
  - pN1a: involvement of single pN1 nodal station
  - pN1b: involvement of multiple pN1 nodal stations
  - pN2a1: involvement of single pN2 nodal station without pN1 (skip pN2)
  - pN2a2: involvement of single pN2 nodal station with pN1
  - pN2b: involvement of multiple pN2 nodal stations

Asamura H et al.
JTO 2015; in press.

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Robinson Classification

Subtypes III A N2

Subtypes	Description
III A1	Incidental nodal metastases found on pathological examination of the resection specimen
III A2	Nodal (single station) metastases recognezed intraoperatively
III A3	Nodal metastases (single or multiple station) recognized by prethoracotomy staging (mediastinoscopy, other nodal biopsy, or PET scan)
III A4	Bulky or fixed multistaion N2 disease

Robinson et al. (Chest 2003; 123:202S-232S)

Prognostic Factors

Good Prognosis	Bad Prognosis
Single station	Multiple stations
Single lymph node	Multiples lymph nodes
Microscopic Invasion	Extracapsular Extension
Station 5 or 6	Station 4L or 9
Little T volume	Bulky Disease
	Mediastinic Invasion
	« Skip Metastasis»

Kassis et al. Thoracic Surg Clin 18 (2008) 333-337

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- **1a** Evidence obtained from meta-analyses of randomized trials

Phases III randomized, meta-analyses

- **1b** Evidence obtained from at least one randomized trial
- **2a** Evidence obtained from one well controlled study without ran

Phases II, pilot studies

- **2b** Evidence obtained from at least one other type of well designed experimental study
- **3** Evidence obtained from well designed non-experiemen e, correlative studies or case-reports

Retrospective studies

- **4** Opinion by experts, consensus conferences etc.

Opinion

Articles

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**

2128 patients (808 stage III)
In 9 Randomized Studies from 1966

Surgery
1072 patients

Surgery + PORT
1056 patients

THE LANCET • Vol 352 • July 25, 1998

Trial	Recruitment	Patients	Disease stage
Belgium[10]	1966–77	202*	I,II,III
LCSG 773[11]	1978–85	230	II,III
CAMS[12]	1981–95	317	II,III
Lille[13]	1985–91	163	I
EORTC 08861	1986–90	106	II,III
MRC LU11[14]	1986–93	308	II,III
GETCB 04CB86	1986–94	189	I,II,III
Slovenia[15]	1988–92	74	III
GETCB 05CB88	1988–94	539	I,II,III

LSCG=Lung Cancer Study Group, CAMS=Chinese Academy of Medical Sciences, EORTC=European Organization for Research and Treatment of Cancer, MRC=Medical Research Council, GETCB=Groupe d'Etude et de Traitement des Cancers Bronchiques. All trials used TNM staging, except Belgium,[10] which used AJC.
*20 patients with small-cell lung cancer excluded.

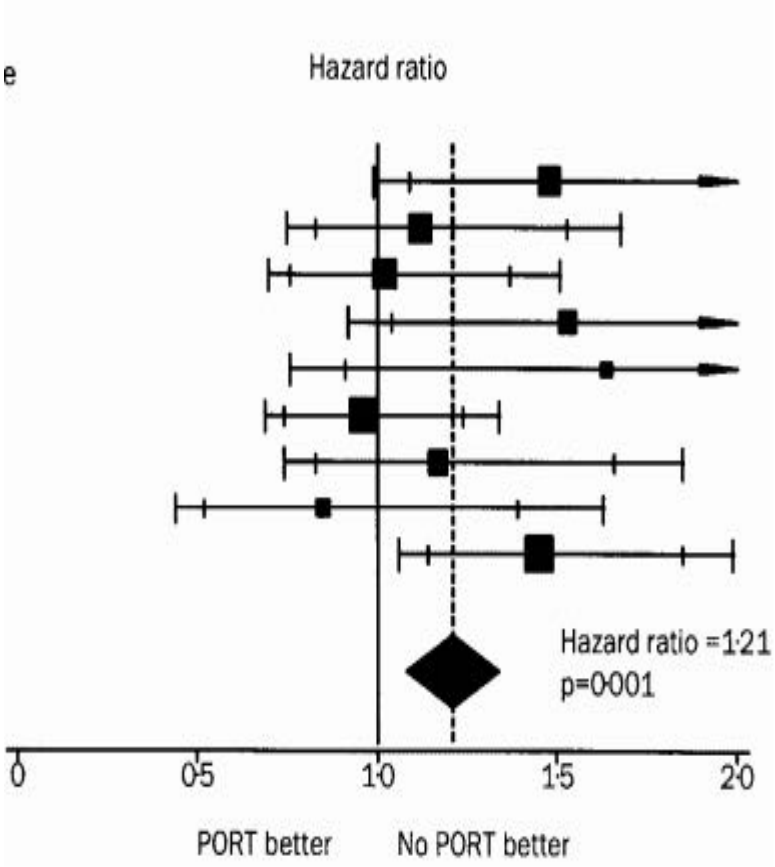
Table 2: **Characteristics of trials in PORT meta-analysis**

Trial	Radiotherapy dose				Prescription technique	Machine used	Average field size (cm)	Clinical target volume	Technique
	Total dose (Gy)	Fractions	Duration (weeks)	Gy/day					
Belgium[10]	60	30	6	2	Isodose 90%	Co60	15x9	Bronchial stump, hilum, mediastinum	SCB,OF,LF
LCSG 773[11]	50	25·0–27·5	5·0–5·5	1·8–2·0	Central axis, at midplane	Co60 & linac	*	Bronchial stump, hilum, mediastinum	SCB,OF,LF
CAMS[12]	60	30	6	2	At midplane	Co60 & linac	6x12	Hilum, mediastinum	SCB,OF,LF
Lille[13]	45–60	22·5–30·0	6	2	Isodose 90%	Co60 & linac	12x12	Hilum, upper mediastinum	SCB,OF,LF
EORTC 08861	56	28	5·5	2	Central axis, at midplane	linac	15x10	Hilum, mediastinum	Composite plans
MRC LU11[14]	40	15	3	2·6	Central axis, at midplane	Co60 & linac	*	Hilum, mediastinum, supraclavicular fossae†	SCB,OF,LF
GETCB 04CB86	60	24–30	6	2·0–2·5	Isocentre	Co60 & linac	*	Bronchial stump, hilum, mediastinum	SCB,OF,LF
Slovenia[15]	30	10–12	2	2·5–3·0	Central axis, at midplane	linac	9x12	Hilum, mediastinum	OF,LF
GETCB 05CB88	60	24–30	6	2·0–2·5	Isocentre	Co60 & linac	*	Bronchial stump, hilum, mediastinum	SCB,OF,LF

SCB = spinal cord blocks; OF = oblique fields; LF = lateral fields; linac=linear accelerator; Co60=cobalt-60.
Only one trial (EORTC 08861) used computed tomography for planning, and two trials (EORTC 08861 and Lille) used lung-factor corrections.
*Information not available; †For upper lobe tumours.

Table 3: **Details of radiotherapy**

OS



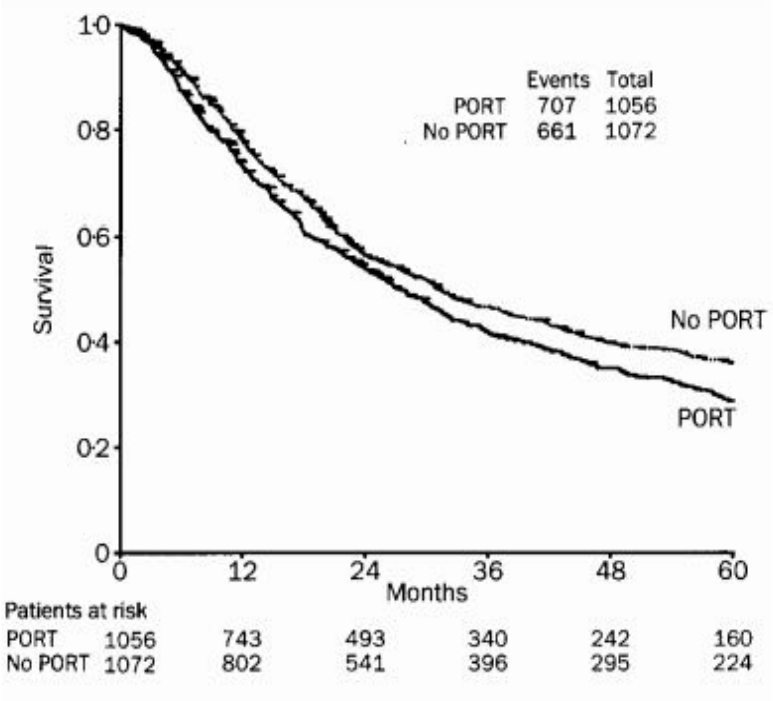
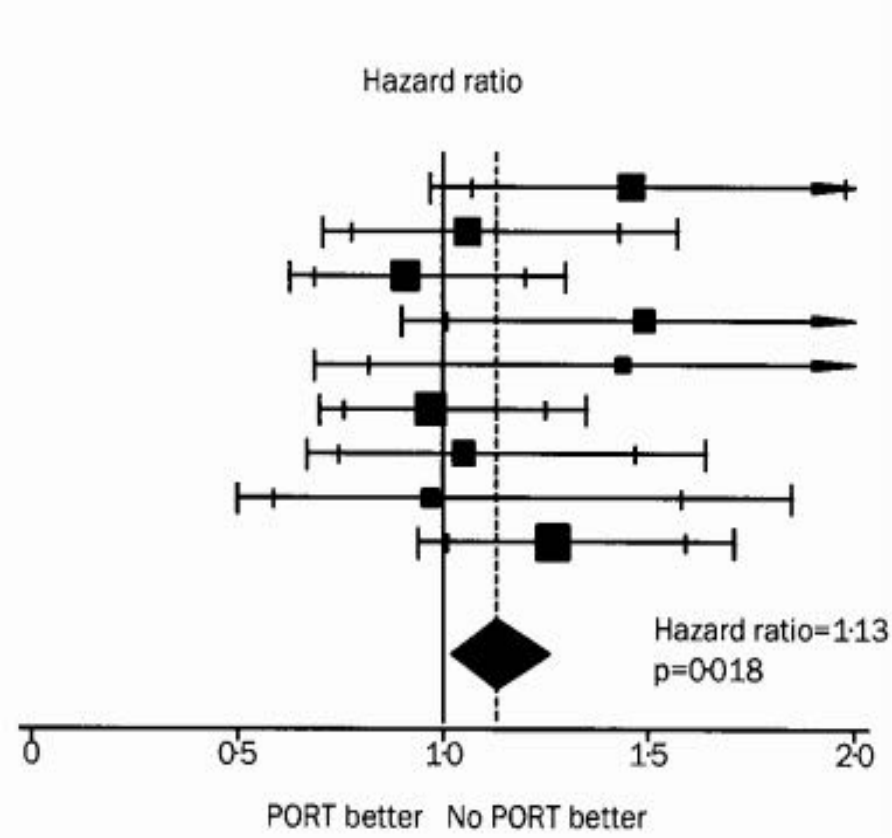


Figure 2: **Kaplan-Meier curve for survival**

Recurrence-Free Survival



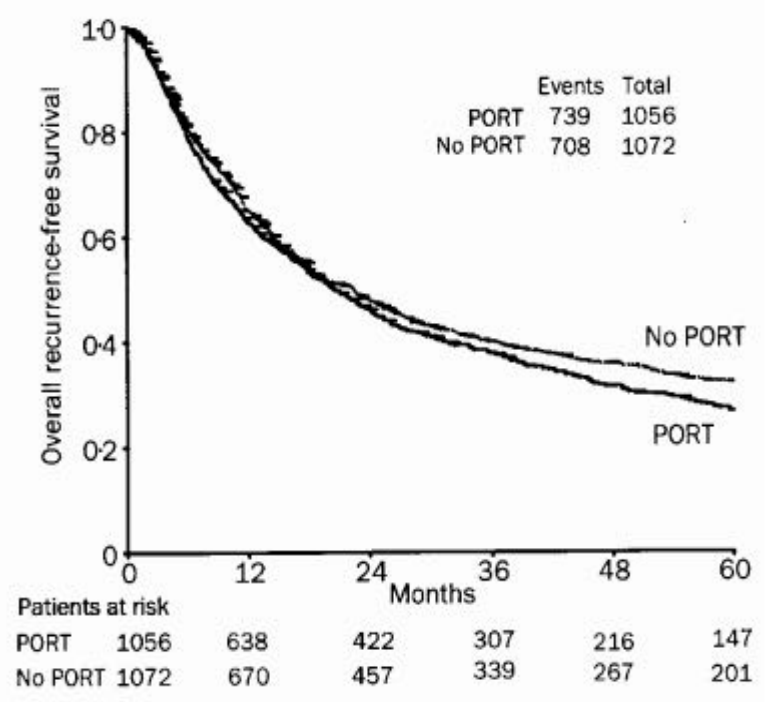


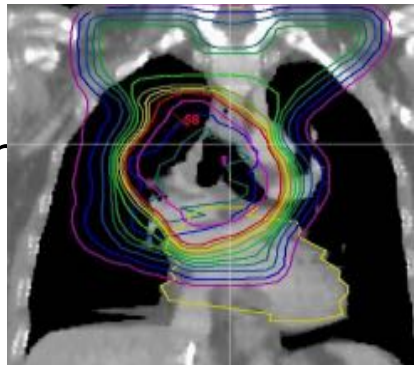
Figure 4: **Kaplan-Meier curve for recurrence-free survival**

Critical Points:

- 3 decades period (from 1966)
- Selection criteria (heterogeneity):

  Histology
  Tumor extent : from T1N0 to T4N2
  Wide range of surgical procedures
- Definitions of complete resection
- Techniques
- FUP procedures
- Variation between trials of local failure definition

Radiotherapy Techniques



- Large Volumes (especially after pneumectom
- Large fractions size > 2 Gy
- Low shielding to lung and heart
- Use of Cobalt 60
- No CT based Treatment Planning
- Total dose as low as 30 Gy, as high as 60 Gy

TOXICITY

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic review

Modern post-operative radiotherapy for stage III non-small cell lung cancer may improve local control and survival: A meta-analysis

Charlotte Billiet [a,*], Herbert Decaluwé [b], Stephanie Peeters [a], Johan Vansteenkiste [c], Christophe Dooms [c], Karin Haustermans [a], Paul De Leyn [b], Dirk De Ruysscher [a]

[a] Radiation Oncology; [b] Thoracic Surgery and Leuven Lung Cancer Group; and [c] Respiratory Oncology (Pneumology) and Leuven Lung Cancer Group, University Hospitals Leuven/KU Leuven, Belgium

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11 randomized phase III trials (2387 patients) available for OS data

- 1: cobalt therapy
- 6: cobalt + Linac RT
- 4: Linac RT

8 randomized phase III trials (1677 patients) available for LR data

- 3: Linac RT

STAGE III

- OS increased only when PORT was administered with linear accelerators.
- With LINAC based PORT LR can be reduced from 30% to 10%
- This study generates the hypothesis that modern PORT can increase both LRR and OS in stage III A N2 NSCLC even in patients treated with surgery and chemotherapy.

C. Billiet et al. / Radiotherapy and Oncology 110 (2014) 3–8

STAGE IIIA N2 only LINAC

No individual data

Lung Cancer 84 (2014) 156–160

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Evidence supporting contemporary post-operative radiation therapy (PORT) using linear accelerators in N2 lung cancer

Suchit H. Patel[a], Yan Ma[b], A. Gabriella Wernicke[a], Dattatreyudu Nori[a], K.S.C. Chao[a], Bhupesh Parashar[a,*]

[a] Stich Radiation Center, New York Presbyterian Hospital/Weill Cornell Medical Center, 525 East 68th Street, New York, NY 10065, United States
[b] Division of Biostatistics and Epidemiology, Weill Cornell Medical College, 1300 York Avenue, New York, NY 10021, United States

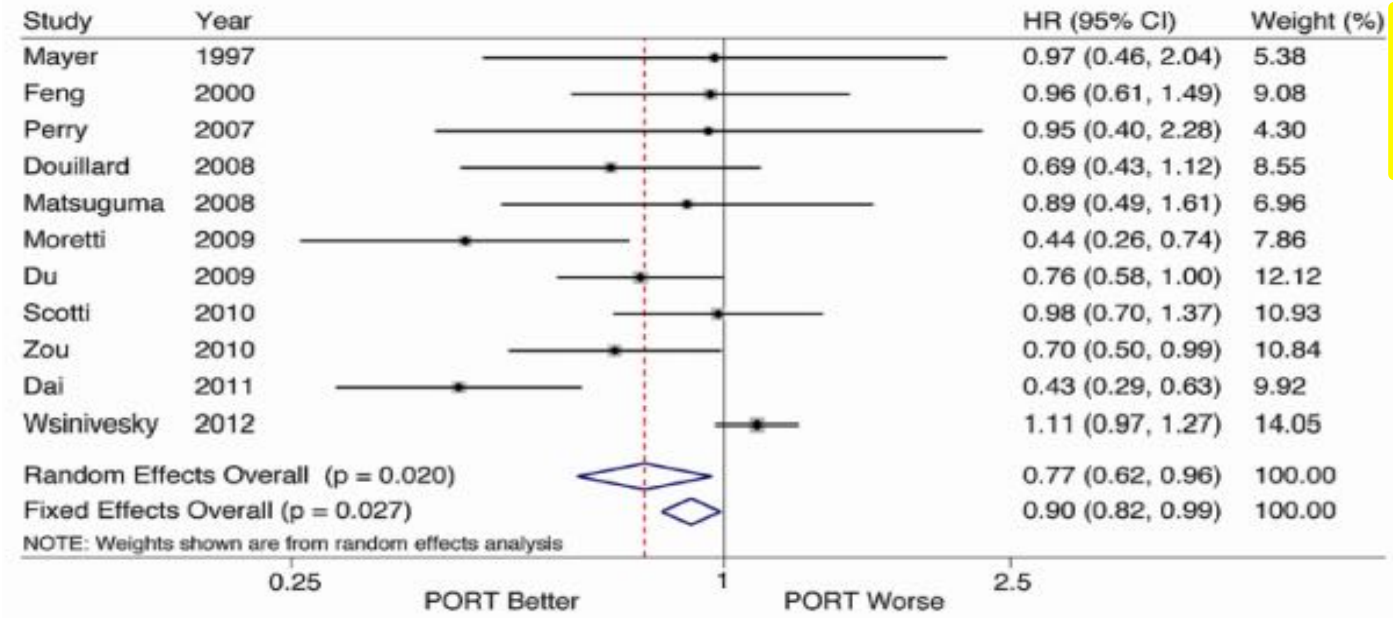
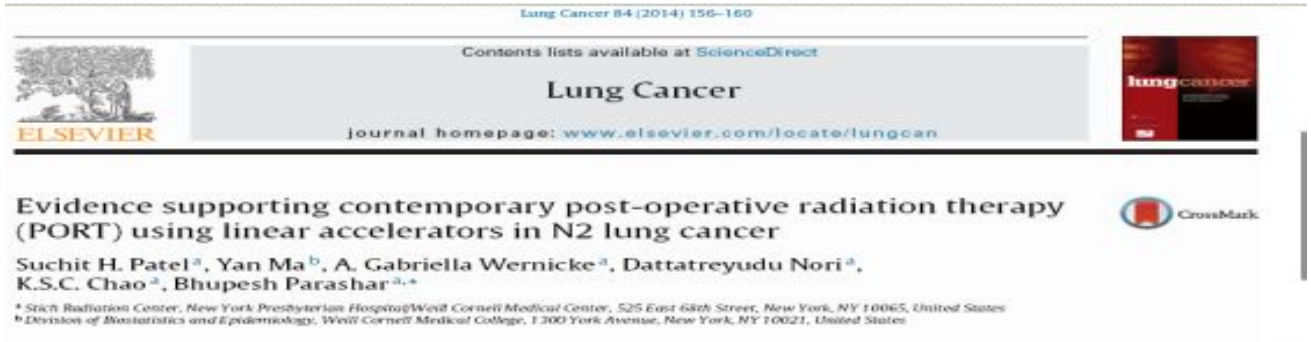


Fig. 1. Meta-analysis of OS outcomes of included studies.

8 retrospective series



Lung Cancer 84 (2014) 156–160

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[b] Division of Biostatistics and Epidemiology, Weill Cornell Medical College, 1300 York Avenue, New York, NY 10021, United States

STAGE IIIA N2 only LINAC

8 retrospective series

- SIGNIFICANT REDUCTION in LRFS HR:0,51 p< 0,01
- DFS available in only 5 of 11 series
- Acceptable toxicity

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 72, No. 3, pp. 695–701, 2008

0360-3016/08/$–see front matter

doi:10.1016/j.ijrobp.2008.01.044

CLINICAL INVESTIGATION **Lung**

IMPACT OF POSTOPERATIVE RADIATION THERAPY ON SURVIVAL IN PATIENTS WITH COMPLETE RESECTION AND STAGE I, II, OR IIIA NON–SMALL-CELL LUNG CANCER TREATED WITH ADJUVANT CHEMOTHERAPY: THE ADJUVANT NAVELBINE INTERNATIONAL TRIALIST ASSOCIATION (ANITA) RANDOMIZED TRIAL

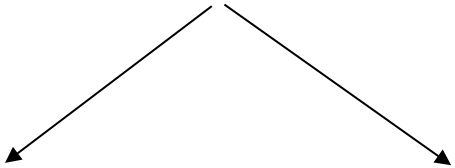
JEAN-YVES DOUILLARD, M.D., PH.D.,* RAFAEL ROSELL, M.D.,† MARIO DE LENA, M.D.,‡ MARCELLO RIGGI, M.D.,§ PATRICK HURTELOUP, M.D.,§ AND MARC-ANDRE MAHE, M.D., PH.D.,* ON BEHALF OF THE ADJUVANT NAVELBINE INTERNATIONAL TRIALIST ASSOCIATION

*Centre R. Gauducheau, Nantes, France; †Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Badalona, Spain; ‡IRCCS Oncologico, Bari, Italy; and §Institut de Recherche Pierre Fabre, Boulogne, France

No RANDOMIZATION FOR RT

ANITA-trial

Resection



Observation

Chemotherapy
Nav 30 mg/mq weekly
CDDP: 100 mg/mq 3 weeks
4 cycles

RT was upon center choice

I. J. Radiation Oncology ● Biology ● Physics Volume 72, Number 3, 2008

Table 3. ANITA trial results: Percentage of patients with 5-year survival, according to treatment received by nodal status

Treatment group	pN0	pN1	pN2
Observation (%)	62.3	31.4	16.6
Observation + PORT (%)	43.8	42.6	21.3
Chemotherapy* (%)	59.7	56.3	34.0
Chemotherapy* + PORT (%)	44.4	40.0	47.4

Abbreviations: ANITA = Adjuvant Navelbine International Trialist Association.; PORT = postoperative radiation therapy.
* Chemotherapy consisted of vinorelbine + cisplatin.

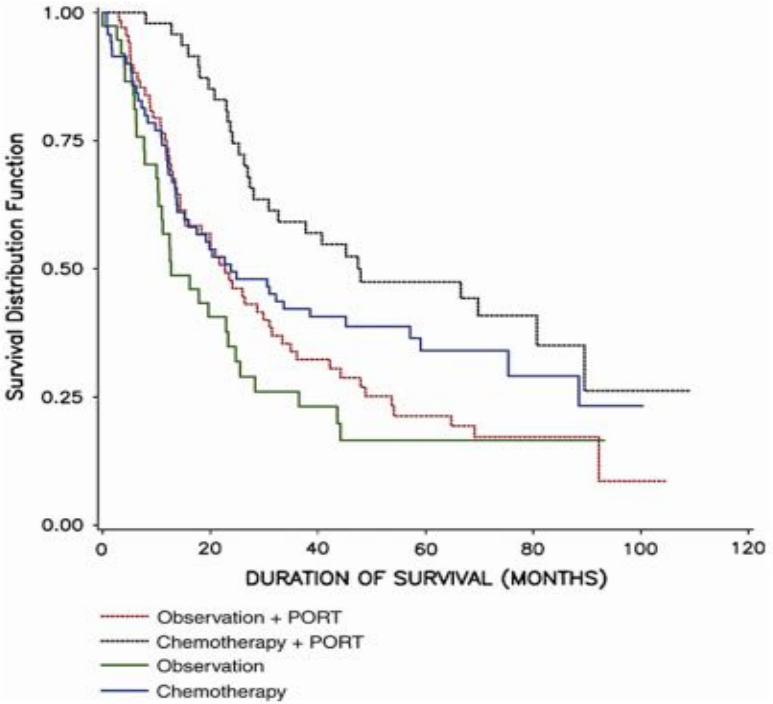


Fig. 3. Overall survival according to treatment received in the pN2 patients in the Adjuvant Navelbine International Trialist Association (ANITA) trial.

N2

PORT in N2 Patients

N2	RADIOTHERAPY		NO RADIOTHERAPY	
N=224	No CT	VRL+CDDP	No CT	VRL+CDDP
Number of patients	68	48	38	70
MS, mos	22.7	47.4	12.7	23.8
1 year survival	73.5 %	97.9 %	56.8 %	71.2 %
2 year survival	47.6%	76.6%	34.8%	49.4 %
5 year survival	21.3%	47.4%	16.6%	34.0 %
% deaths	54 (79%)	28 (58 %)	30 (79%)	46 (66%)

Combined use of chemotherapy plus PORT increases the chance of survival by a factor of almost 3 in pN2 patients compared with those treated with surgery alone

I. J. Radiation Oncology ● Biology ● Physics Volume 72, Number 3, 2008

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Comparison of efficacy for postoperative chemotherapy and concurrent radiochemotherapy in patients with IIIA-pN2 non-small cell lung cancer: An early closed randomized controlled trial

Wen-yi Shen [b,1], Jian Ji [a,1], Yang-song Zuo [b], Juan Pu [b], Yan-mei Xu [a], Cheng-dong Zong [c], Guang-zhou Tao [a], Xiao-fei Chen [a], Fu-zhi Ji [a], Xi-lei Zhou [a], Ji-hua Han [a], Cheng-shi Wang [b], Jiang-guo Yi [c], Xi-long Su [d], Wei-guo Zhu [a,*]

[a] *Department of Radiation Oncology, Huai'an First People's Hospital, Nanjing Medical University;* [b] *Department of Radiation Oncology, People's Hospital of Lianshui County, Huai'an;* [c] *Department of Radiation Oncology, Oncology Hospital of Huai'an; and* [d] *Department of Radiation Oncology, Huai'an No. 2 People's Hospital, PR China*

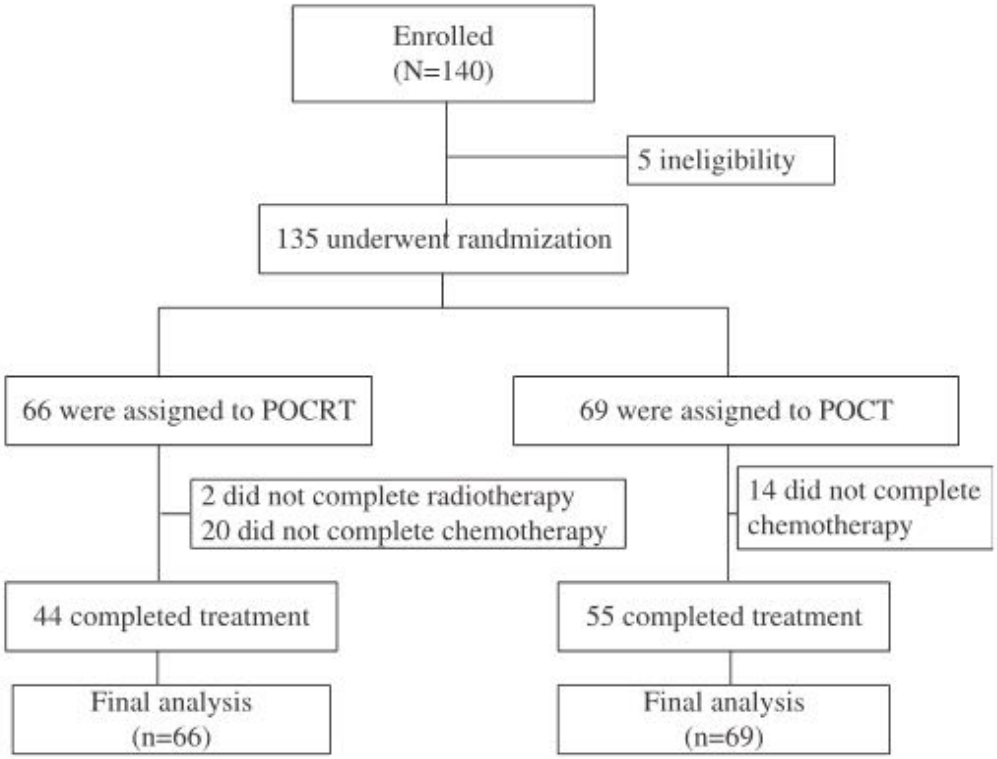

Fig. 1. Study enrollment. Of the 140 patients who underwent randomization, five were excluded, 66 were included in the POCRT group, and 69 in the POCT group for the final analysis.

Pts were stratified for:

- Hystology
- T dimension
- 1 vs ≥2 N2 nodes
- Loss of weight
- Nodal dissection vs nodal sampling
- Type of surgery

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Univariate analysis for OS:
- Weight loss (p=0,01)
- Early Tstage (p=0,01)
- Single pN2 (p=0,008)

Multivariate analysis for OS:
- Single vs ≥ 2 node

POCRT lower LR (p=0,0069)

POCRT lower DM (p=0,05)

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POCRT vs POCT
increases both LRC and DFS in patients with stage III A N2 NSCLC.
Single pN2 involvment is related to OS
Further studies are requested considering the small size of the sample

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Recent results in favor of PORT

PORT in N2 completely resected patients ??

- In favor of PORT....
  - SEER or NC Data base Studies (Lally 2006; Robinson 2015 4483 pts ;Mikell 2015 2115 pts)
    - 5-yr Survival in 1987 N2 pts 20% (Surg) vs 27% (S+PORT) (p=0,0077)
    - 5-yr S^{al} in 4483 N2 pts 34,8% (S+CT) vs 39,3% (S+CT+PORT) (p=0,014)
    - 5-yr S^{al} in 2115 N2 pts 34,7% (S+CT) vs 39,8% (S+CT+PORT) (p=0,021)

elcc

This cannot be considered robust evidence in favour of PORT

Lally JCO 2006; Mikell JTO 2015; Robinson JCO 2015

Courtesy of C. le Pecheu

ASTRO Guidelines Revised by ASCO

VOLUME 33 · NUMBER 18 · JUNE 20 2015

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Definitive and Adjuvant Radiotherapy in Locally Advanced Non–Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Evidence-Based Clinical Practice Guideline

Andrea Bezjak, Sarah Temin, Gregg Franklin, Giuseppe Giaccone, Ramaswamy Govindan, Melissa L. Johnson, Andreas Rimner, Bryan J. Schneider, John Strawn, and Christopher G. Azzoli

A B S T R A C T

Purpose
The American Society for Radiation Oncology (ASTRO) produced an evidence-based guideline on external-beam radiotherapy for patients with locally advanced non–small-cell lung cancer (NSCLC). Because of its relevance to the American Society of Clinical Oncology (ASCO) membership, ASCO endorsed the guideline after applying a set of procedures and a policy that are used to critically examine and endorse guidelines developed by other guideline development organizations.

Methods
The ASTRO guideline was reviewed by ASCO content experts for clinical accuracy and by ASCO methodologists for developmental rigor. On favorable review, an ASCO expert panel was convened and endorsed the guideline. The ASCO guideline approval body, the Clinical Practice Guideline Committee, approved the final endorsement.

Results
The recommendations from the ASTRO guideline, published in *Practical Radiation Oncology*, are clear, thorough, and based on the most relevant scientific evidence. The ASCO Endorsement Panel endorsed the guideline and added qualifying statements.

Recommendations
For curative-intent treatment of locally advanced NSCLC, concurrent chemoradiotherapy improves local control and overall survival compared with sequential chemotherapy followed by radiation. The standard dose-fractionation of radiation is 60 Gy given in 2-Gy once-daily fractions over 6 weeks. There is no role for the routine use of induction therapy before chemoradiotherapy. Current data fail to support a clear role for consolidation therapy after chemoradiotherapy; however, consolidation therapy remains an option for patients who did not receive full systemic chemotherapy doses during radiotherapy. Important questions remain about the ideal concurrent chemotherapy regimen and optimal management of patients with resectable stage III disease.

J Clin Oncol 33:2100-2105.

don, Washington University, St Louis, MO; Melissa L. Johnson, Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL; Andreas Rimner, Memorial Sloan Kettering Cancer Center; Bryan J. Schneider, Weill Cornell Medical College, New York, NY; John Strawn, Patient Representative, Houston, TX; and Christopher G. Azzoli, Massachusetts General, Boston, MA.

Published online ahead of print at www.jco.org on May 5, 2015.

Clinical Practice Guideline Committee approval: August 7, 2014.

Editor's note: This American Society of Clinical Oncology (ASCO) clinical practice guideline endorsement provides recommendations based on the review and analyses of the relevant literature for each recommendation in "Definitive and Adjuvant Radiotherapy in Locally Advanced Non-Small Cell Lung Cancer: An American Society for Radiation Oncology (ASTRO) Evidence-Based Clinical Practice Guideline." Additional information, which may include a methodology supplement, data supplements, slide sets, patient versions, and other clinical tools and resources, is available at:

- **PORT should be reccommended in completely resected N2 patients to increase LRC, but should be admnistered sequentially or concomitant to chemotherapy**

- **PORT is reccommended in incompletely resected patients sequentially or concomitant to chemotherapy**

ASTRO Guidelines
Revised by ASCO

J Clin Oncol 33:2100-2105. © 2015 by American Society of Clinical Oncology

EXPERT OPINION

Adjuvant radiotherapy for resectable locally advanced non–small cell lung cancer: Benefit or harm?

Linda W. Martin, MD, MPH, FCCP, FACS,[a] Gail E. Darling, MD, FRCSC FACS,[b] a
Dennis A. Wigle, MD, PhD[c]

SURGEONS point of view

- **Surgery alone** is clearly **not** an **acceptable** treatment strategy
- PORT metanalysis show a reduction of LRR without benefit in therms of OS: the lack of survival benefit is likely due to death from excessive early and late toxicity
- Positive impact of PORT on outcomes for patients with surgically resected pN2 is expected; but **await confirmatory trial data to change practice** for this difficult and controversial disease stage

RT for all N_2?

3 Risk groups for local relapse

Regression-tree analysis

→ 1 N_2 station or more involved

Retrospective review of 224 pts with N_2; 1987-1993, Mayo Clinic

→ Survival rate according to the risk group
(>1 N_2 or 1 N_2)

SURGEONS point of view

S_4 37% vs 4% in high risk p = 0.0002
10 fold increase

→ The pts at highest risk benefited the most

Identified prognostic categorization for resected N_2 pts

Sawyer TE Ann Thorac Surg 1997 64; 1402-1408

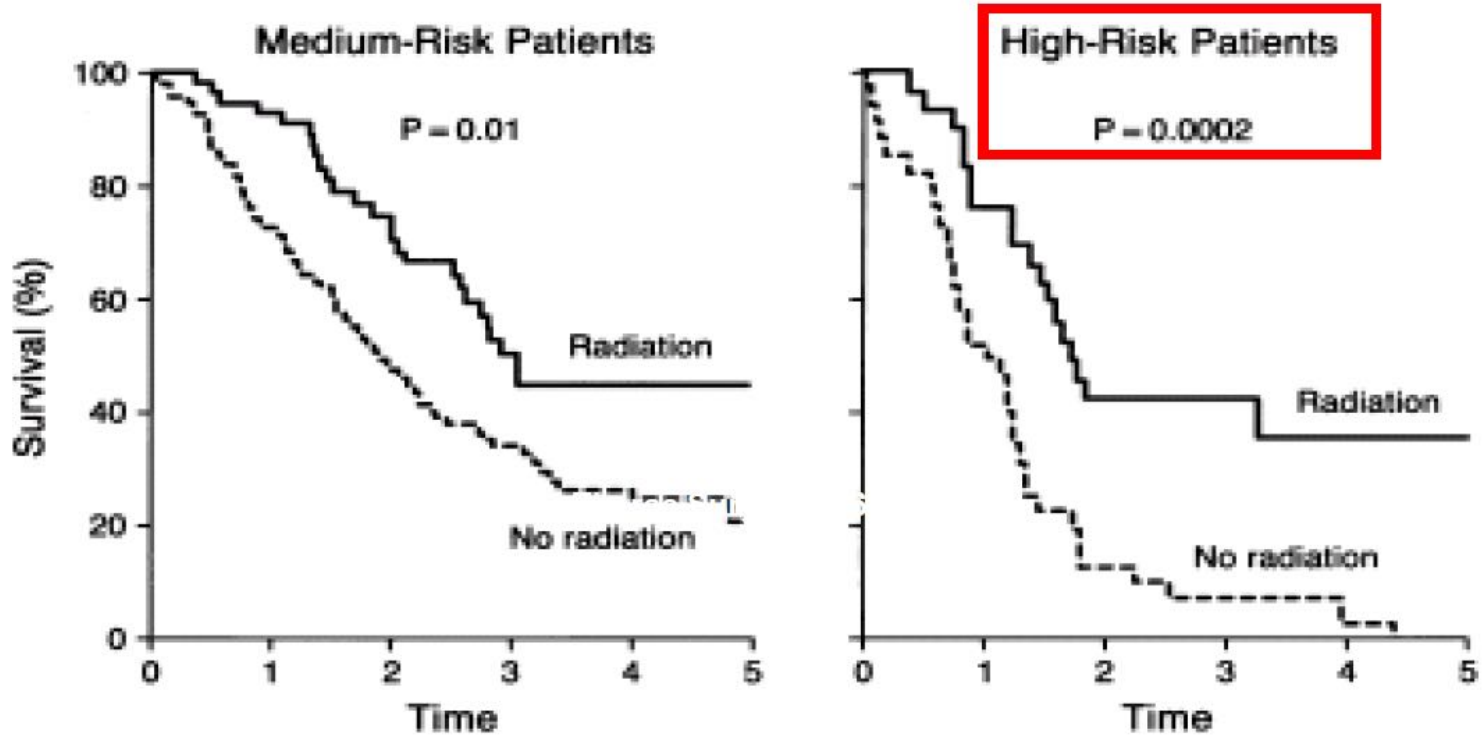

Fig 6. Adjuvant irradiation was associated with a higher survival rate in patients at both high risk (right; 65 patients) and intermediate risk (left; 149 patients) for death. There were only 9 patients in the low-risk category.

Sawyer, Ann Thorac Surg 1997;64:1402– 8

SURGEONS point of view

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Introduction

Heterogeneity of Stage III Disease

Levels of Evidence and hystorical development of PORT

Adjuvant Radiotherapy in N2 positive disease: what is going on

PORT : Which Volumes?

PORT in R+ patients and after neoadj CT

LUNG ART phase III Trial

(IFCT 0503-UK group-EORTC 22055-08053)

Trial registry: NCT00410683

Completely resected NSCLC with mediastinal histo or cytologically proven nodal involvement

IFCT

Lung ART UK

Possibility of adjuvant CT

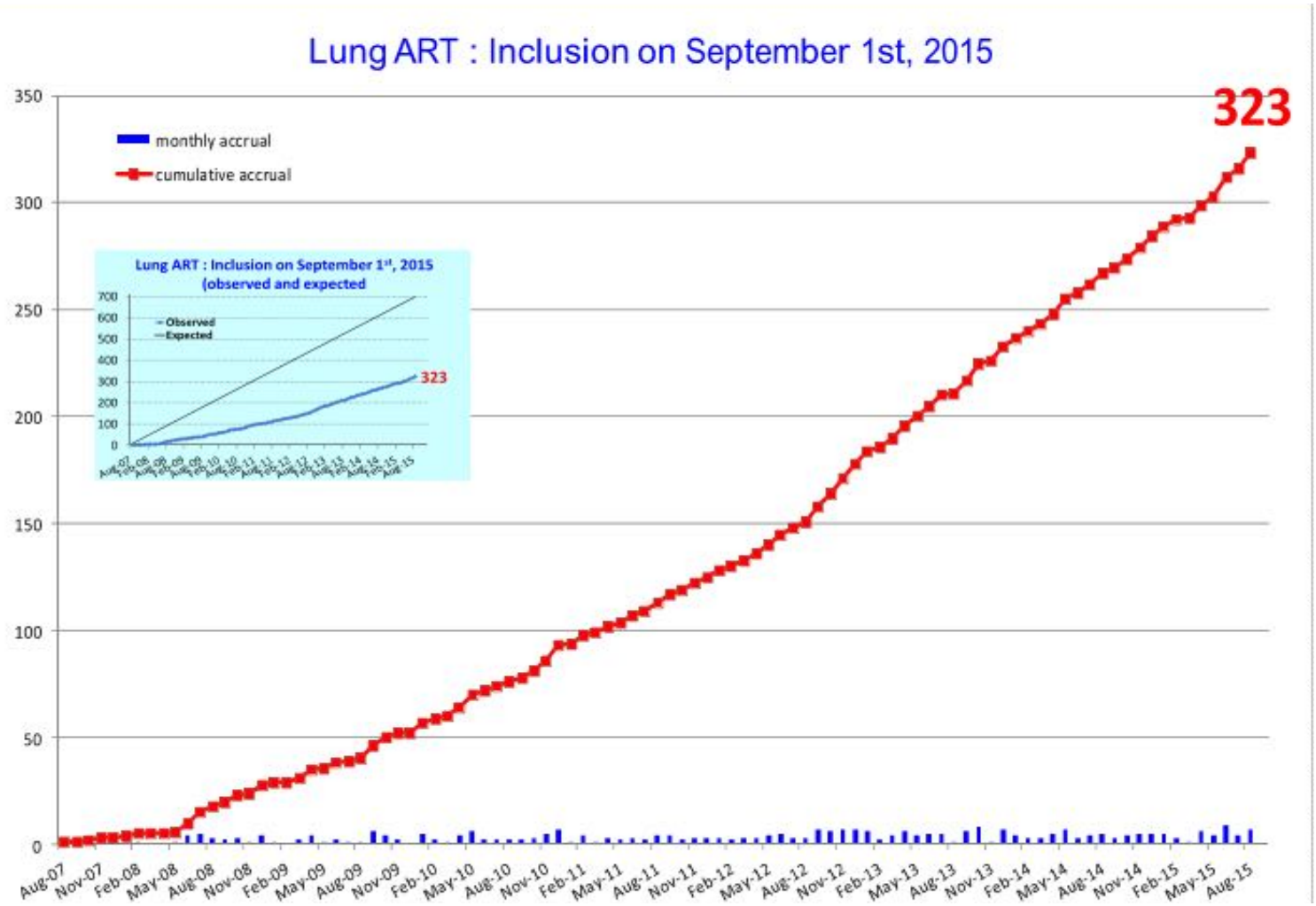
R

Pre-op and/or Post-op CT

Control

Conformal PORT (54 Gy)

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


Lung ART : Inclusion on September 1st, 2015
323
monthly accrual
cumulative accrual
350
300
250
200
150
100
50
0
Aug-07
Nov-07
Feb-08
May-08
Aug-08
Nov-08
Feb-09
May-09
Aug-09
Nov-09
Feb-10
May-10
Aug-10
Nov-10
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May-13
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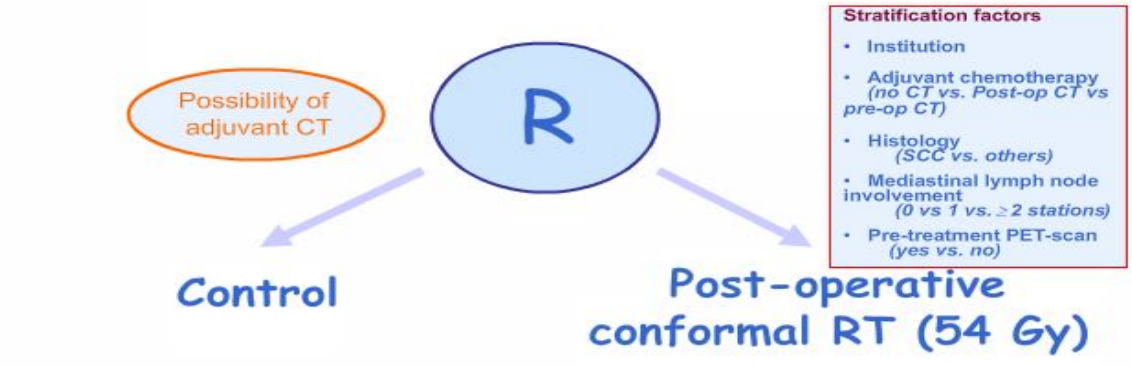
Feb-14
May-14
Aug-14
Nov-14
Feb-15
May-15
Aug-15
Lung ART : Inclusion on September 1st, 2015
(observed and expected
Observed
Expected
323

Slow Accrual

- Different pattern of care in stage III in last 10 years
- Staging
- Better Radiotherapy Techniques
- Different chemotherapy schedules

… Updates from Denver 2015



"Quality of resection in pathological N2 NSCLC in the Phase III Lung ART trial"

Emphatized the importance of an external committee to evaluate the SURGEON…
but not shown any outcome data
……slow accrual

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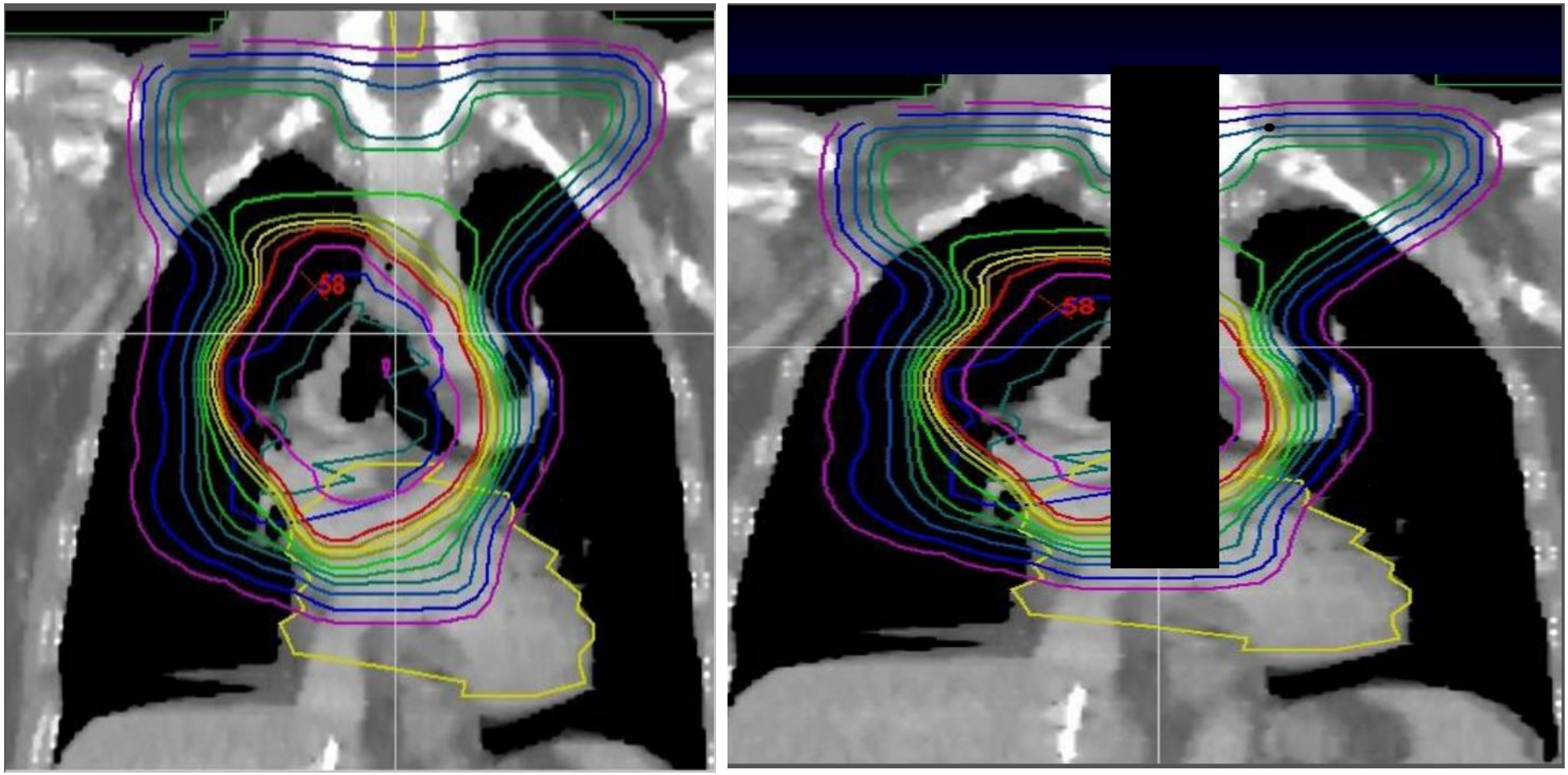
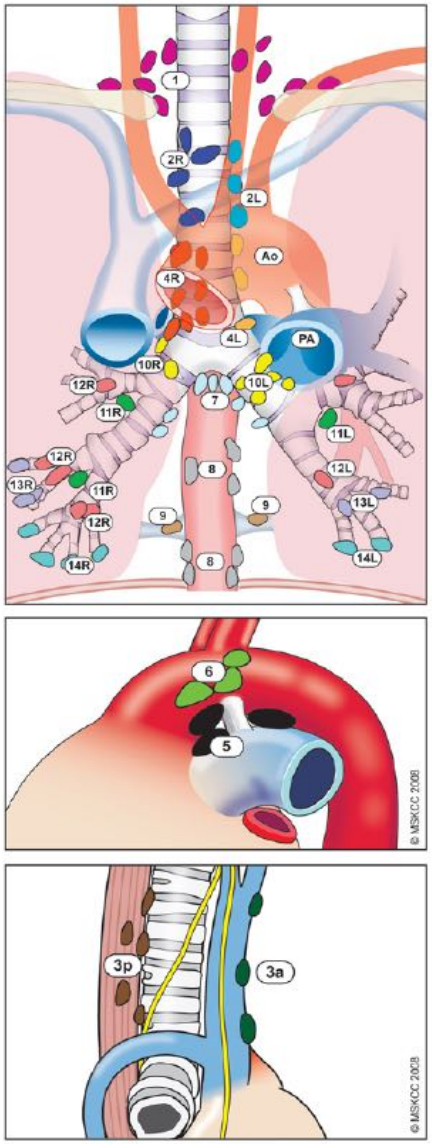


Recostructed volume of the era of «the» metanalysis



Supraclavicular zone

- **1** Low cervical, supraclavicular, and sternal notch nodes

Superior Mediastinal Nodes

Upper zone

- **2R** Upper Paratracheal (right)
- **2L** Upper Paratracheal (left)
- **3a** Pre-vascular
- **3p** Retrotracheal
- **4R** Lower Paratracheal (right)
- **4L** Lower Paratracheal (left)

Aortic Nodes

AP zone

- **5** Subaortic
- **6** Para-aortic (ascending aorta or phrenic)

Inferior Mediastinal Nodes

Subcarinal zone

- **7** Subcarinal

Lower zone

- **8** Paraesophageal (below carina)
- **9** Pulmonary ligament

N_1 Nodes

Hilar/Interlobar zone

- **10** Hilar
- **11** Interlobar

Peripheral zone

- **12** Lobar
- **13** Segmental
- **14** Subsegmental

IASLC Map (Rusch et al. JTO 2009 TNM 7)

Several **CT based atlases** of mediastinal lymph nodes have been published, an excellent examples of which was published at the University of Michigan and delineates lymph **nodes level 1-11**

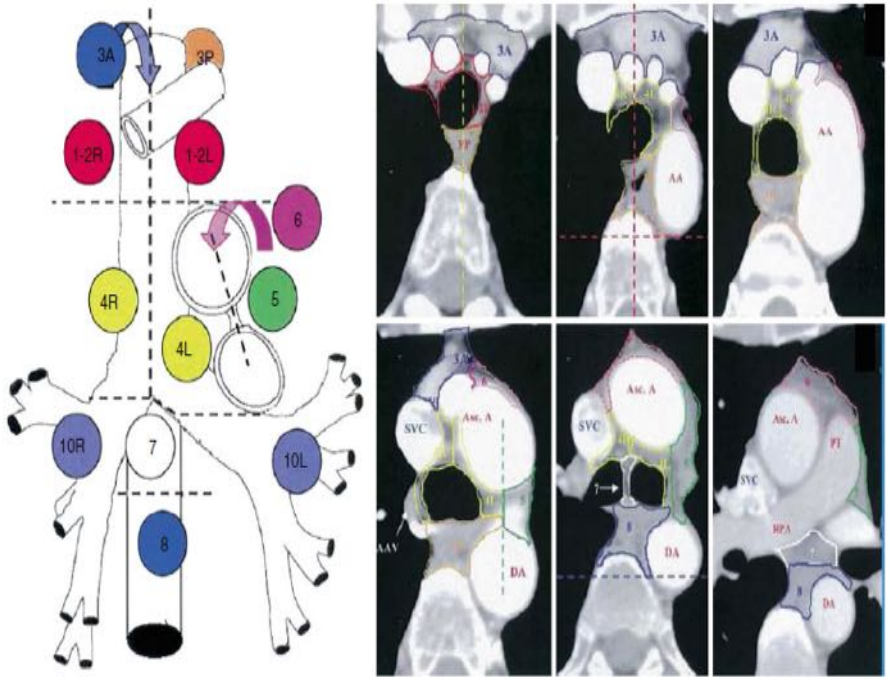


Fig. 1 Mediastinal lymph node station atlas (taken from Chapet et al., 2005)

Surgically involved mediastinal nodes	LN stations to be included in the CTV
1-2R	1-2R, 4R, 7, 10R Maximal upper limit: 1 cm above sternal notch but homolateral subclavicular node station may be treated if needed Maximal lower limit: 4 cm below the carina* (unless other nodes are involved)
1-2L	1-2L, 4L, 7, 10L Maximal upper limit: 1 cm above the sternal notch but homolateral subclavicular node station may be treated if needed Maximal lower limit: 4 cm below the carina*
3 (Right sided Tumour)	3, 4R, 7, 10R Maximal upper limit: 1 cm above the sternal notch Maximal lower limit: 4 cm below the carina*
3 (Left sided Tumour)	3, 4L, 7, 10L Maximal upper limit: 1 cm above the sternal notch Maximal lower limit: 4 cm below the carina*
4R	**4R**, 7, 10R Maximal upper limit: sternal notch Maximal lower limit: 4 cm below the carina*
4L	**4L**, 7, 10L Maximal upper limit: sternal notch Maximal lower limit: 4 cm below the carina*
5	4L, 5, 7, 10L Maximal upper limit: Top of aortic arch Maximal lower limit: 4 cm below the carina*
6	4L, 6, 7, 10L Maximal upper limit: sternal notch Maximal lower limit: 4 cm below the carina*
7 (Right sided Tumour)	4R, 7, 10R. Maximal upper limit: Top of aortic arch Maximal lower limit: 5 cm below the carina*
7(Left sided Tumour)	4L, 7, 10L Maximal upper limit: Top of aortic arch Maximal lower limit: 5 cm below the carina*
8 (Right Tumour)	4R, 7, 8, 10R. Maximal upper limit: Top of aortic arch The maximal lower limit should be the gastro-oesophageal junction

Lung ART-IGR 2006/1202

8 (Left sided Tumour)	4L, 7, 8, 10L. Maximal upper limit: Top of aortic arch The maximal lower limit should be the gastro-oesophageal junction

* (unless other nodes are involved)

Definition and **limits of nodal Areas** according to LUNG-ART protocol

Definition **of rCTV-CTV-PTV** according to LUNG-ART protocol

rCTV (**resected Clinical Tumor Volume**): lymph nodes involved according to pathological report. Bronchial stump, homolateral hilar node region and eventual extension to mediastinal pleura

CTV (**Clinical Target Volume**): rCTV+1 cm.
CTV should not exceed maximal upper and lower limit (see tables). All nodes not included in non contigous node station should be included in CTV.

PTV (**Planning TargetVolume**): CTV+ 5 mm lateral, anterior and posterior. CTV + 10 mm superior and inferior

Definition of OAR costraints according to LUNG-ART protocol

Spinal Cord: maximal dose 45 Gy

Lungs: each lung should be contured separately. V20 should be calculated as both lungs volumes minus PTV and should not exceed 31% after lobectomy and 22% after pneumonectomy

Oesophagus: should be contured (outer muscular conour) from lower limit of larynx to gastro-oesophageal junction.
Mean and maximum oesophageal dose should be recorded.

Heart: dose to 30% of cardiac volume < 35 Gy

Target Volumes

- **Positive Margins or gross disease (R1 and R2 resections)**

  The region of positive margins or gross disease. Clips may also be placed in the appropriate region. In the case of gpotential gross disease, postoperative imaging can assist in elucidating this region

D. Gomez et al 2005

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Controversial statements

No specific trial on PORT after neo adjuvant treatment in Literature…
….still waiting for LUNG ART results

Impact of Adjuvant Treatment for Microscopic Residual Disease After Non-Small Cell Lung Cancer Surgery

Jacquelyn G. Hancock, BS, Joshua E. Rosen, BAS, Alberto Antonicelli, MD, Amy Moreno, MD, Anthony W. Kim, MD, Frank C. Detterbeck, MD, and Daniel J. Boffa, MD

Section of Thoracic Surgery, Yale University School of Medicine, New Haven, Connecticut

The National Cancer Data Base was queried for surgically pathological stage I-III NSCLC from 2003 to 2006
A positive surgical margin was identified in 3102 NSCLC including microscopically positive R1 margins in 1688 patients
and PORT decreas LR

(Ann Thorac Surg 2015;99:406–13)

Take Home Messages

- Negative Meta-analysis , …but obsolete
- Changing pattern of staging and pattern of care in N2 disease
- Prognostic role of number of N2 to select pts for PORT
- PORT need in R+ pts

WAITING FOR MODERN FASHION
STAGE III STUDY

N2 disease: A symbolic paradigm of progress

N2 and PORT:

A long, complex and demanding story
Difficult to summarize but so interesting...


THANK YOU