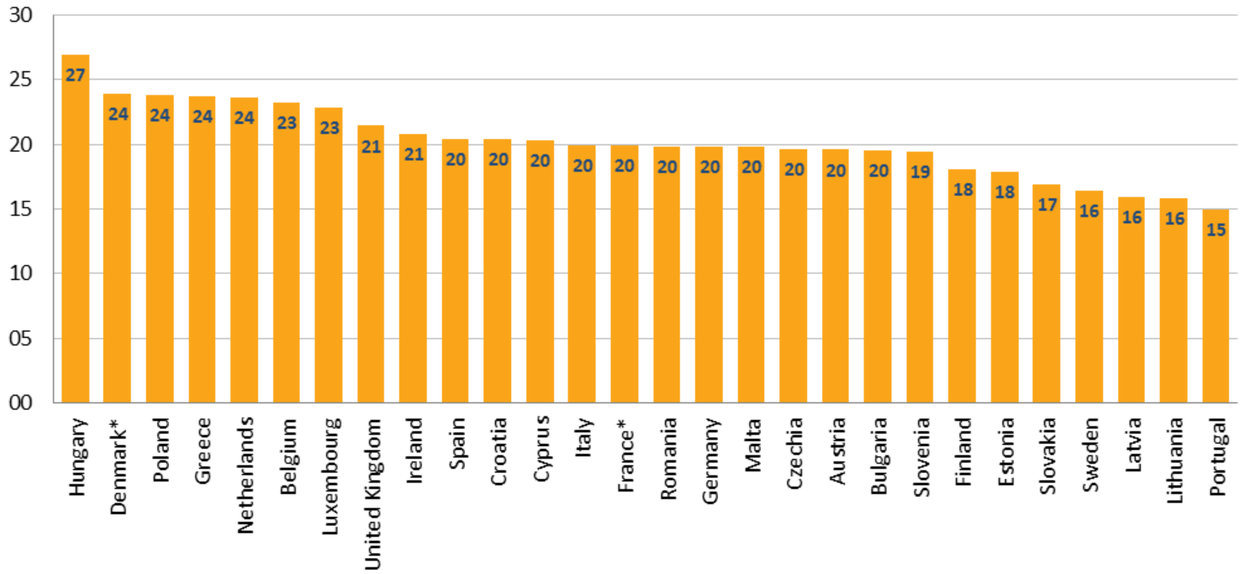
Innovation, effectiveness and compliance in lung cancers

Cecile Le Pechoux, Angela Botticella
Antonin Levy (Thoracic RadOnc Team)
Physics Team: A Traoré-Diallo, G Auzac, C Berthold, I Chabert, A Gasnier, A Beaudré

Radiation Oncology Department

- Leading cause of cancer death worldwide.
- Most patients have metastatic disease at diagnosis
- Until 15 yrs ago, considerable pessimism and guilt among patients (current or former smokers)
- but also pessimism among physicians ...

Lung cancer :21% of all cancer-related deaths.



*2015 data

- video-assisted thoracoscopic surgery (VATS, RATS..)
- Emphasis on quality of resection

- Better combined modality treatments: CTRT, CTRT+consolidation IO
- Adjuvant or neo adju
  st II,III NSCLC

2020 Innovation-Based Optimism for Lung Cancer Outcomes

**RT which wa
tre
come
ign tech » and
an important component
in the management of
lung cancer at all stages**

- otherapy (Check Point Inhibitors)
- Combined CT-IO
- Targeted agents TKIs

Schenk Oncologist 2021, Rami-Porta 2020

Stage I NSCLC: Innovative treatment vs « Gold Standard »

	SABR	Surg	p
N pts	31	27	
Est 3yr OS	95%	79%	0,037
Est 3yr RFS	86%	80%	0,54
Recurrence	1 Local R 4 Nodal R 1 DM	1 Nodal R 2 DM	
Grade 3/4 AE	3 gr **Rib fracture**	**infections**	
Gr 5 AE	0	1 death **Surg cpl**	

Poor compliance : on the side of investigators, patients

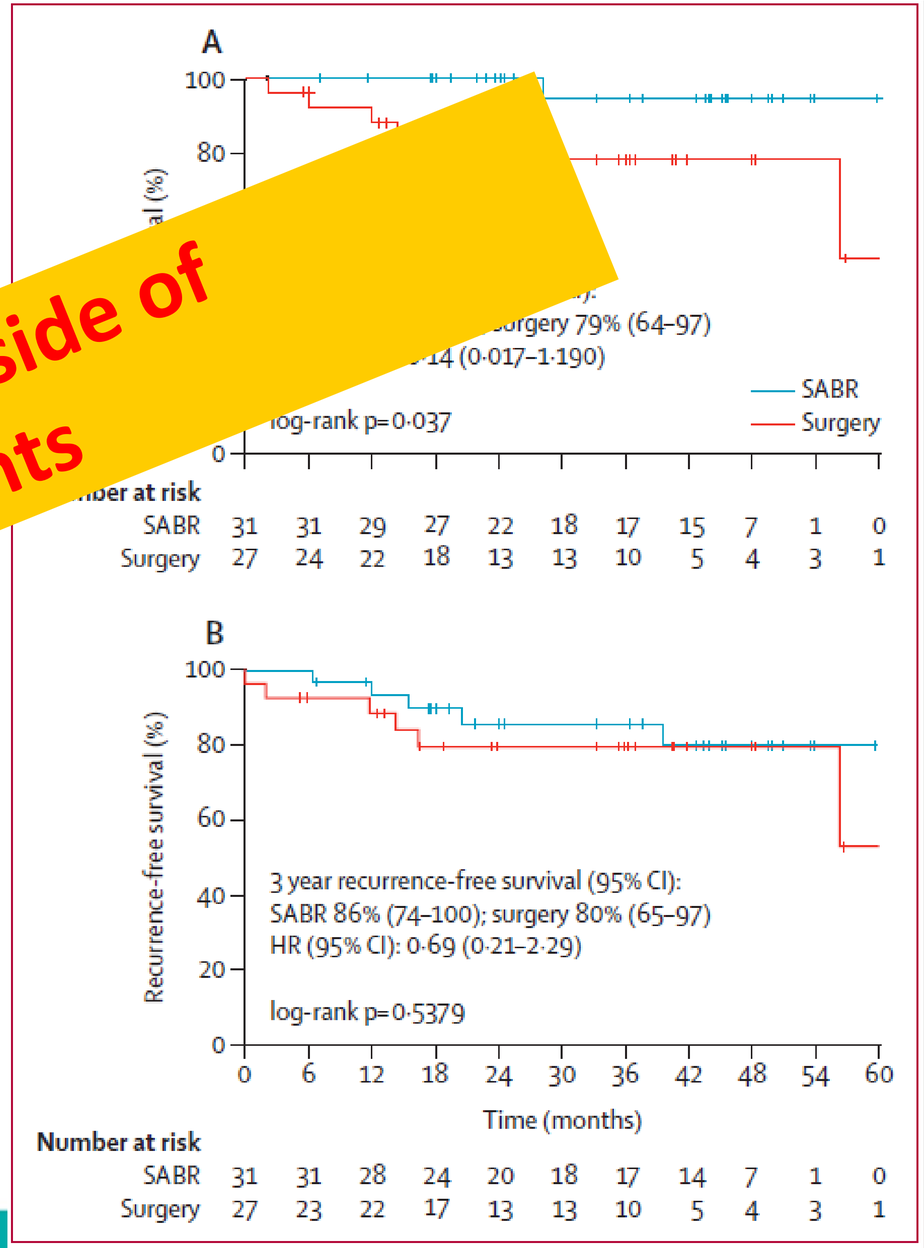
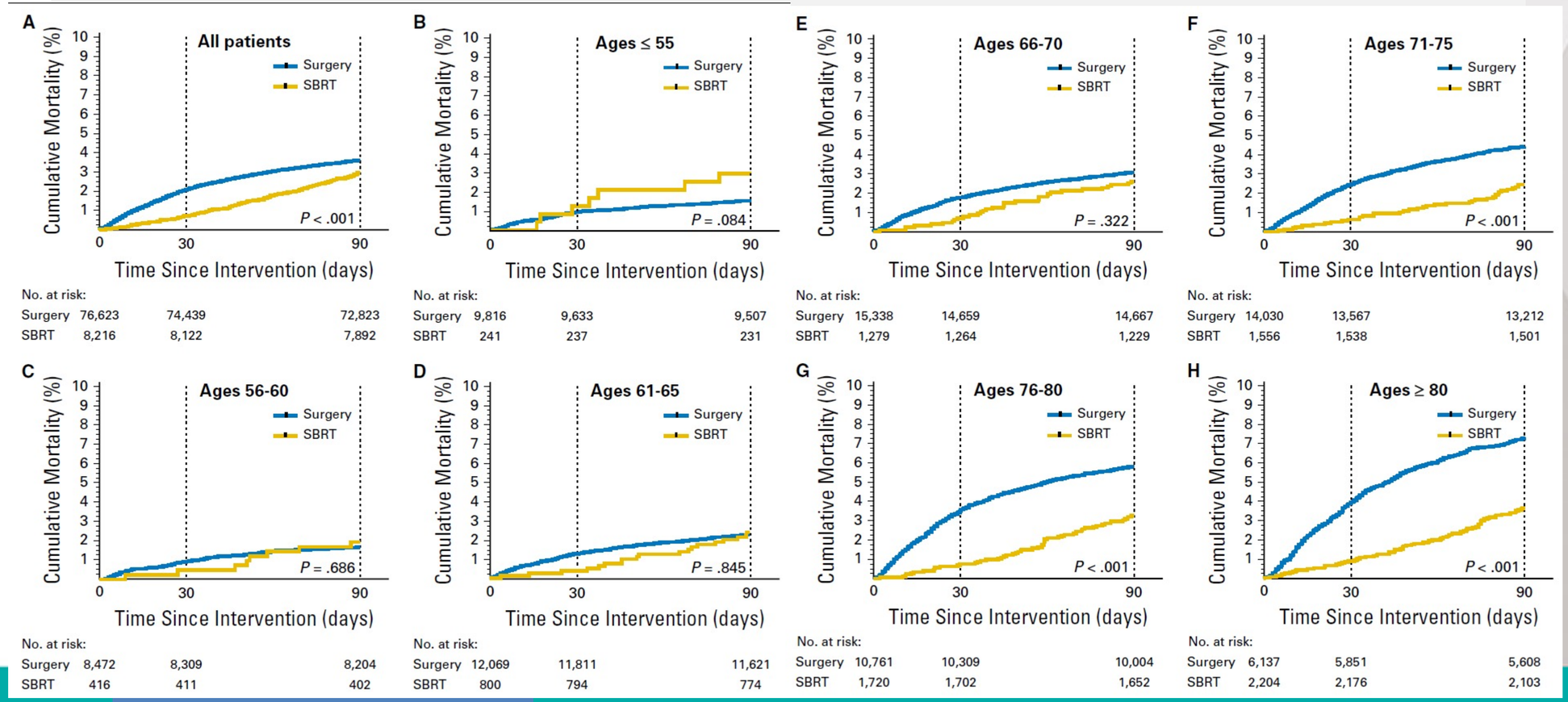


Figure 2: Overall survival (A) and recurrence-free survival (B)

Chang et al, Lancet Oncol 2015

Post-Treatment Mortality After Surgery and Stereotactic Body Radiotherapy for Early-Stage Non–Small-Cell Lung Cancer

- NCI Data base, cT1-T2a, N0,M0; 2004 and 2013; 30 and 90-day post-ttt mortality %
- 76,623 pts: surgery (78% lobectomy, 20% sublobar resection, 2% pneumonectomy)
- 8,216 pts: SBRT
- Differences in mortality ↑ with age, P<0.001 at 30 and 90 days
- Surgical mortality rates higher with increased extent of resection



Stokes et al, JCO 2018

Importance of Individual Patients Data (IPD) Meta analyses / SOC for management lung cancer and best way to combine treatments

original article

Annals of Oncology 17: 473–483, 200
doi:10.1093/annonc/mdj117

Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): A meta-analysis of individual data from 1764 patients

A. Aupérin[1]*, C. Le Péchoux[2], J. P. Pignon[1], C. Koning[4], B. Jeremic[5], G. Clamon[6], L. Einhorn[7], D. Ball[8], M. G. Trovo[9], H. J. M. Groen[10], J. A. Bonner[11], T. Le Chevalier[3] & R. Arriagada[2,12]
On behalf of the Meta-Analysis of Cisplatin/carboplatin based Concomitant Chemotherapy in non-small cell Lung Cancer (MAC3-LC) Group

VOLUME 28 · NUMBER 13 · MAY 1 2010
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data

NSCLC Meta-analyses Collaborative Group*

Lancet 2010

Preoperative chemotherapy for non-small cell lung cancer: a systematic review and meta-analysis of individual participant data

NSCLC Meta-analysis Collaborative Group*

Lancet 2014

The New England Journal of Medicine

PROPHYLACTIC CRANIAL IRRADIATION FOR PATIENTS WITH SMALL-CELL LUNG CANCER IN COMPLETE REMISSION

ANNE AUPÉRIN, M.D., RODRIGO ARRIAGADA, M.D., JEAN-PIERRE PIGNON, M.D., PH.D., CÉCILE LE PÉCHOUX, M.D., ANNA GREGOR, M.D., RICHARD J. STEPHENS, PAUL E.G. KRISTJANSEN, M.D., PH.D., BRUCE E. JOHNSON, M.D., HIROSHI UEOKA, M.D., HENRY WAGNER, M.D., AND JOSEPH AISNER, M.D.,
FOR THE PROPHYLACTIC CRANIAL IRRADIATION OVERVIEW COLLABORATIVE GROUP*

From the Unit of Biostatistics and Epidemiology and Radiation Oncology, Institut Gustave-Roussy, Villejuif; Institut de Cancérologie de la Loire, Department of Medical Oncology, Saint Etienne; Institut Universitaire de Recherche Clinique, Université Montpellier I – Statistical Unit, Montpellier; University of Paris-South, Paris, France; Bodine Center, Department of Radiation Oncology; Department of Radiation Therapy Oncology Group Statistics, American College of Radiology, Philadel-

Meta-Analysis of Concomitant Versus Sequential Radiochemotherapy in Locally Advanced Non–Small-Cell Lung Cancer

Anne Aupérin, Cecile Le Péchoux, Estelle Rolland, Walter J. Curran, Kiyoyuki Furuse, Pierre Fournel, Jose Belderbos, Gerald Clamon, Hakki Cuneyt Uludin, Rebecca Paulus, Takeharu Yamanaka, Marie-Cecile Bozonnat, Apollonia Uitterhoeve, Xiaofei Wang, Lesley Stewart, Rodrigo Arriagada, Sarah Burdett, and Jean-Pierre Pignon

VOLUME 30 · NUMBER 22 · AUGUST 1 2012
JOURNAL OF CLINICAL ONCOLOGY REVIEW ARTICLE

review

Annals of Oncology 00: 1–11, 2016
doi:10.1093/annonc/mdw263

Impact of thoracic radiotherapy timing in limited-stage small-cell lung cancer: usefulness of the individual patient data meta-analysis†

D. De Ruysscher[1,2,‡], B. Lueza[3,4,‡], C. Le Péchoux[5,6], D. H. Johnson[7], M. O'Brien[8], N. Murray[9], …g[11], M. Takada[12], B. Lebeau[13], W. Blackstock[14], D. Skarlos[15], P. Baas[16], …e[18], L. Seymour[19], R. Arriagada[20,21] & J.-P. Pignon[3,4*] on behalf of the RTT-SCLC …up[§]

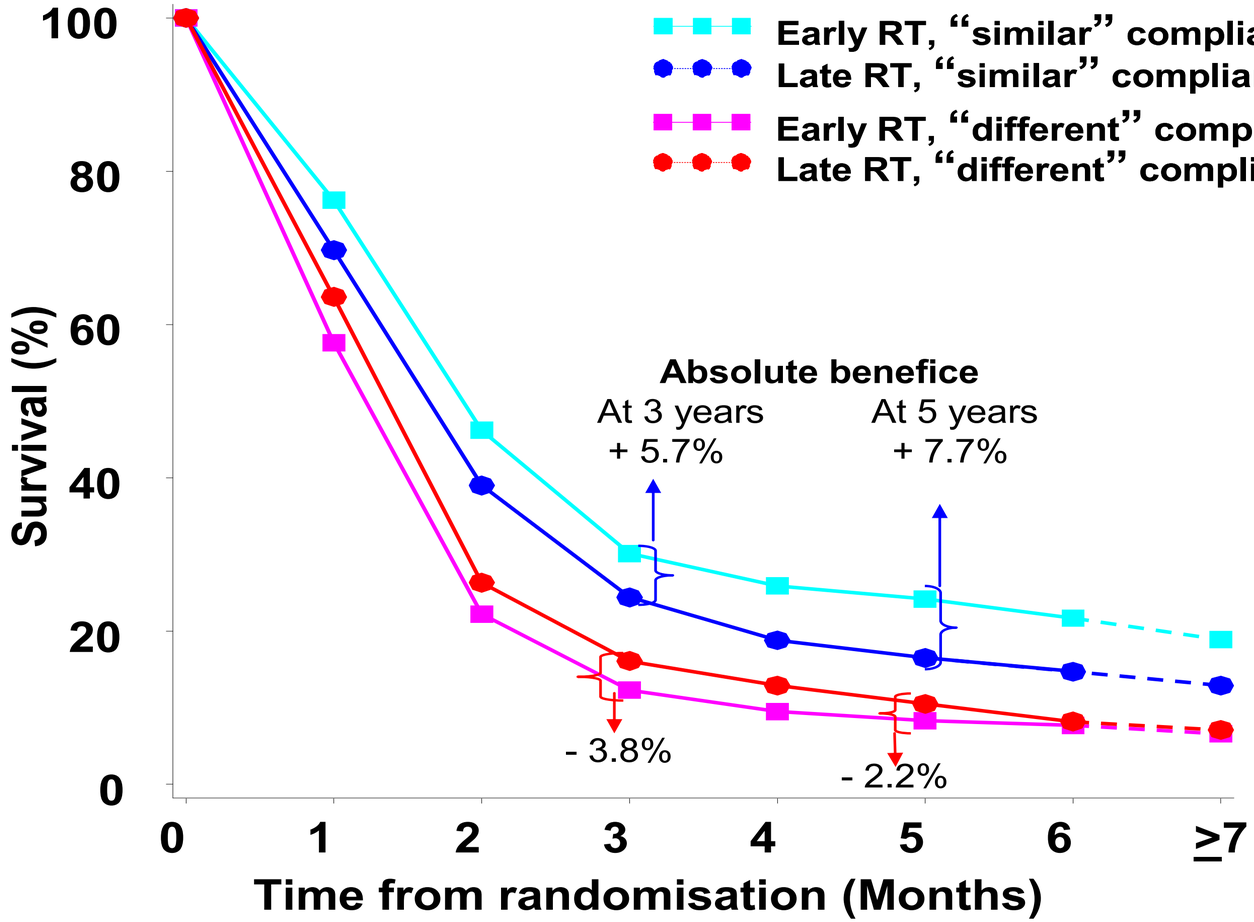
Similar advantage in terms of outcome (+5%)

Compliance to neo-adjuvant CT (Around 90%) better than adjuvant CT (60%)

Hyperfractionated or Accelerated Radiotherapy in Lung Cancer: An Individual Patient Data Meta-Analysis

Audrey Mauguen, Cécile Le Péchoux, Michele I. Saunders, Steven E. Schild, Andrew T. Turrisi, Michael Baumann, William T. Sause, David Ball, Chandra P. Belani, James A. Bonner, Aleksander Zajusz, Suzanne E. Dahlberg, Matthew Nankivell, Sumithra J. Mandrekar, Rebecca Paulus, Katarzyna Behrendt, Rainer Koch, James F. Bishop, Stanley Dische, Rodrigo Arriagada, Dirk De Ruysscher, and Jean-Pierre Pignon

SCLC: Difficulty to evaluate combined modality strategies
RT very interdependant of CT but also patient compliance++

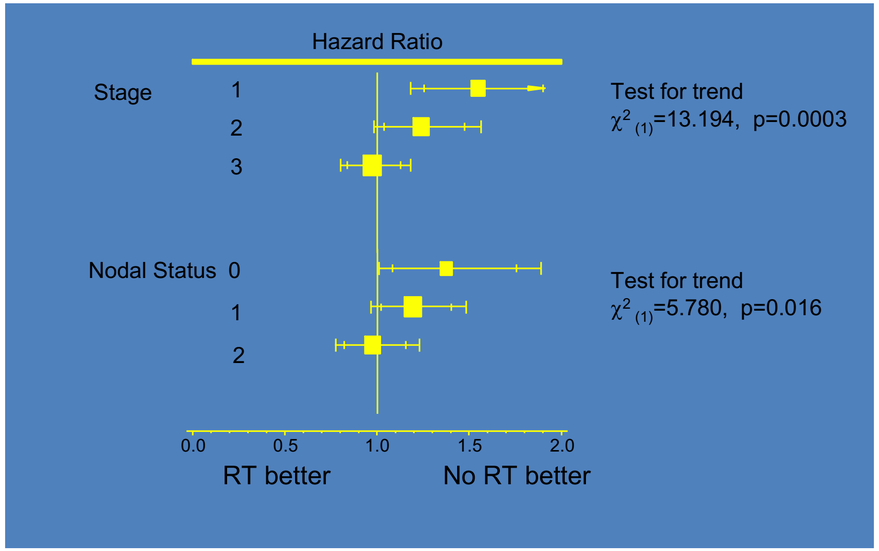


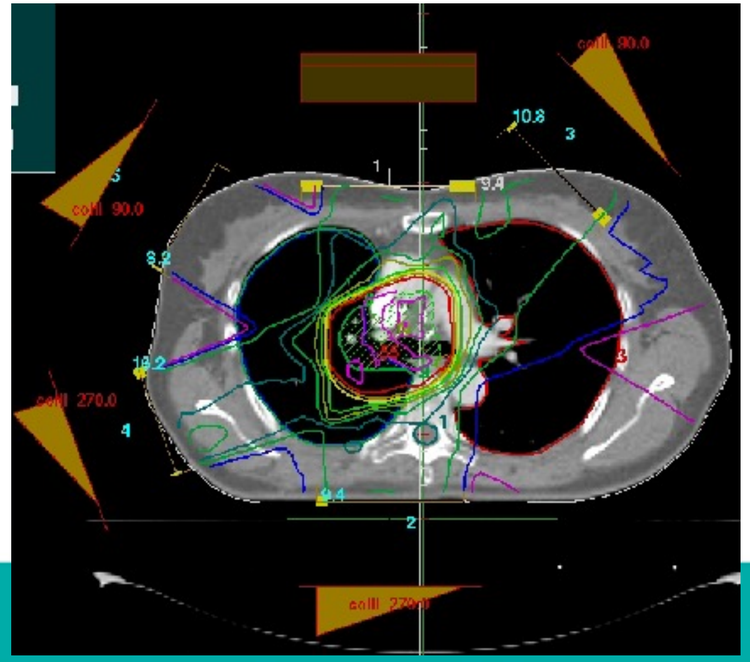
Differences in CT compliance between arms within trials mostly explains the heterogeneity of the effect of early RT on OS

Benefit of early RT in terms of 5-yr survival only in trials where CT compliance is « similar » in both arms

De Ruysscher et al, IASLC 2011, Ann Oncol 2016

Lessons learned from PORT Meta-analysis which evaluated 2DRT in NSCLC



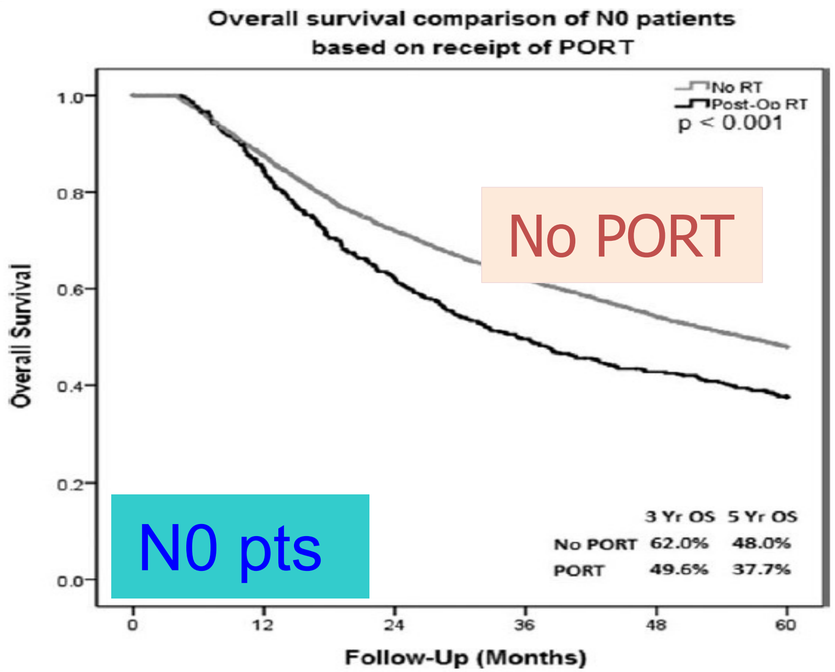


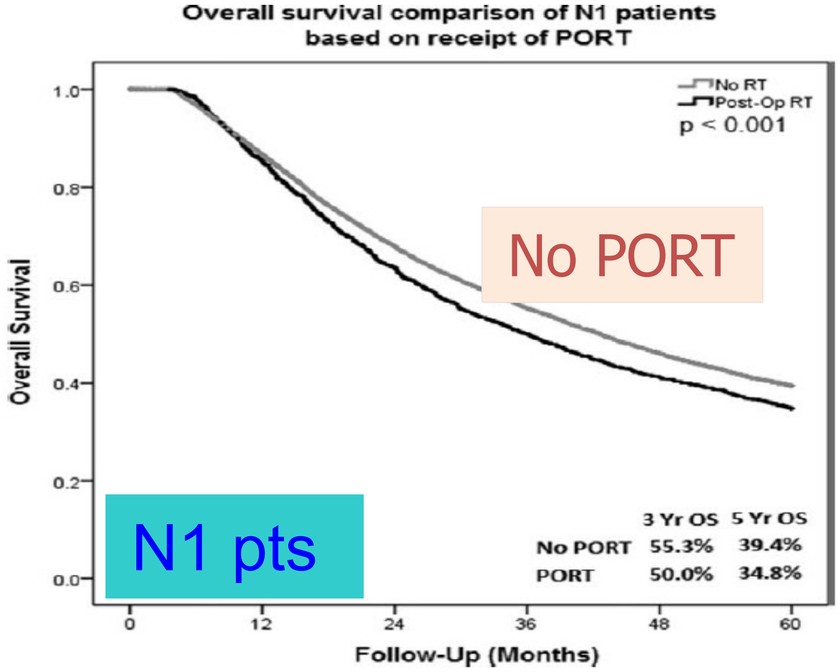
- **PORT should be reevaluated in high risk patients : N2**

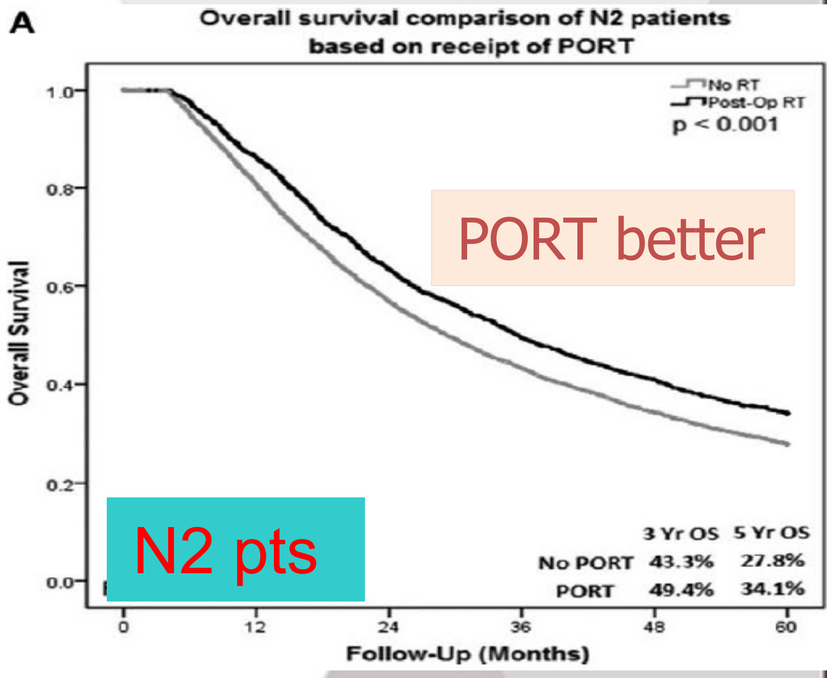
- **More conformal RT Radiotherapy volume customized according to results of nodal exploration…**
- **Less toxicity……**

Re evaluation of the role of PORT

National Cancer Data base Corso and al, JTO 2015







30,552 Pts st II-III treated 1998-2006		No PORT	PORT	p
N0 pts 5-yr Survival	N=5836 (19,1%)	5387 (20%) 48%	449 (13,1%) 37,7%	0,009
N1 pts 5-yr Survival	N=17,737 (58,1%)	16,416 (60,5%) 39,4%	1321 (38,5%) 34,8%	<0,001
N2 pts 5-yr Survival	N=6979 (22,8%)	5319 (19,6%) 27,8%	1660 (48,4%) 34,1%	<0,001

LUNG ART phase III Trial

(IFCT-0503, UK NCRI, SAKK)

Trial registry: NCT00410683

Study design

Completely resected NSCLC with N2 histo/ cytologically proven nodal involvement

PS 0-2

Stratification factors : by Center,
Administration of Chemotherapy
Histology,
Extent of mediastinal lymph node involvement,
use of pre-treatment PET-scan

R

Pre-op and/or Post-op CT

1:1 randomization

Control

Conformal PORT (54 Gy/5,5 wks)

Primary end-point: Disease-free survival

Secondary end-points: Overall survival, patterns of relapse, local failure, second cancers, and treatment-related toxicity

Statistical Hypothesis: 500 patients to show a 12% improvement of 3-yr DFS (30% in control arm vs 42% in PORT arm (HR = 0.72).

Treatment characteristics Lung ART (Sept 2007 to July 2018..)

	Control arm (n = 249)	PORT arm (n = 252)
Age (median [min;max])	61 [38;85]	61 [36;79]
Pre-treatment PET scan	90%	92%
pTNM or ypTNM Number of N2 stations involved: 0/1/ ≥ 2	2% / 45% / 52%	4% / 45% / 52%
Type of surgery (n(%)) - Lobectomy// Bilobectomy - Pneumonectomy	81%// 7% 10%	78%//8% 12%
pTNM pN0/pN1 (down staging after preop CT) pN2	pN0: 1% pN1: 2% pN2: 98%	pN0: 2% pN1: 1% pN2: 96%
Total dose (in Gy) (median (min;max)) received PORT technique and dose constraints		54 Gy (21;70) in 241 pts (96%) 3DRT : 201 (89%)// IMRT: 25 (11%)

Dosimetric parameters	Median (min - max)
Lungs V20	23% (3 – 36)
MLD	12.7 Gy (2.5 – 22)
Mean heart dose	13.4Gy (0.7 – 36,2)
Heart V35	15% (0 – 50)

Stratification factors

Percents calculated on non missing data,
Primary database lock (June 2020)

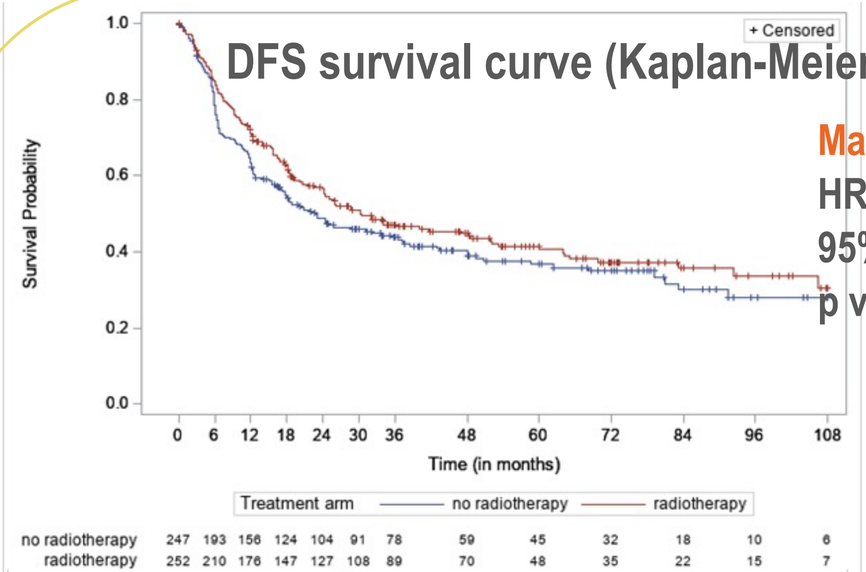
Disease-Free Survival 1/3 (Primary Endpoint; ITT)

	Control	PORT
Median DFS	**22.8 mo** (95% CI = [17;37])	**30.5 mo** (95% CI = [24;49])
3-yr DFS	**43.8%** (95% CI = [37;51])	**47.1 %** (95% CI = [40;54])

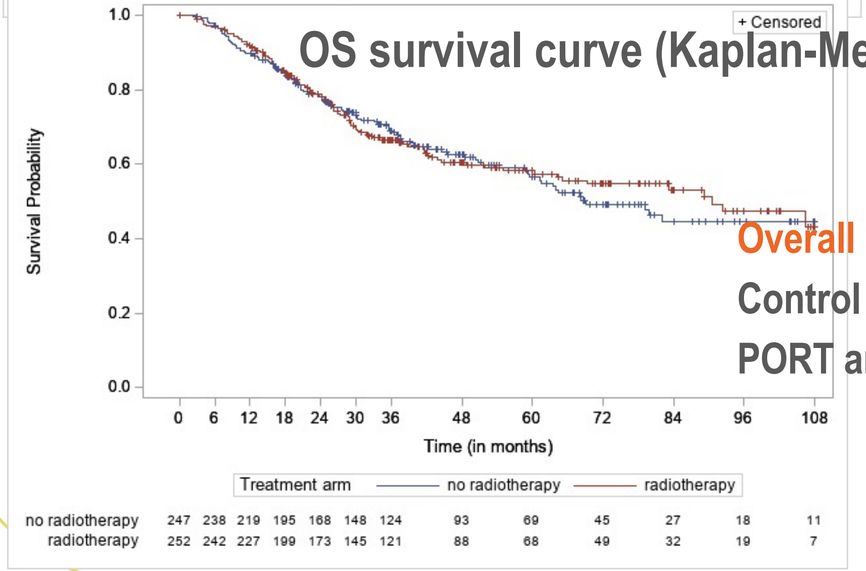
95%CI = 95% bilateral Confidence Interval

DFS components (First Event)

	Control	PORT
All DFS events*	152	144
Mediastinal relapse	70 (46.1 %)	36 (25.0%)
Brain metastasis	27 (17.8%)	34 (23.6%)
Other metastasis	71 (46.7%)	71 (49.3%)
Death	8 (5.3%)	21 (14.6%)

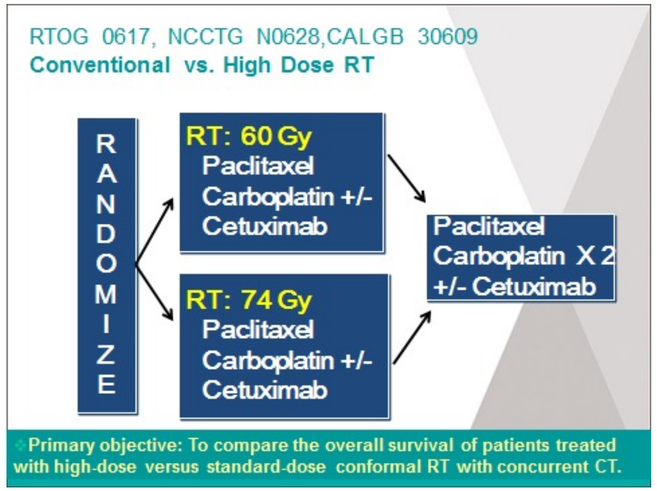


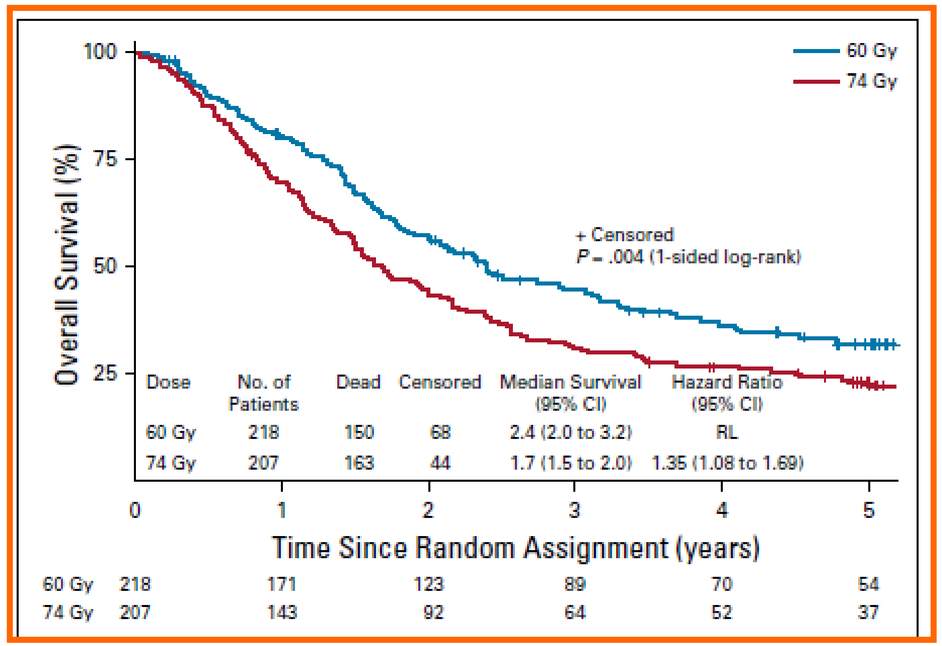
Main analysis (Adj Cox Model)
HR = 0.85
95% CI = [0.67;1.07]
p value = 0.16



Overall Survival rates at 3 years
Control arm: 68.5% (95% CI = [61;75])
PORT arm: 66.5% (95% CI = [59;73])

RTOG 0617: Long-Term Results Standard (60 Gy)- Vs High-Dose (74 Gy)
Chemoradiotherapy With or Without Cetuximab for Unresectable Stage III NSCLC





At 5 Yrs
32,1%
23%

MST: 28,7 months 60 Gy
MST: 20,3 months 74 Gy

Cetuximab:
no effect on OS

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

Bradley, ASCO 2013, Lancet Oncol 2015, JCO 2020

Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non–Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial

- **Technique of RT: 3D or IMRT stratification factor**

	RTOG 0617 74 Gy	RTOG 0617 60 Gy	p
Median OS	20,3 mo	28,7 mo	0,04
2-yr Survival	44,6%	57%	
Median PFS	9,8 mo	11,8 mo	0,12
2-yr LF Rate	38,6%	30,7%	0,13
Pneumonitis	12%	10%	NS
Esophagitis>	21%	7%	<0,0001

RTOG 0617 IMRT		RTOG 0617 3DRT		p
53,2%		49,4%		0,597
30,8%		37,1%		0,498
>gr3	3,5%	>gr3	7,9%	0,039
13,2%		15,4%		0,534

IMRT associated with lower rates of severe pneumonitis and lower cardiac doses

Bradley et al RTOG 0617, Lancet Oncology 2015; Chun et al JCO 2017; Bradley et al, JCO 2020

Non compliance in RTOG 0617: a main issue

- **Cc CT more difficult to complete in the HD group**
- **Rates of protocol non-compliance > HD arm, 26% vs. 17% (P=0.02)**
  - > Longer treatment delays.
  - > Radiation therapy planning more likely to be non-compliant in the HD group
  - > Planning target volume coverage by the 95% isodose line poorer in HD group.
- **Concerns that non-compliance in the HD groups produced these results led to analysis of OS only in patients with radiation plans compliant with the protocol**
- **OS was still better in the StD groups than in the HD groups.**

Imaging-based target volume reduction in chemoradiotherapy for locally advanced non-small-cell lung cancer (PET-Plan): a multicentre, open-label, randomised, controlled trial

Nestle Lancet Oncol 2020

- Primary endpoint : time to locoregional progression from randomisation with the objective to test non-inferiority of ^{18}F-FDG PET-based planning with a prespecified hazard ratio (HR) margin of 1·25
- **Cumulative incidence for locoregional progression**

23% (12–32) at 3 years (^{18}F-FDG-based target group)

vs 42% (30–53) at 3 years in the conventional target group

- **no increased toxicity**
- **Ccl Could be SOC**
- **Strong QA component**

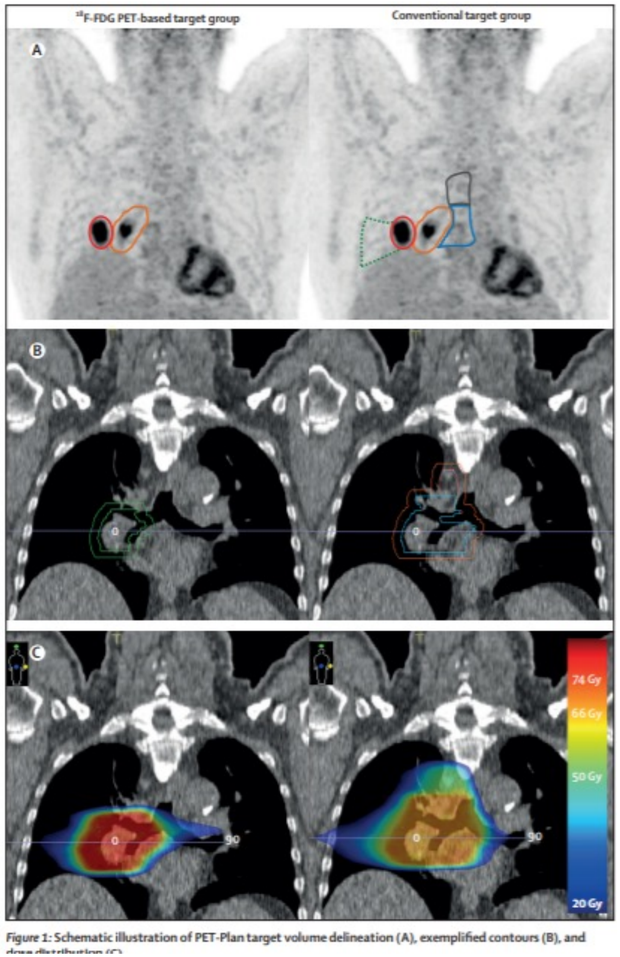
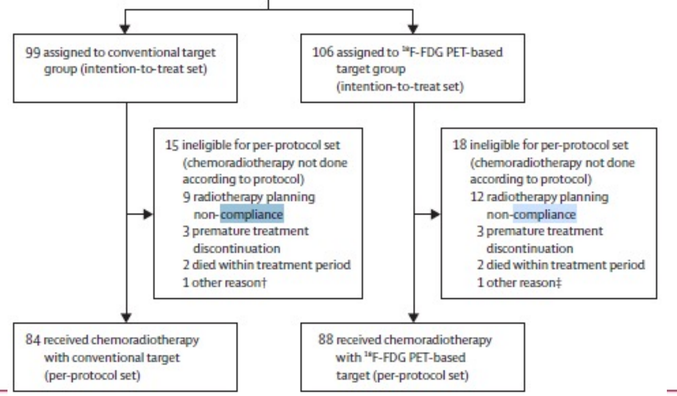
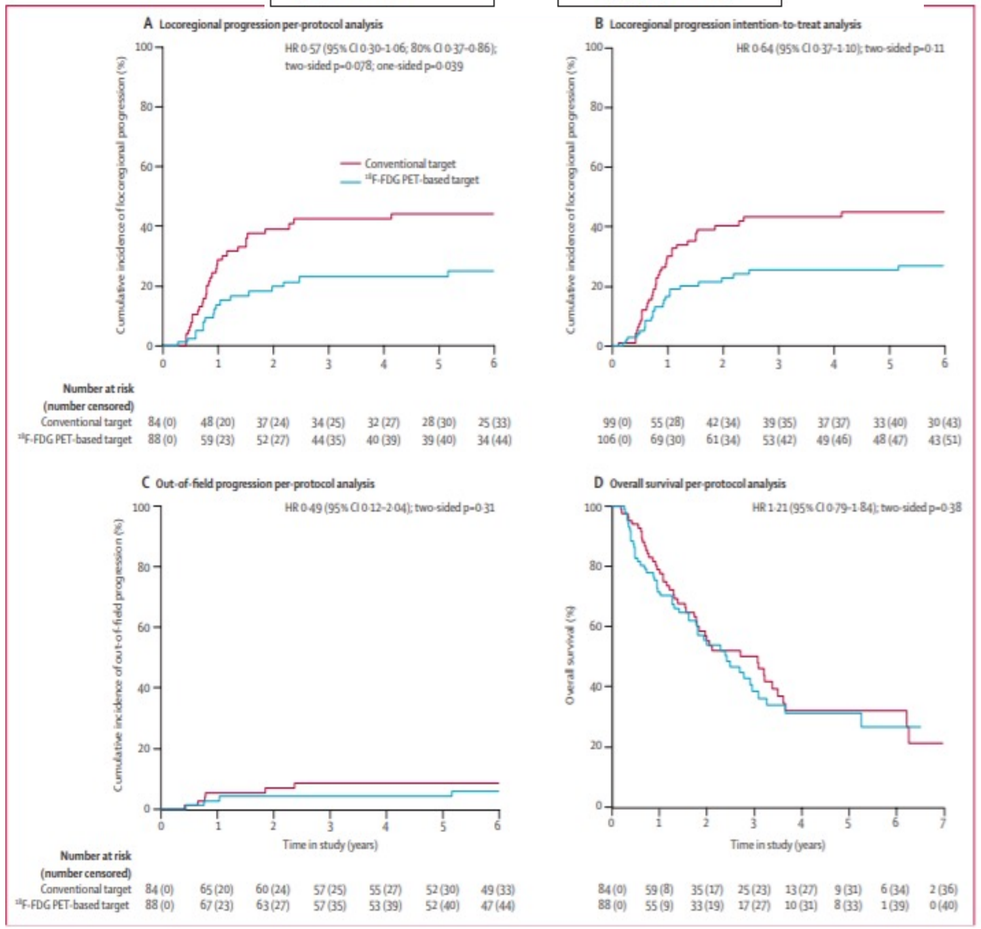


Figure 1: Schematic illustration of PET-Plan target volume delineation (A), exemplified contours (B), and



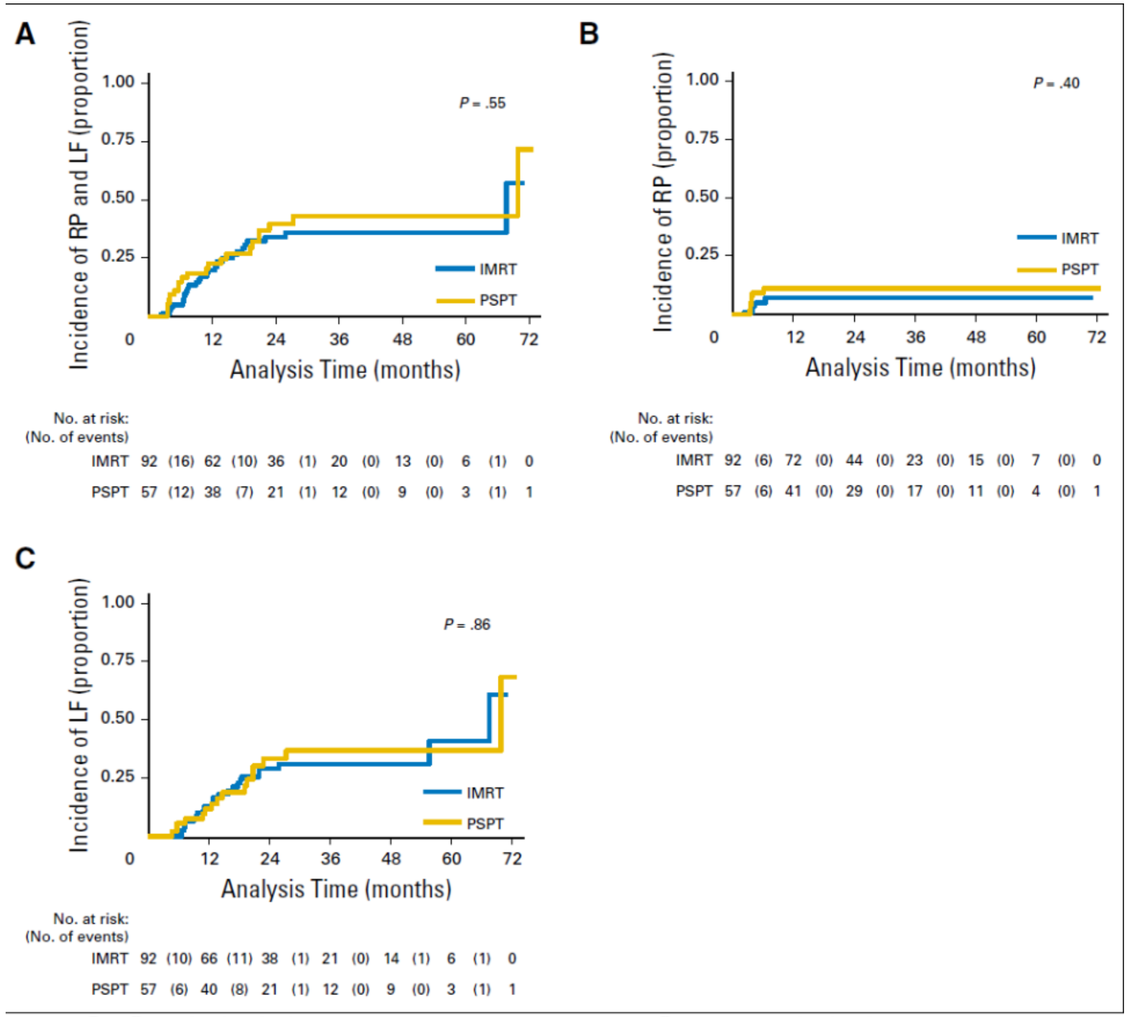


From May 13, 2009, to Dec 5, 2016, 205 of 311 recruited patients were randomized

Bayesian Adaptive Randomization Trial of Passive Scattering Proton Therapy and Intensity-Modulated Photon Radiotherapy for Locally Advanced Non–Small-Cell Lung Cancer

JCO 2018

Zhongxing Liao, J. Jack Lee, Ritsuko Komaki, Daniel R. Gomez, Michael S. O'Reilly, Frank V. Fossella,



- PSPT did not improve dose-volume indices for lung but did for heart.
- No benefit was noted in RP or LF after PSPT.
- Improvements in both end points were observed over the course of the trial

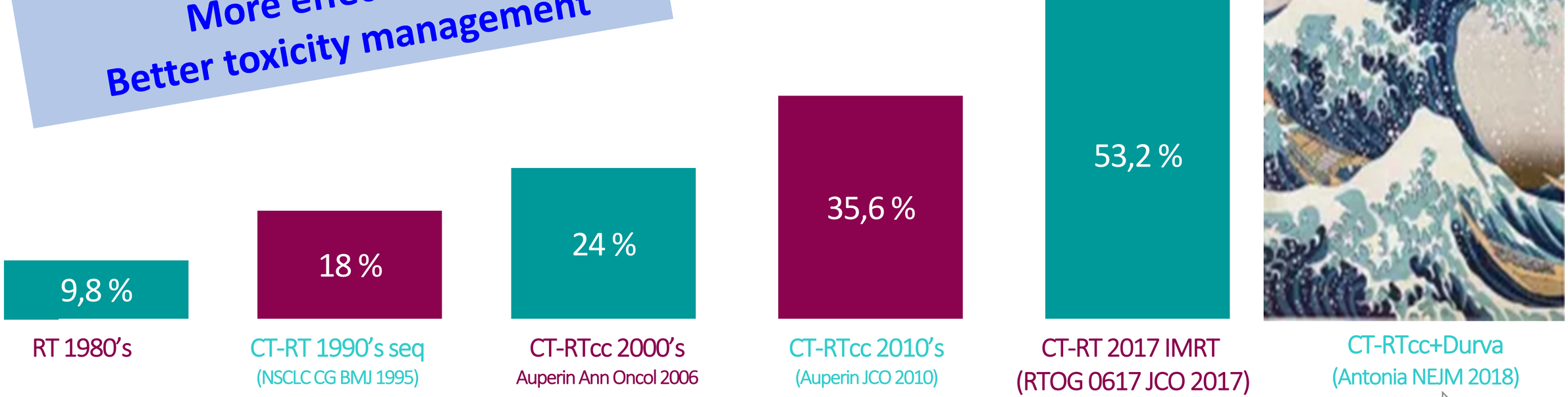
- NCDB study: total of 243,822 pts (photons: 243,474; protons:348) included in the analysis
- Propensity matched analysis, Proton therapy associated with better 5-year OS //non-proton RT: 22% versus 16% (P=0.025).

Liao JCO 2018, Higgins IJROBP 2017

Stage III Locally Advanced NSCLC : better integration of high technology RT, CT and then IO

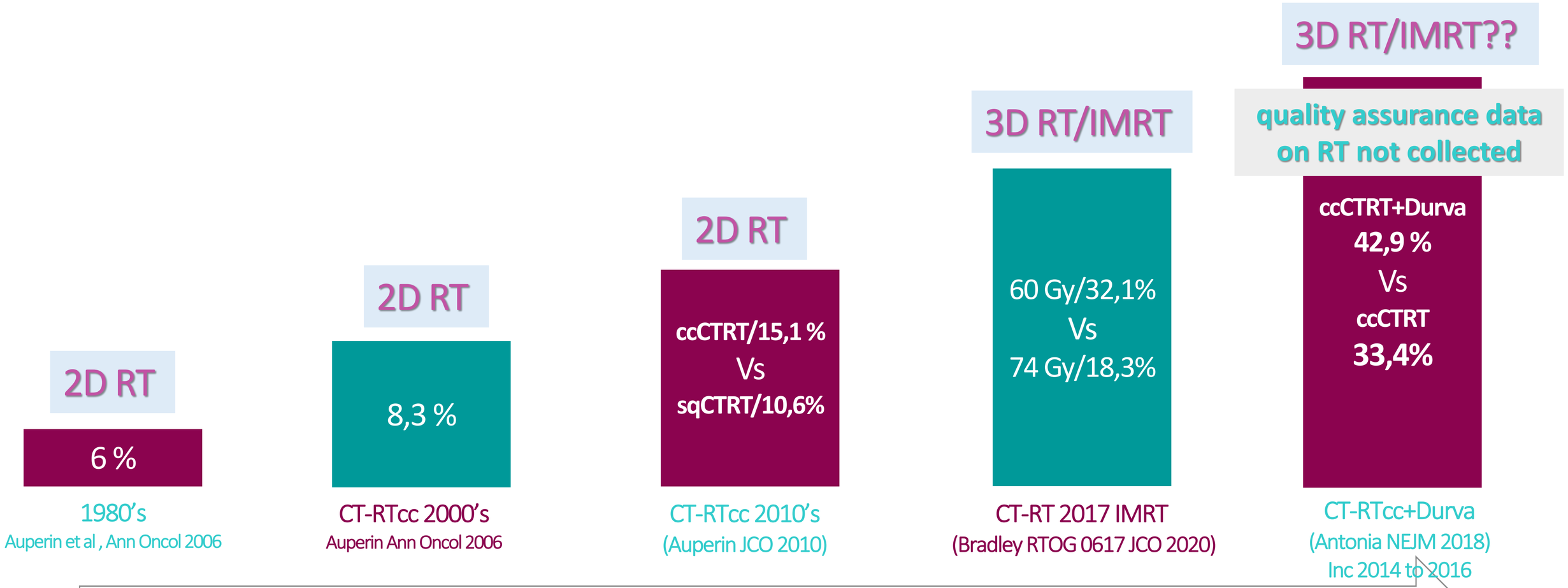
Outcome in terms of 2 year survival…

Improvement of RT 3D, IMRT
More effective CT
Better toxicity management



Better selection of patients (Brain MRI, EBUS, PET Scan)

Stage III better integration of high technology RT, CT and IO has improved outcome of patients Outcome in terms of 5 year survival..
On going studies for oligometastatic disease, metastatic disease and early lung cancer



Conclusion

- **Between 2000-04 and 2010-14, 5-yr net survival following diagnosis of lung cancer increased from 11% to 15% on average across EU countries…**
- **Considerable improvement in the management of lung cancer pts**
- **Radiotherapy is part of treatment in stage I, II, III and IV**
- **Evaluating the efficacy of innovating treatments or techniques in lung cancer is a great challenge**
  - High risk of distant failure
  - High risk of toxicity because of comorbidities and because of its location (Heart matters!!, Lung..)
- **Randomized evidence (RCT) AND Real World Evidence (RWE) based on routine data should probably help to accelerate process of validation of innovative treatments in Lung Cancer**

Thank you!! Grazie per l'invito!

GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

UNIVERSITÉ PARIS SUD
FACULTÉ DE MÉDECINE

ÉCOLE DES SCIENCES DU CANCER GUSTAVE ROUSSY