Individualised Radiotherapy: How biology, physics and genetics meet

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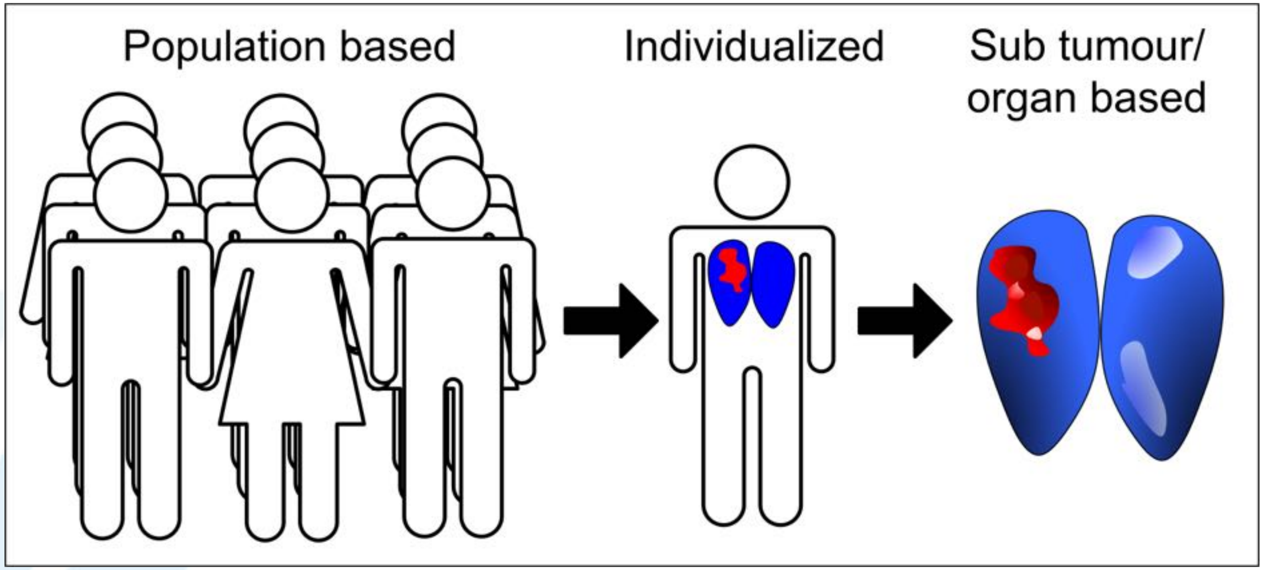
Taking advantage of heterogeneity

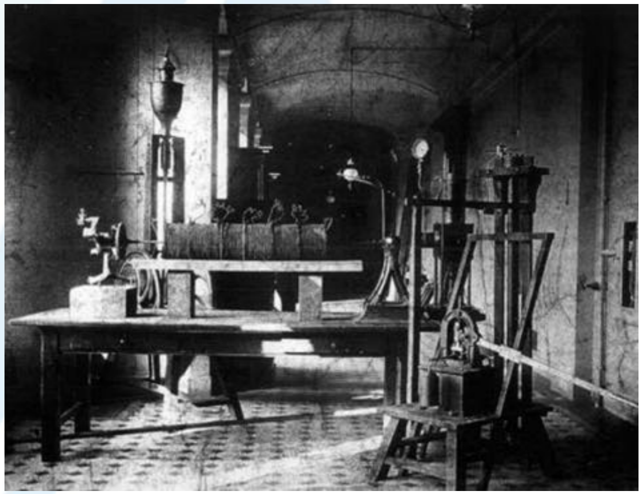


Lambin et al. Radiother Oncol 2010

Technological evolution is unprecedented and unpredictable … for telephones …

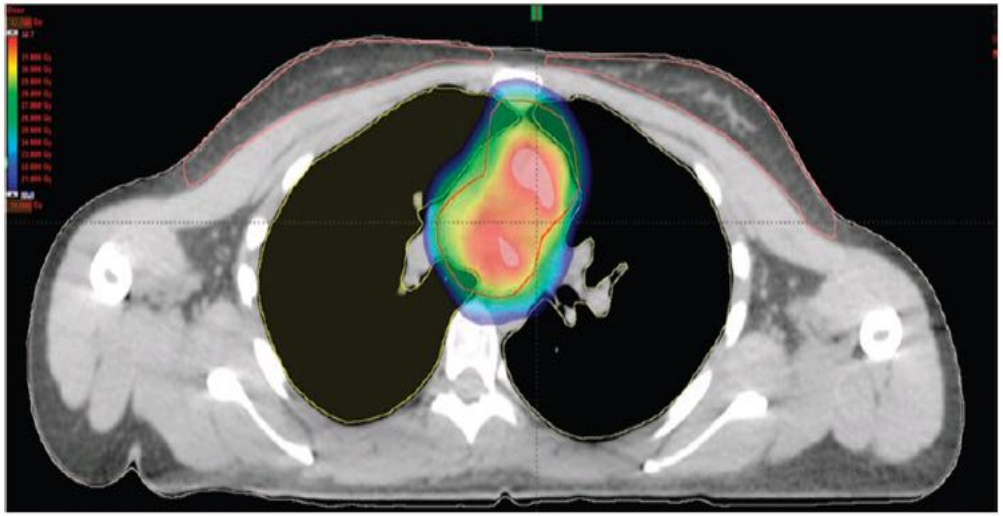
1890: First radiotherapy

1965: Mantle field radiotherapy



1985: Many phase III trials

2014: Are mostly not used telephones anymore …

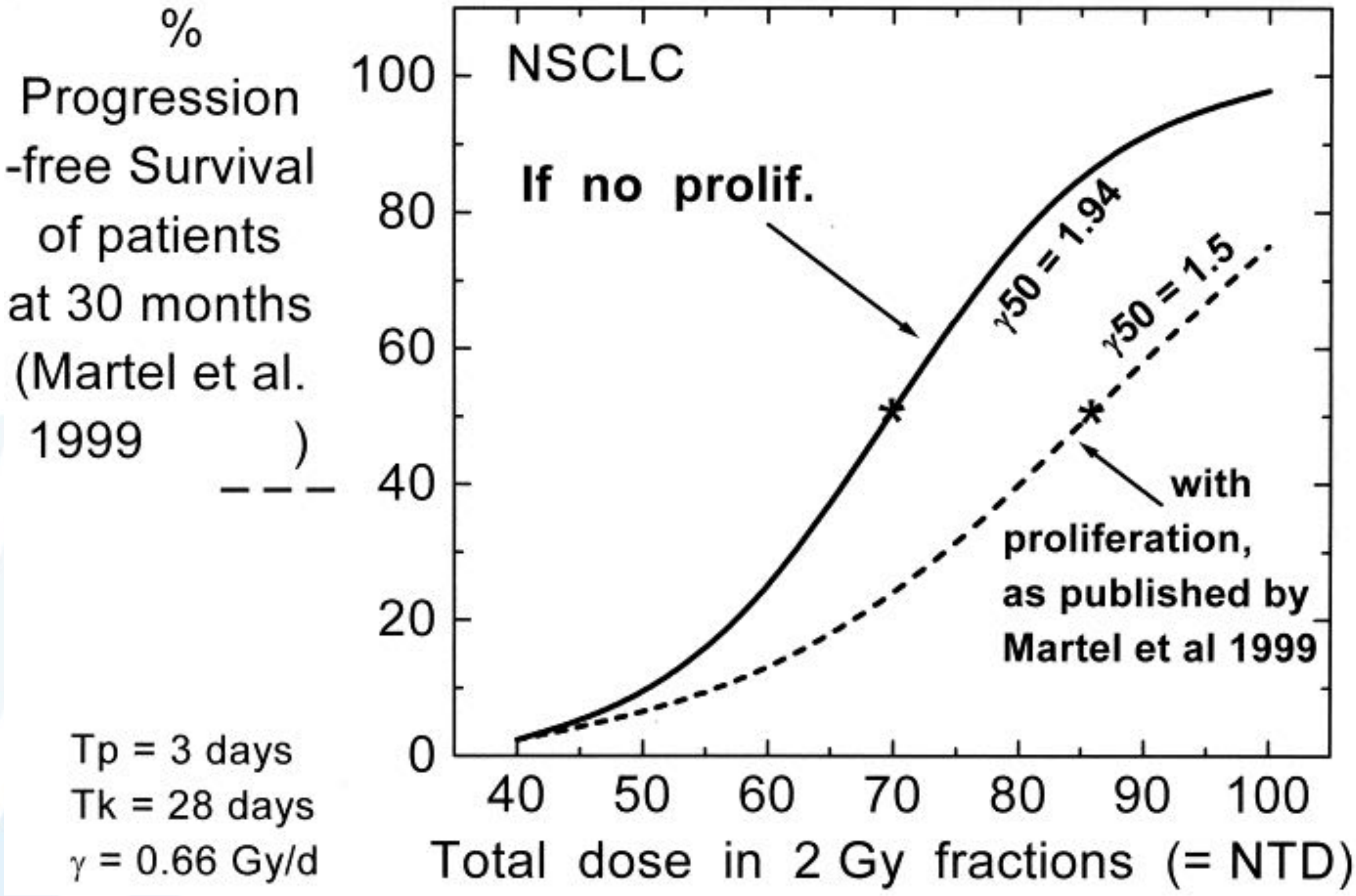


Volumetric Arc Therapy (VMAT)

Successful radiotherapy

- Dose
- Time
- Volume

→ Appropriate target volume definition
→ Avoiding normal tissues
→ Adequate delivery and QA

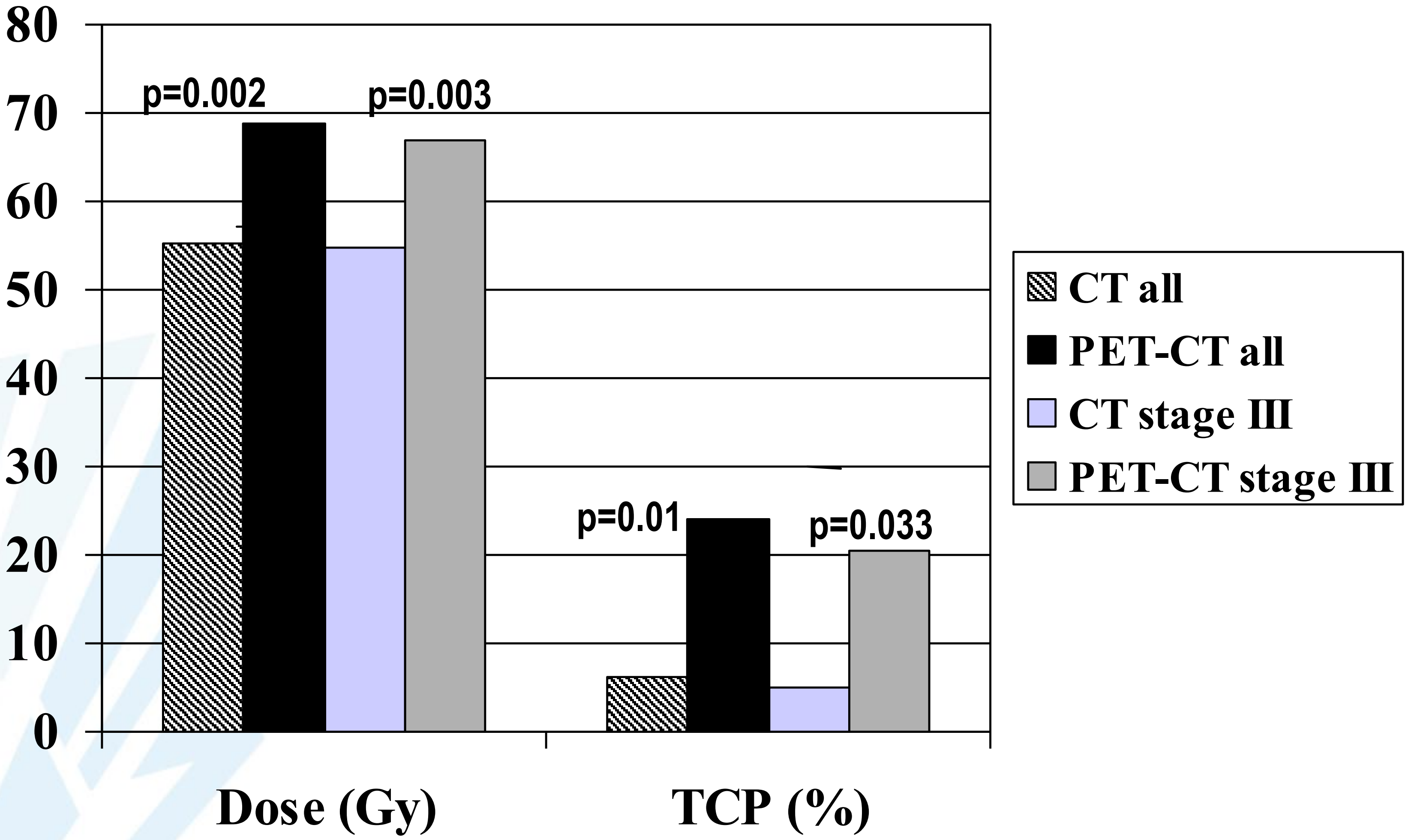


Fowler J et al. Int. J. Radiation Oncology Biol. Phys. 60: 1241–1256, 2004

Optimising target volume definition with FDG-PET-CT scans

Non-Small Cell Lung Cancer

Theoretical radiation dose escalation with the *same toxicity* with FDG-PET-CT planning



van der Wel et al. Int J Radiat Oncol Biol Phys 2005

De Ruysscher et al. Radiother Oncol 2005

Non-Small Cell Lung Cancer

- median follow-up time post-radiotherapy 16 months (95 % CI 11-21)
- median actuarial overall survival: 21 months (95 % CI 14-28)
- median progression free survival: 18 months (95 % CI 12-24)
  - 11/44 (25 %) local recurrence
  - Only 1/44 isolated nodal failure

    (crude rate 2.3 %, upper bound 95 % CI 10.3 %)

    (CT and PET T2N0M0 left upper lobe SqCC 16 mo after RT in nodes 5 and 6)

De Ruysscher et al. Int J Radiat Oncol Biol Phys 2005

Small Cell Lung Cancer

Recurrences	N° patients	%
None	21	35
Local (prim. tumor)	9	15
Exclusively in-field	3	5
Local and distant	7	11.7
Isolated nodal	2	3.3
Nodal	20	33.3
Exclusively in-field	8	13.3
Nodal and distant	18	30.0
Distant	34	56.7
Isolated distant	19	31.7
Distant and local/nodal	15	25.0
Isolated brain	9	15.0

van Loon et al Int J Radiat Oncol Biol Phys 2009

Optimising the overall treatment time

Non-Small Cell Lung Cancer

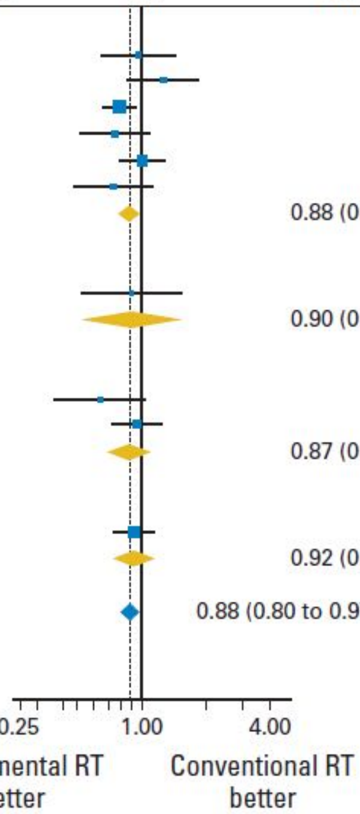
VOLUME 30 · NUMBER 22 · AUGUST 1 2012

JOURNAL OF CLINICAL ONCOLOGY | REVIEW ARTICLE

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

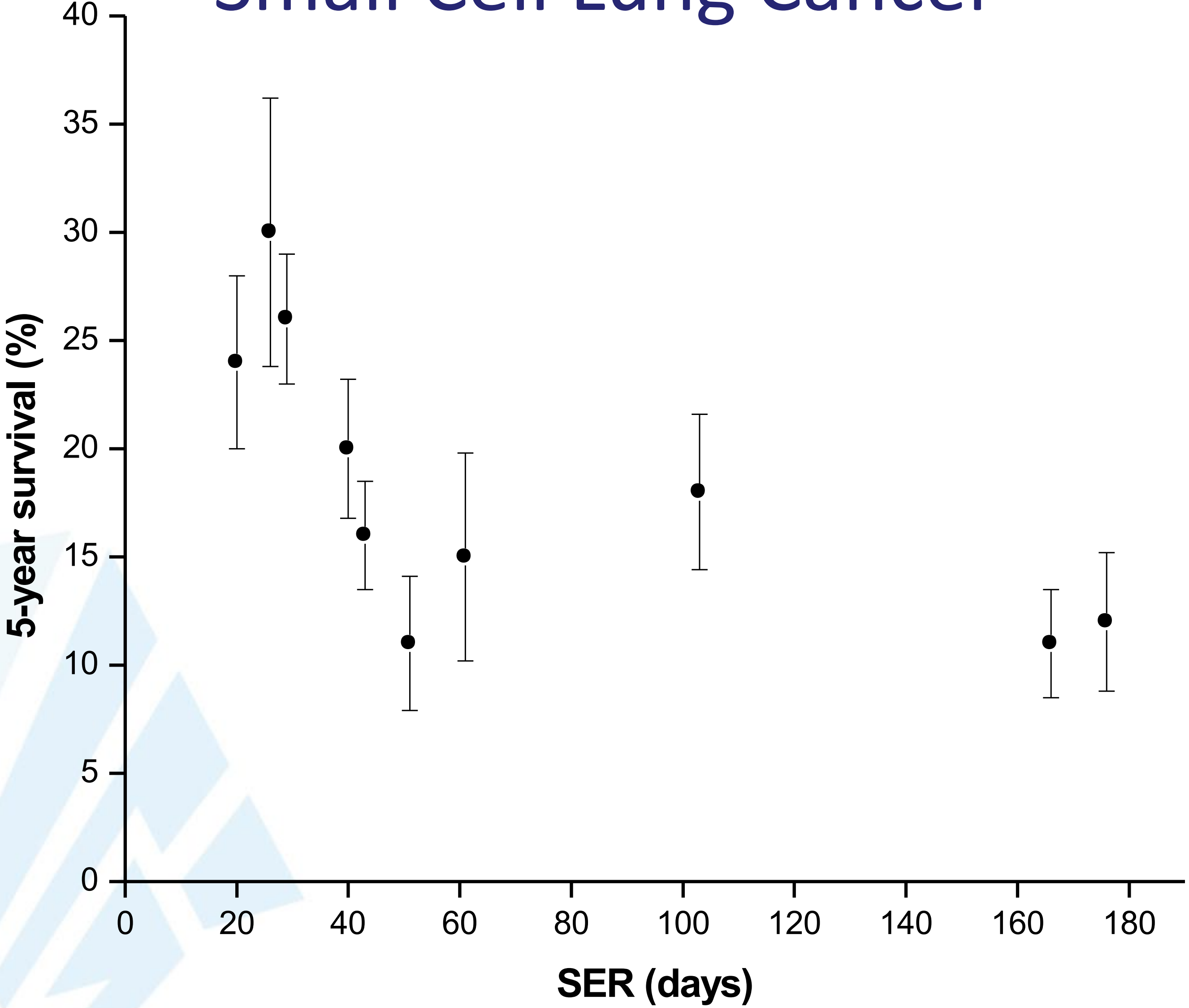
Category Trial	No. Deaths / No. Entered Exp. RT	 Conv. RT	O-E	Variance	HR	HR (95% CI)
Very accelerated RT						
PMCI 88C091	48/48	52/53	-0.8	24.3		
PMCI 88C091 CT	51/51	56/56	6.0	25.6		
CHART	316/338	217/225	-29.4	120.7		
ECOG 2597	51/60	55/59	-7.4	25.8		
CHARTWEL	132/150	132/150	0.2	65.8		
CHARTWEL CT	40/53	47/53	-6.4	21.2		
Subtotal	638/700	559/596	-37.8	283.4		0.88 (0.78 to 0.98)
Moderately accelerated RT						
Gliwice 2001	26/29	27/29	-1.4	13.2		
Subtotal	26/29	27/29	-1.4	13.2		0.90 (0.52 to 1.54)
Hyperfractionated RT–identical total dose						
NCCTG 902451	34/39	35/35	-7.0	15.7		
NCCTG 942452	111/125	108/121	-2.6	54.6		
Subtotal	145/164	143/156	-9.6	70.3		0.87 (0.69 to 1.10)
Hyperfractionated RT–increased total dose						
RTOG 8808	155/163	156/163	-6.4	76.9		
Subtotal	155/163	156/163	-6.4	76.9		0.92 (0.74 to 1.15)
Total	964/1,056	885/944	-55.2	443.7		0.88 (0.80 to 0.97), *P* = .009



Test for heterogeneity: $\chi^2_9 = 9.74$, $P = .37$, $I^2 = 8\%$

Test for interaction: $\chi^2_3 = 0.17$, $P = .98$

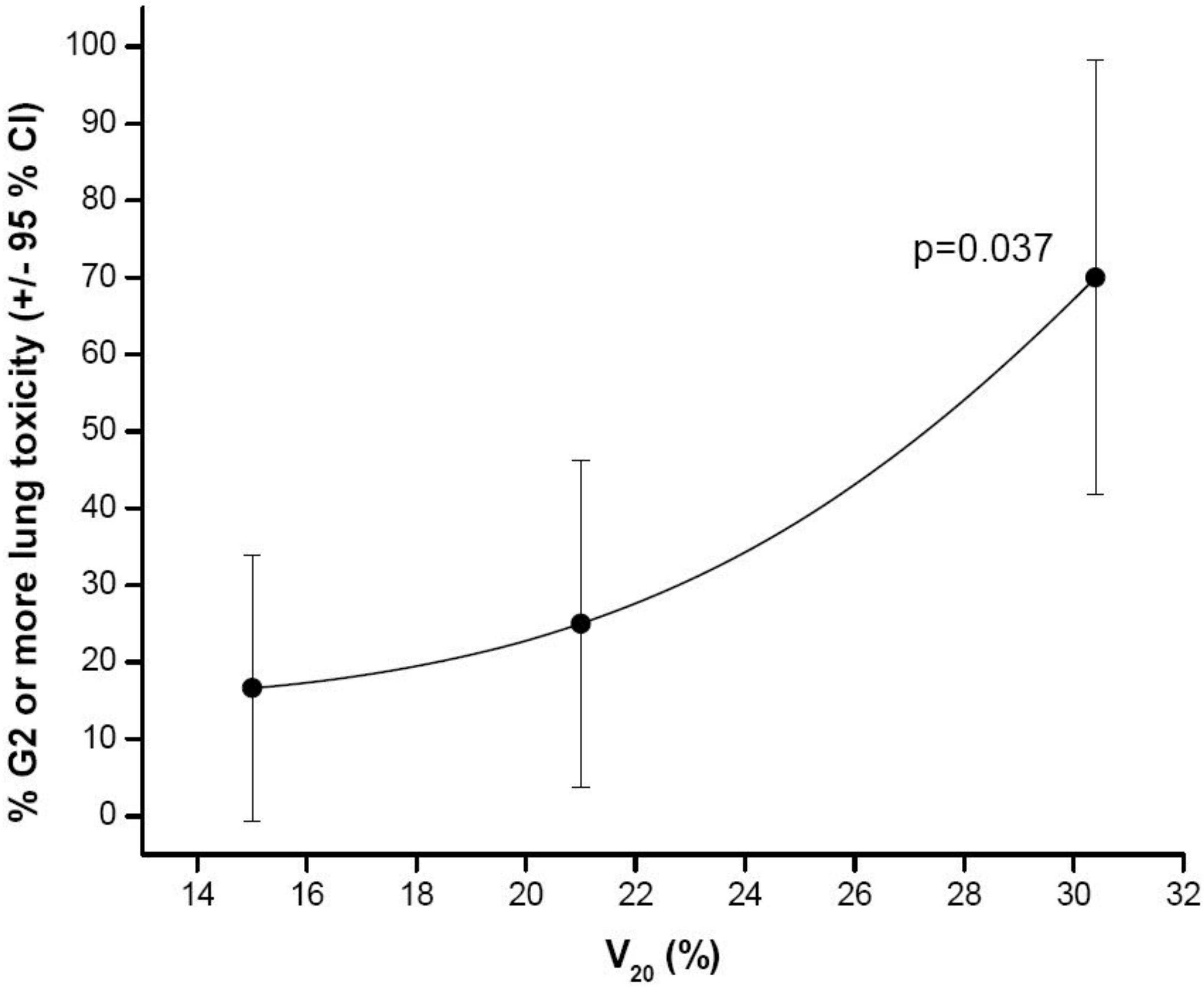
Small Cell Lung Cancer



De Ruysscher et al. J Clin Oncol 2006

Van Meerbeeck, Fenell, De Ruysscher. Lancet 2011

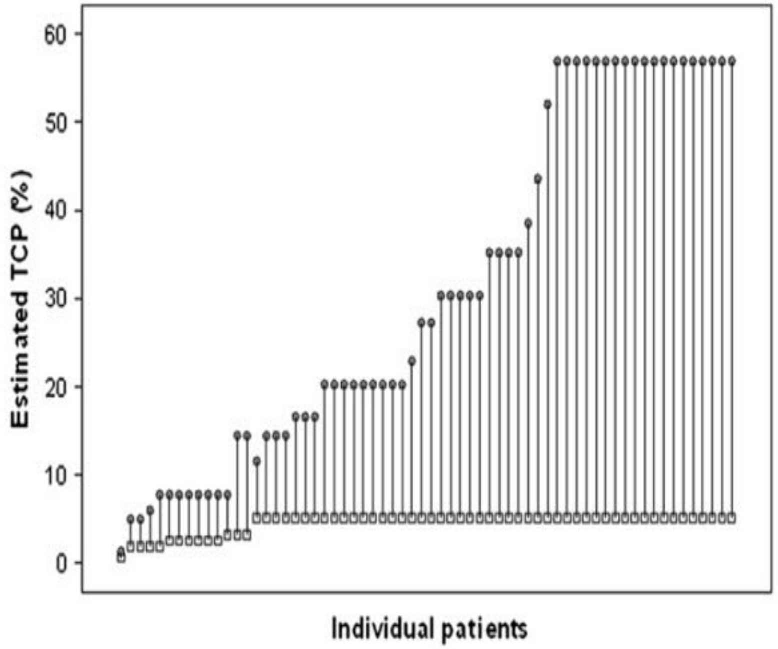
Individualisation based on optimal target volume definition short overall treatment time physical constraints



De Ruysscher et al. Int J Radiat Oncol Biol Phys 2008

INDividualised Accelerated Radiotherapy (INDAR)

- Escalate the dose to the maximum tolerance
- Delivered in a short overall treatment time
- Directed to areas that are 18F-deoxyglucose (FDG) positive



Van der Wel et al. Int J Radiat Oncol Biol Phys 2005
De Ruysscher et al. Radiother Oncol 2005
De Ruysscher et al. Int J Radiat Oncol Biol Phys 2005
De Ruysscher et al. Int J Radiat Oncol Biol Phys 2008
Van Baardwijk et al. Int J Radiat Oncol Biol Phys 2008
Van Baardwijk et al. Int J Radiat Oncol Biol Phys 2008

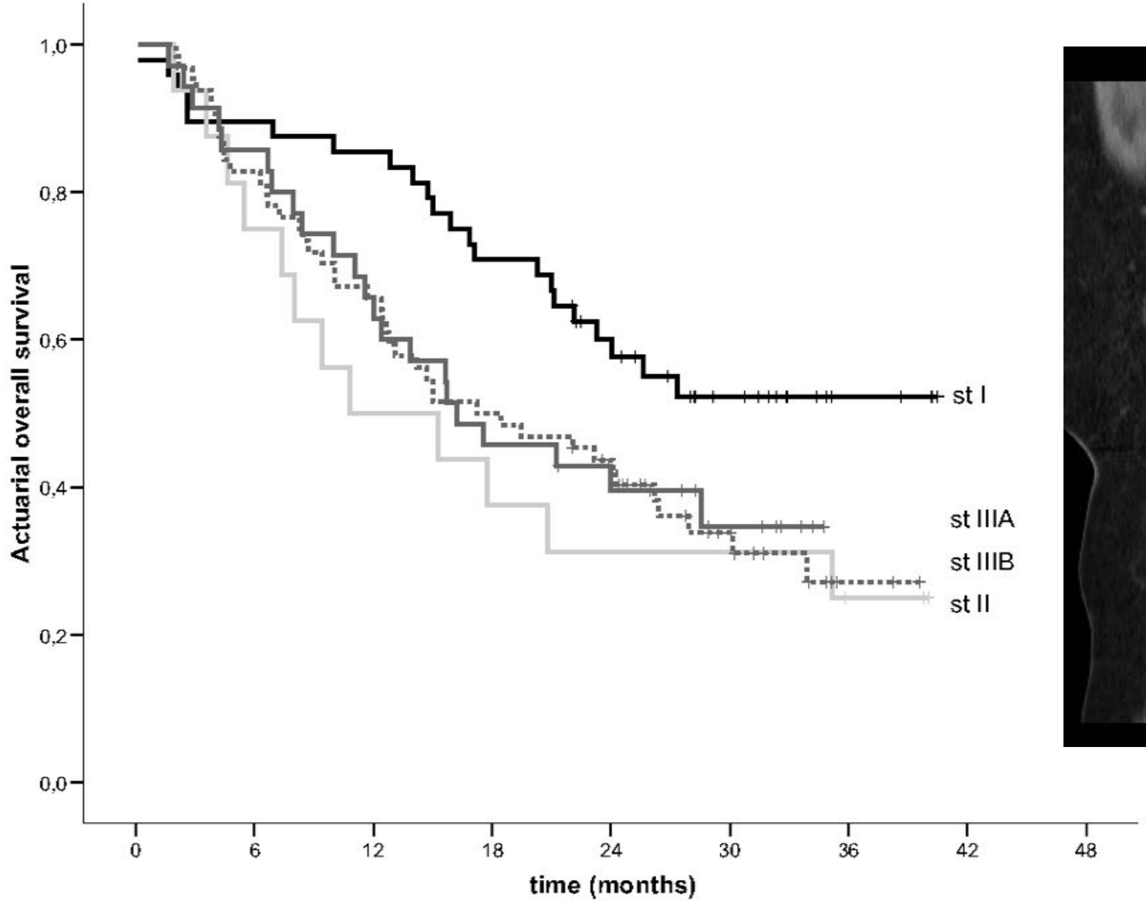
54 Gy/ 30 F/ 3 wks

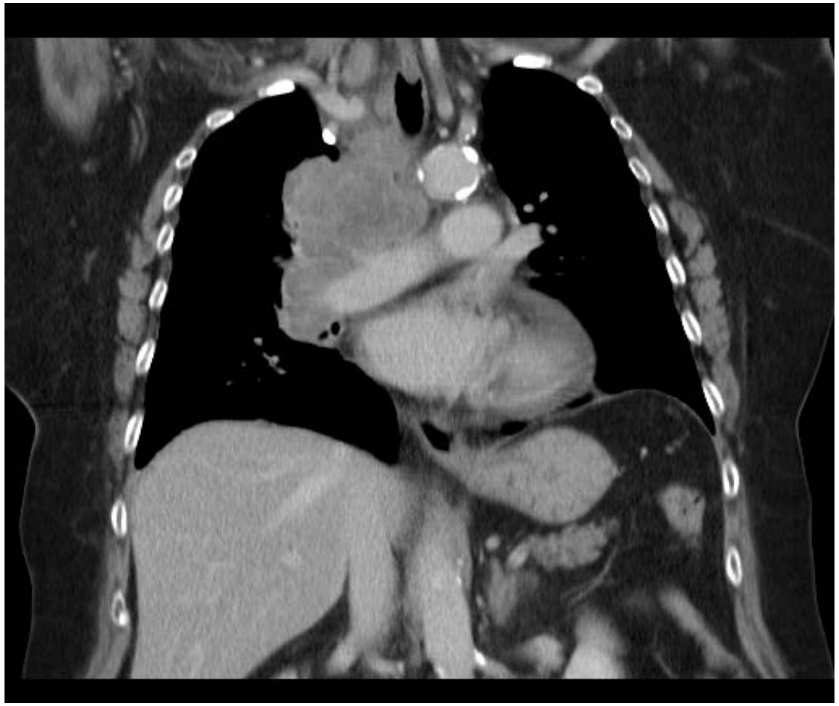
T3N0M0

79.2 Gy/ 44 F/ 4.4 wks

pT4pN2M0

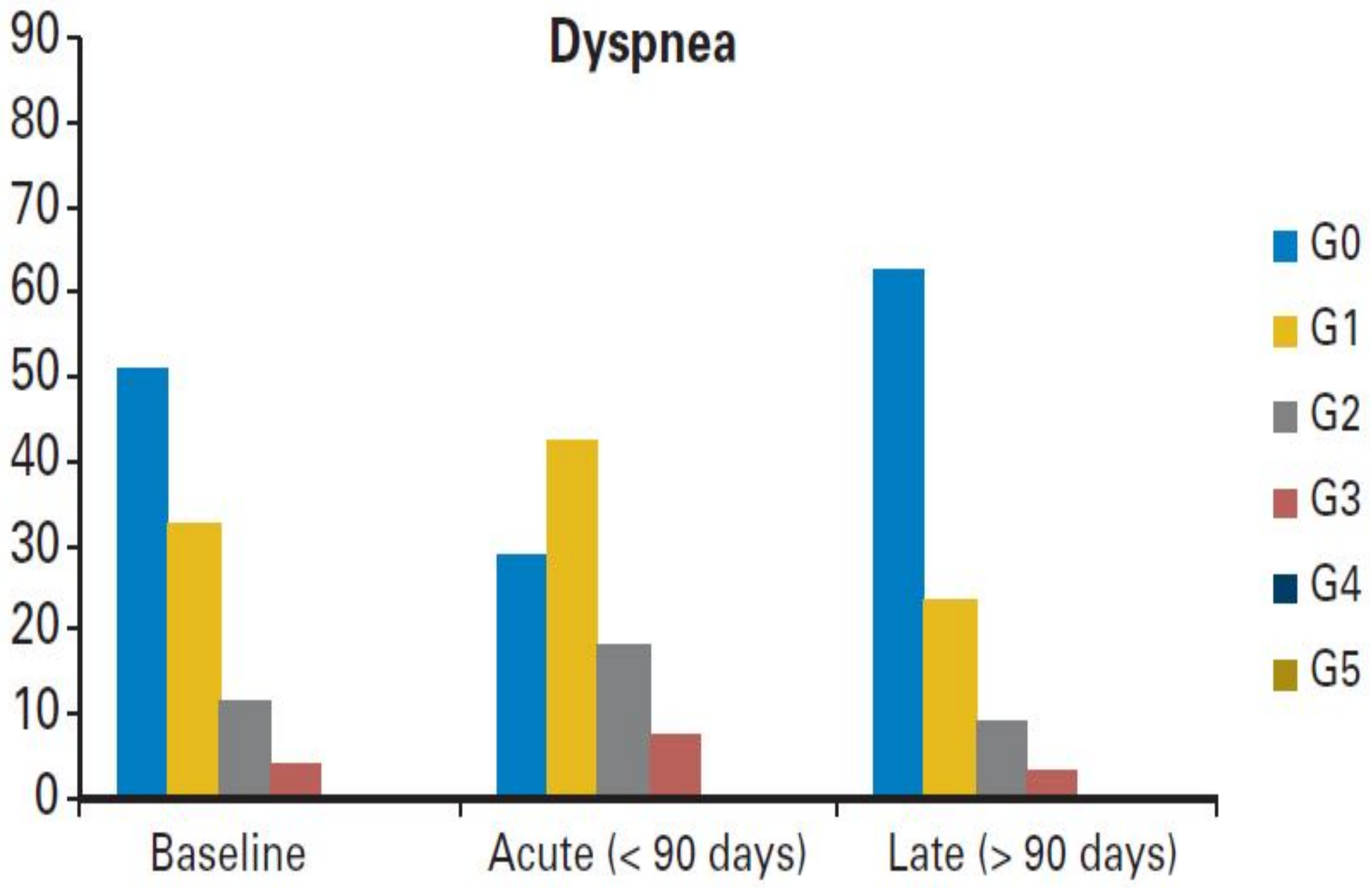
Survival by stage (large volume, multi-level N+, 25 % WHO PS 2), sequential chemo-radiation





van Baardwijk et al. J Clin Oncol 2010

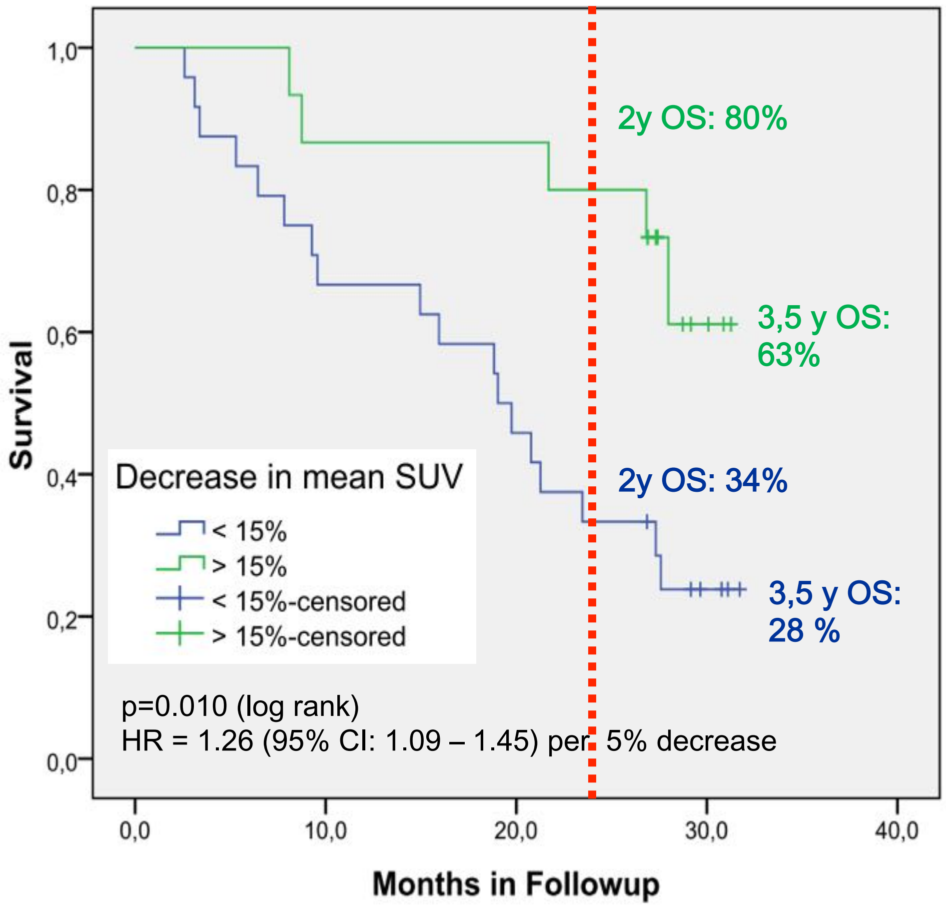
Dyspnea evolution after individualised radiotherapy: 10 % less patients with dyspnea



van Baardwijk et al. J Clin Oncol 2010

Early response: FDG changes during first week of chemo-RT and survival

- FDG-PET:
  - Cut-off: 15% (EORTC response)
  - Changes in maximum SUV and mean SUV significant predictive for 2-year overall survival
    - HR 1.26 (95% CI: 1.09 – 1.45) per 5% decrease of SUV
- CT (volume)
  - Tumour volume pre RT is predictive for survival
    - HR 1.040 (95% CI: 1.005 – 1.076) per 10 cm^3 increase
  - Change in tumour volume (CT) is not correlated to survival



Van Elmpt W et al. J Nucl Med 2012

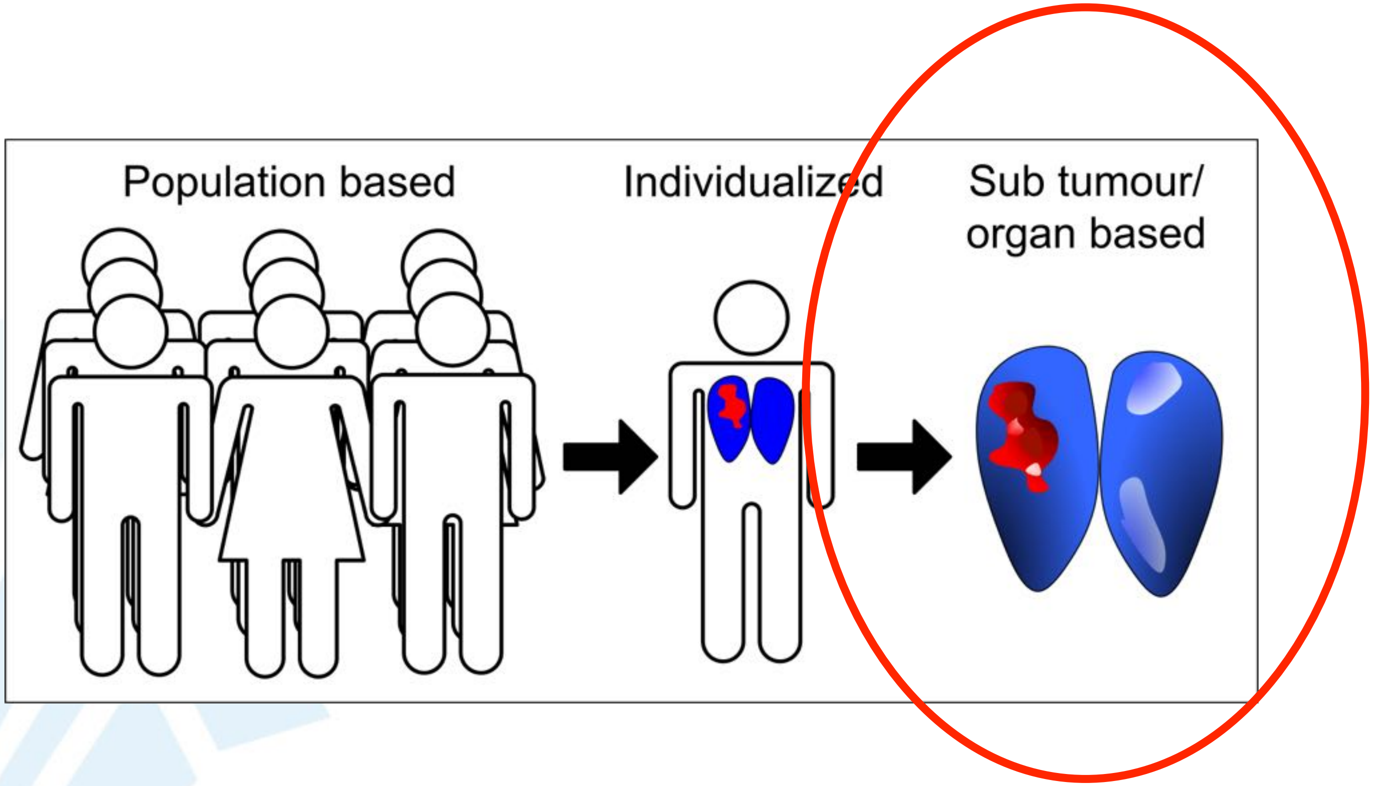
OPEN

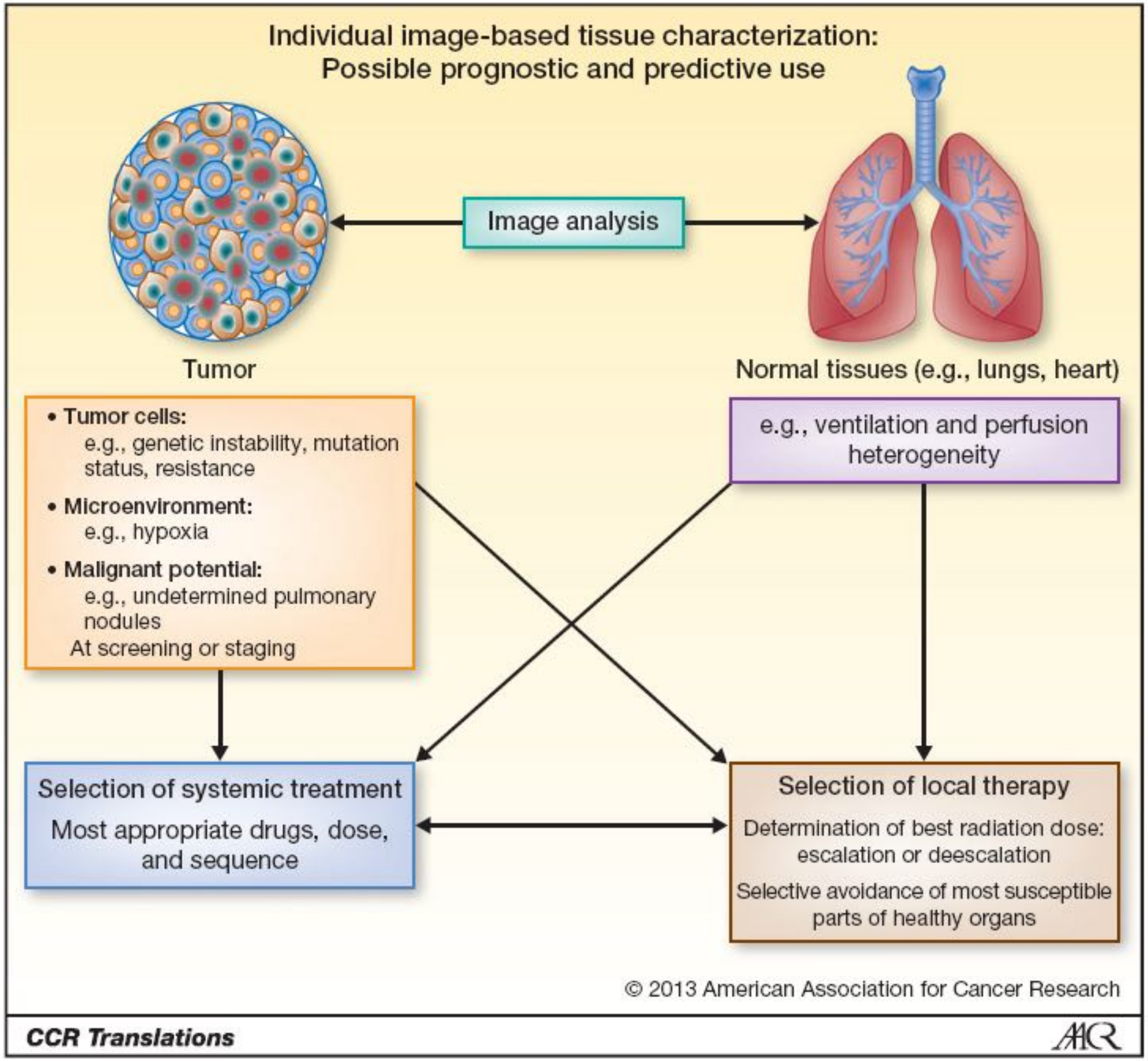
A Phase I Study of Concurrent Individualized, Isotoxic Accelerated Radiotherapy and Cisplatin–Vinorelbine–Cetuximab in Patients With Stage III Non–Small-Cell Lung Cancer

Anne-Marie C. Dingemans, MD, PhD,, Gerben Bootsma, MD, PhD,† Angela van Baardwijk, MD, PhD,‡ Bart Reymen, MD,‡ Rinus Wanders, MD,‡ Boudewijn Brans, MD, PhD,§ Marco Das, MD, PhD,|| Monique Hochstenbag, MD, PhD,* Arne van Belle, MD,* Ruud Houben, MSc,‡ Philippe Lambin, MD, PhD,‡ and Dirk de Ruysscher, MD, PhD‡¶*

J Thorac Oncol 2014

Optimising by taking advantage of intra-tumour and intra-organ heterogeneity

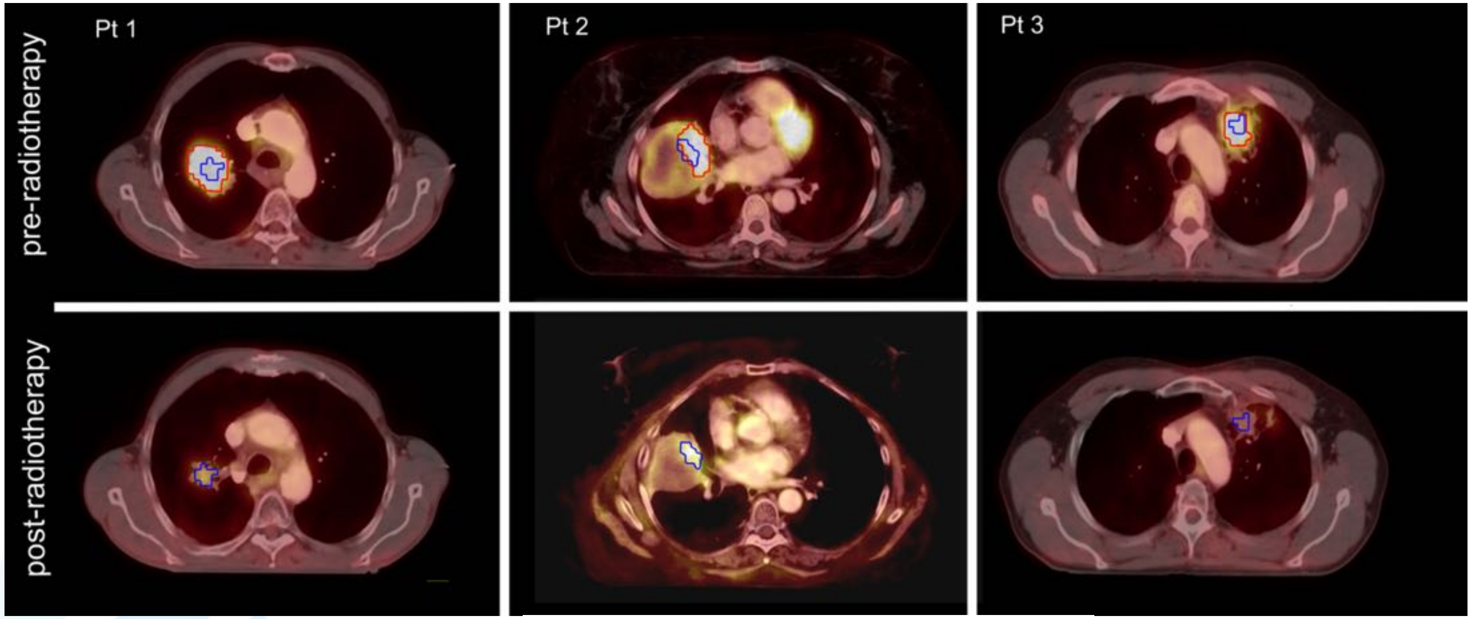


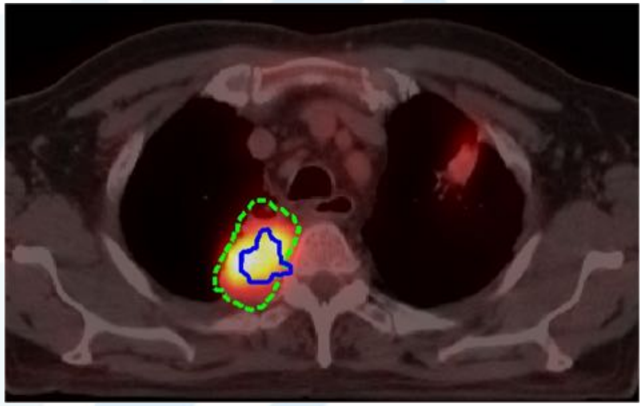


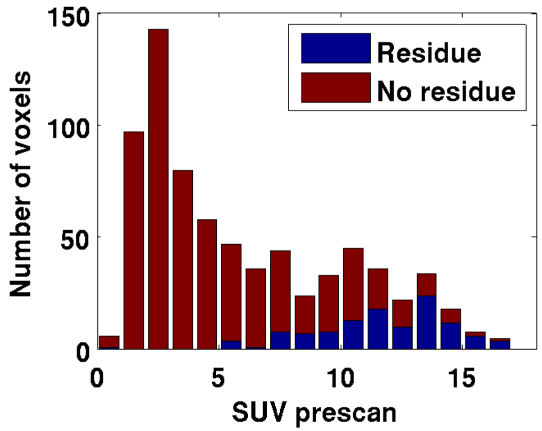
De Ruysscher D. Clin Cancer Res 2013

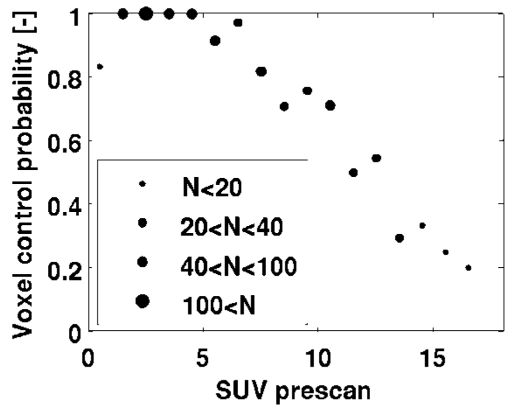
Heterogeneity in the tumour

Taking advantage of intra-tumour heterogeneity: PET-boost



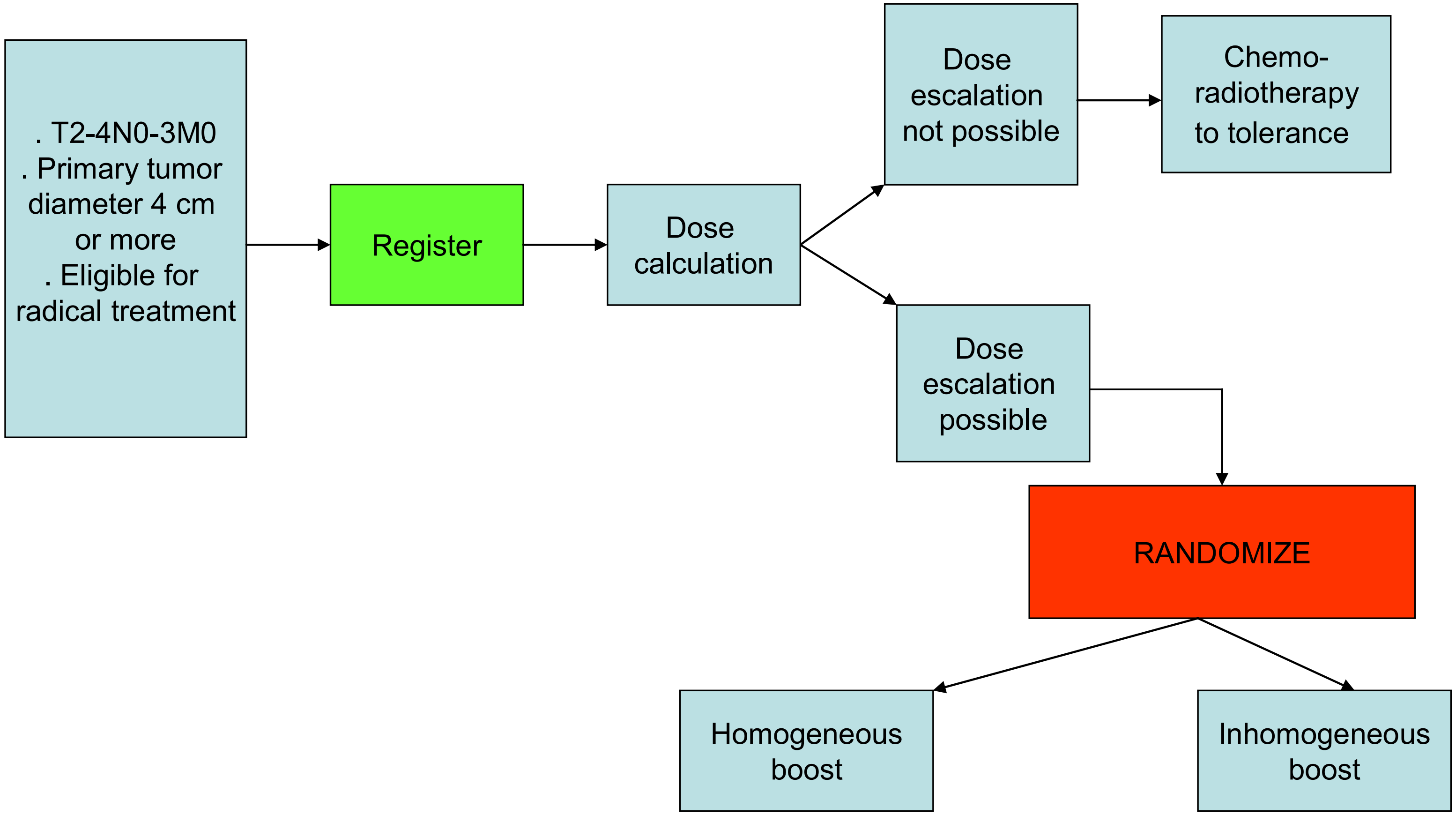






Aerts et al. Int J Radiat Oncol Biol Phys 2009; Aerts et al. Radiother Oncol 2009, Petit et al. Radiother Oncol 2009; Aerts et al. Lung Cancer 2012

Concurrent chemo-radiotherapy

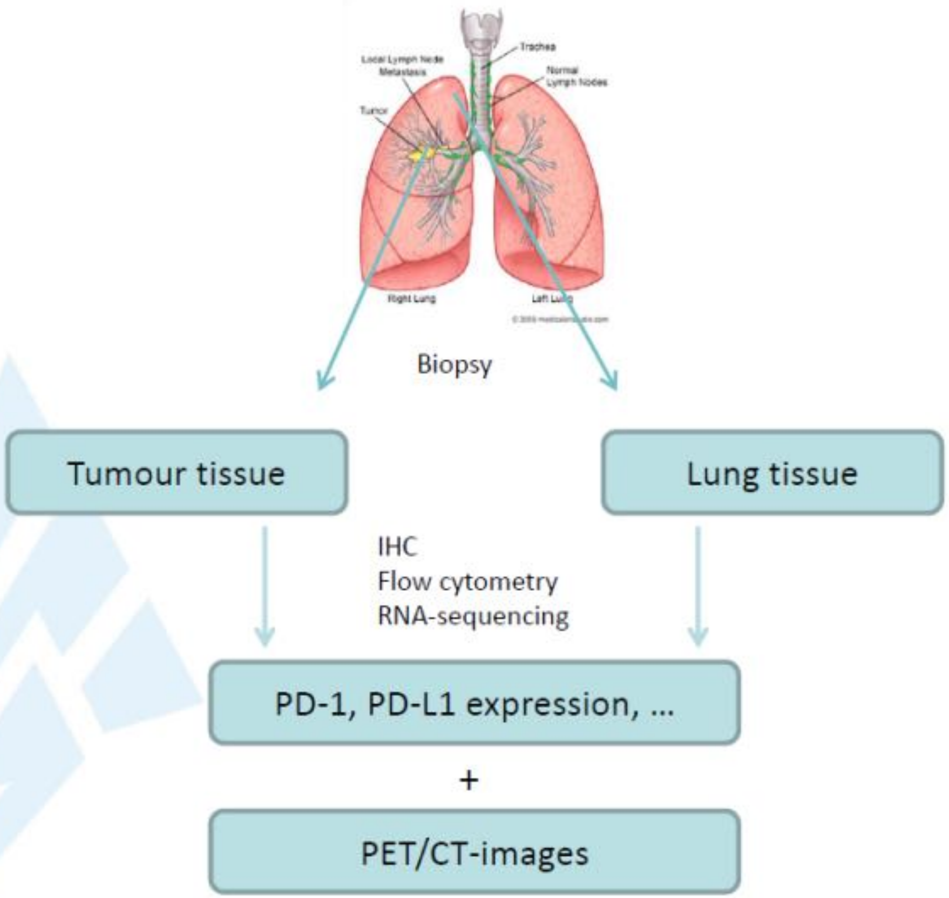


Upregulation of TAAs by radiation

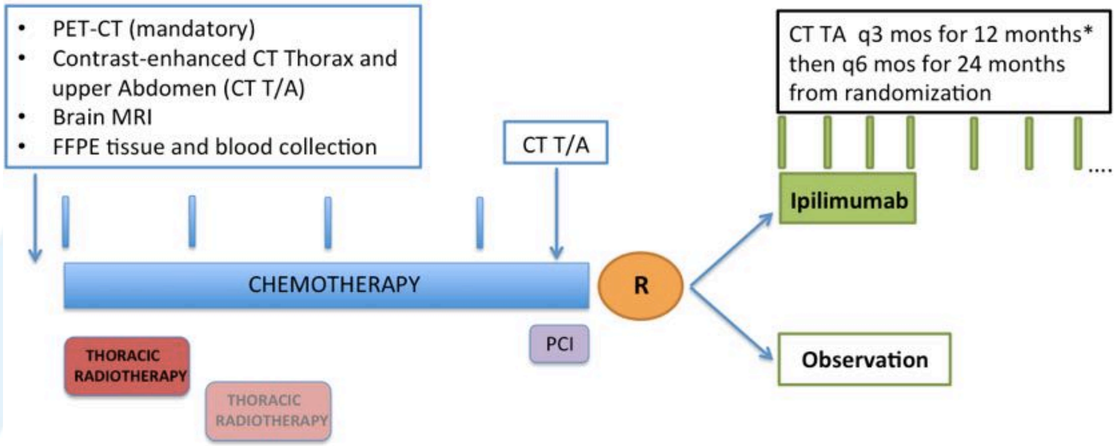
- Caco-2, HCT116, WiDr, HT-29, LS 174T, SW1463, SW403, SW480, SW620, T84, LoVo, and COLO 205
- A549, SK-LU-1, SW900, HLF-a, NCI-H23, NCI-H647, Calu-1, H460, Calu1 and Calu3
- 22Rv1, DU 145, PC-3, PC3, DU145 and LNCaP
- MelJuSo, SK-MEL-37, CaSki and SiHa
- MDA-MB-469, MDA-MB-231 and MCF 7
- Saos, LM5, 143B, HOS, HU09, and M132

Dudek et al. Cyt Growth Fact Rev 2013

Immune characteristics



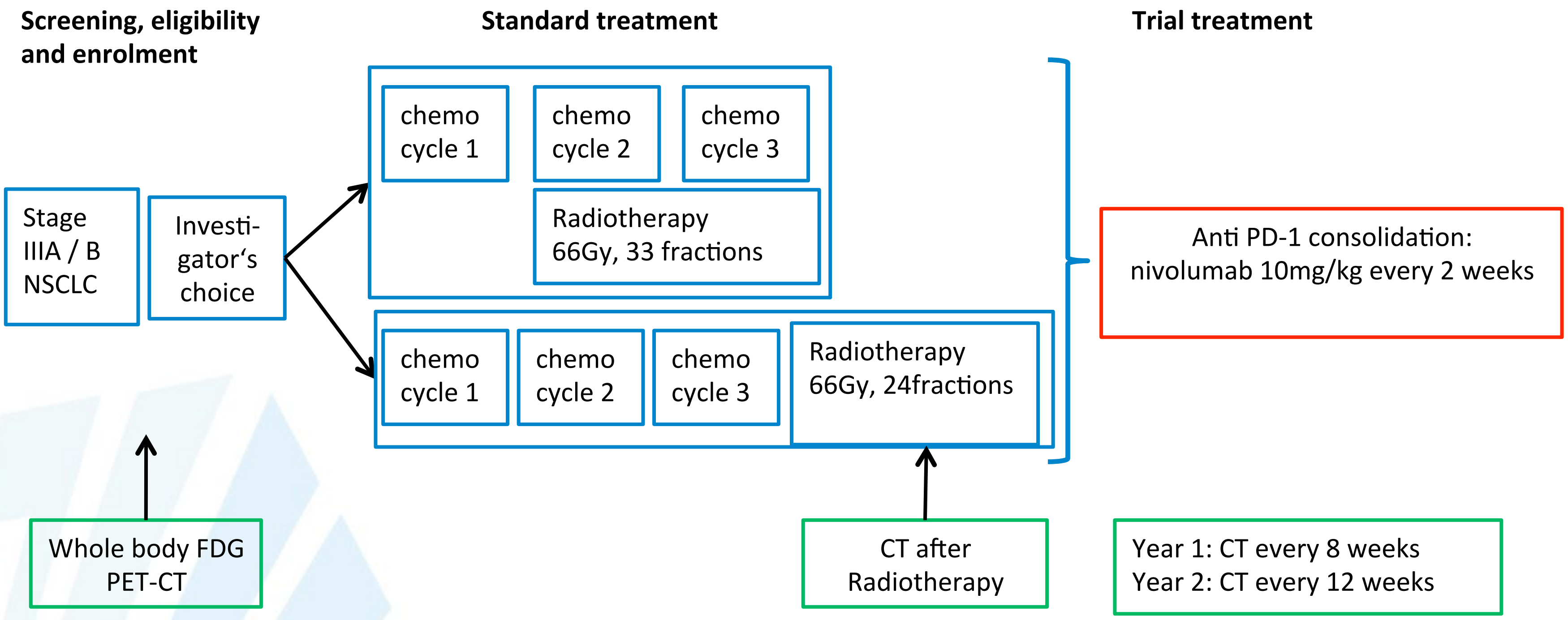
Phase II trial stage I-III small cell lung cancer



Chemotherapy: *4 cycles of Cisplatin 25 mg/m2 iv D1-3 or 75 mg/m2 D1 Etoposide 100 mg/m2 iv D1-3 q21d.*
Thoracic Radiotherapy: *Accelerated twice-daily, administration of 1.5 Gy x 30 over three weeks (preferred) or once-daily radiotherapy, administration 1.8-2Gy per fraction up to 55-60Gy. Two options are allowed: start from D1 of cycle 1 or cycle 2.*
Prophylactic Cranial Irradiation (PCI): *25 Gy in 10 fractions started between D8 and D15 of cycle 4 (to D22-29)*
Randomization: *should take place 5-6 weeks after Day 1 (between D35-42) of cycle 4*
Ipilimumab schedule: *Induction course of ipilimumab, at a dose of 10 mg/kg, once every 3 weeks x4, started 6-8 weeks after cycle 4 of chemotherapy (Day 42-56 of cycle 4)*
Maintenance: 10mg/kg, once every 12 weeks, for a maximum of 3 years after randomization

* CT at 8, 16 and 24 weeks and then every 3 months during 1st yr then every 6 months for 2 yrs until interim/safety analysis

NICOLAS: Schema

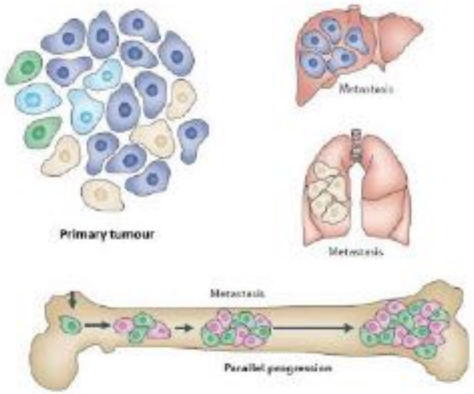


Chemotherapy: Cisplatin (or Carboplatin) doublet

Primary endpoint: Grade ≥3 pneumonitis (CTCAE V4.0) up to 6 months post-radiotherapy

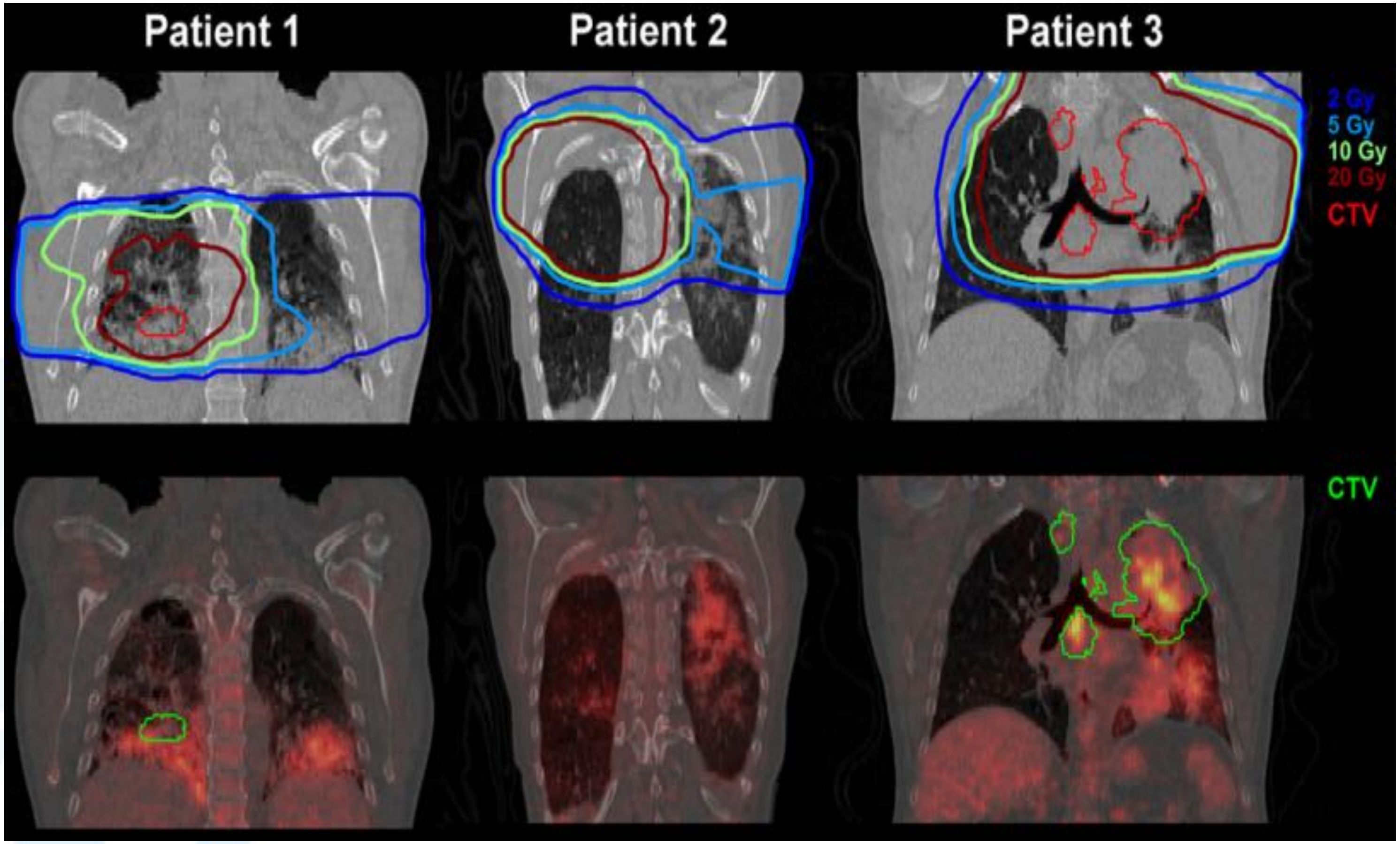
Secondary endpoints: Time to first grade ≥3 pneumonitis; PFS, OS; objective response (RECIST 1.1); time to treatment failure; Adverse events by CTCAE 4.0

Heterogeneity between the tumour and metastases with



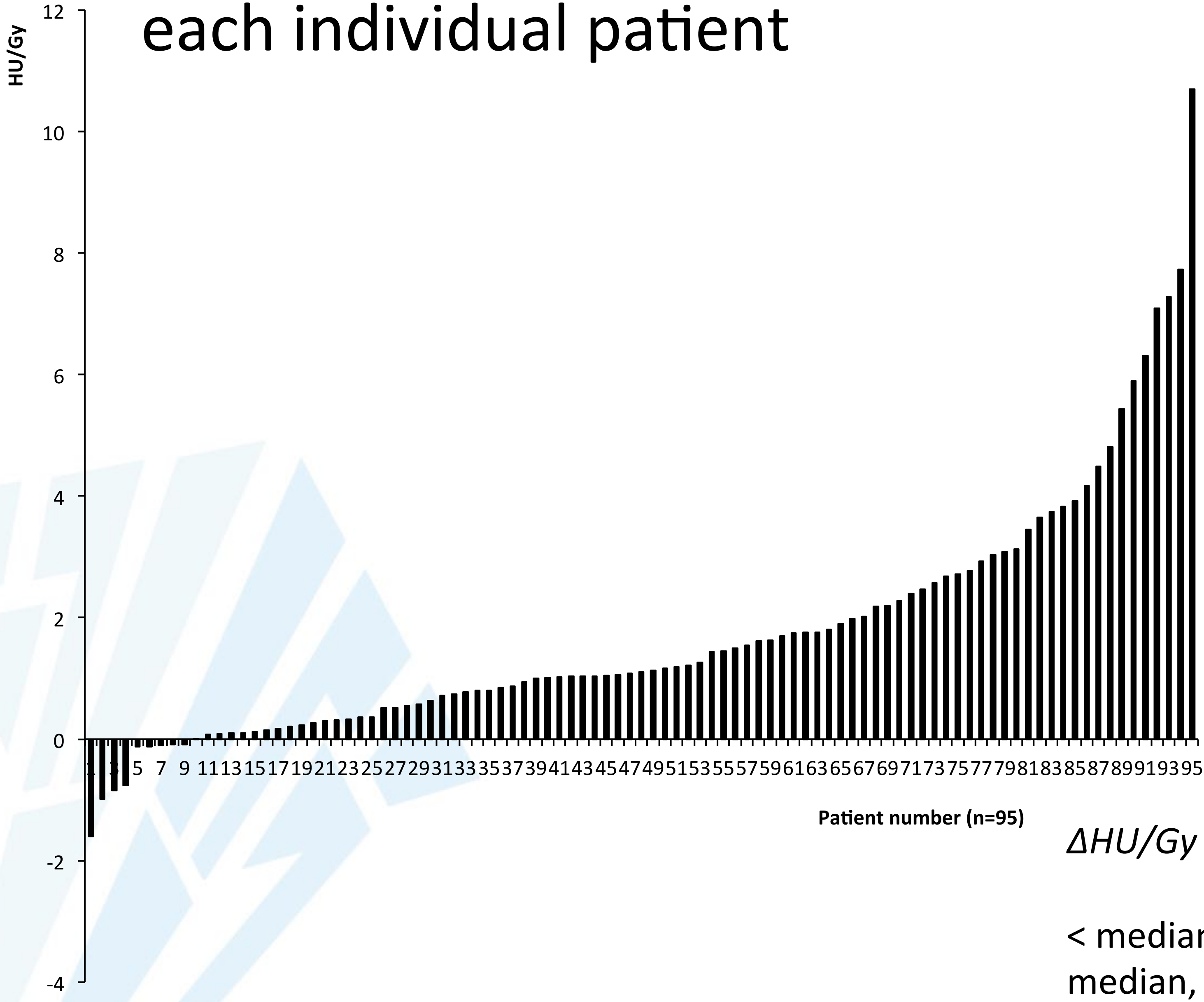
Heterogeneity in the lungs

FDG uptake in the lung before treatment correlates with subsequent radiopneumonitis



Petit et al. Int J Radiat Oncol Biol Phys 2010

Changes in Hounsfield Units (HU) per Gy for each individual patient



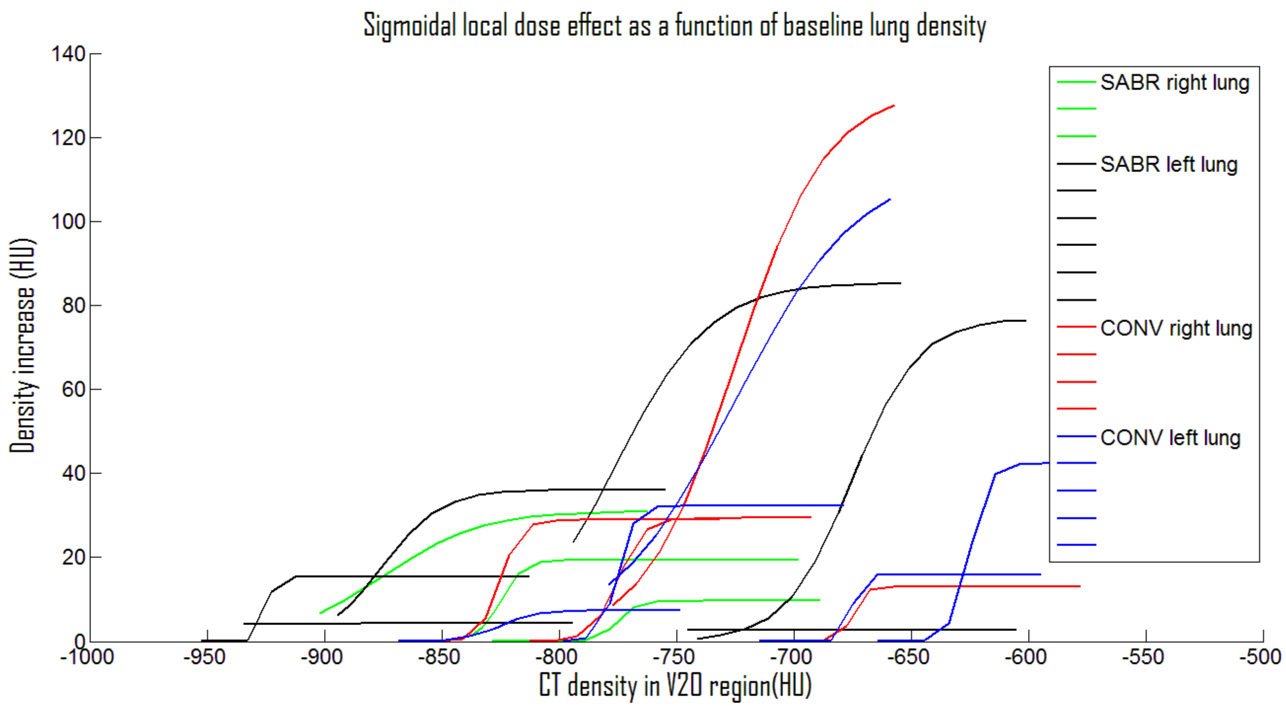
ΔHU/Gy and dyspnoea ≥ G2

< median, 16/48 (33.3 %) > median, 17/47 (36.1 %)
(p=0.77)

De Ruysscher et al. Acta Oncol 2013

Step 1: Baseline HU of lung

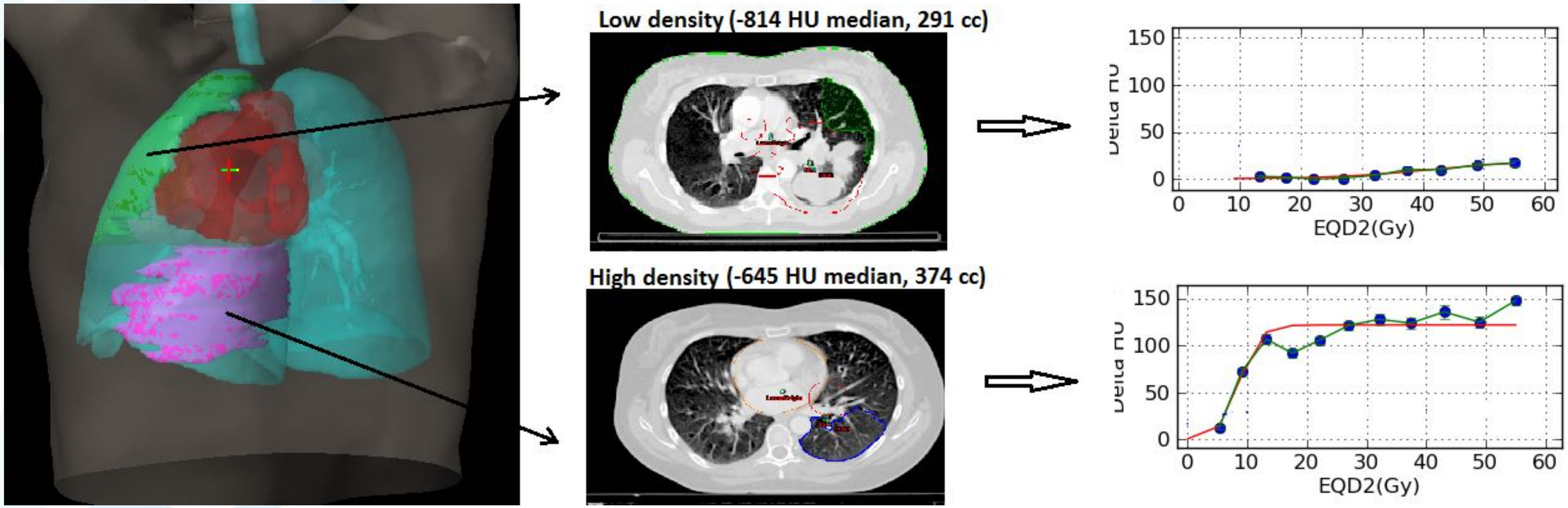
- Saturation level of sigmoidal dose effect is a function of the background HU



p=0.04 in multivariate analysis

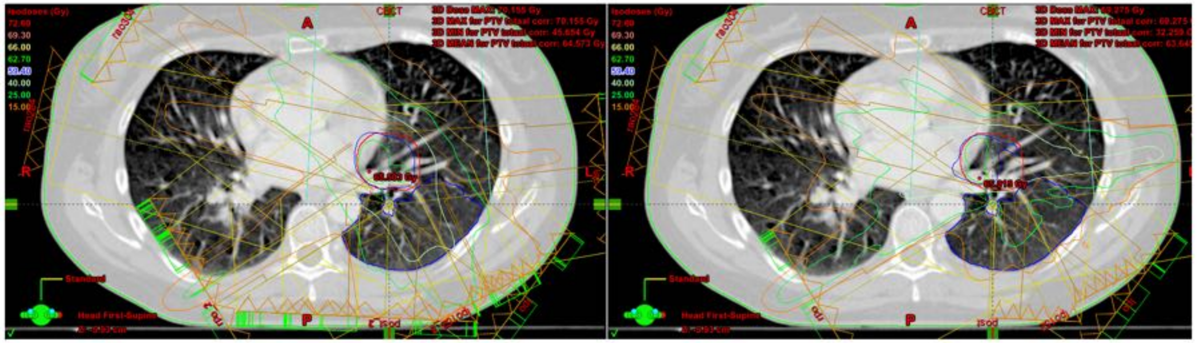
Step 2: Heterogeneity within the lungs

- Concept
  - Denser region more sensitive
  - Limit radiation dose to denser regions



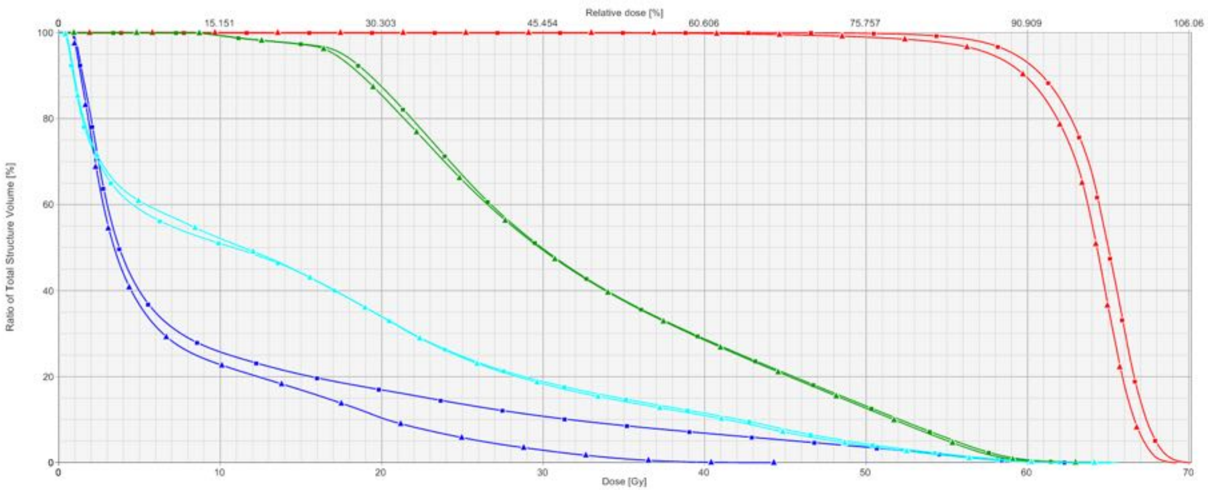
Step 2: Heterogeneity within the lungs

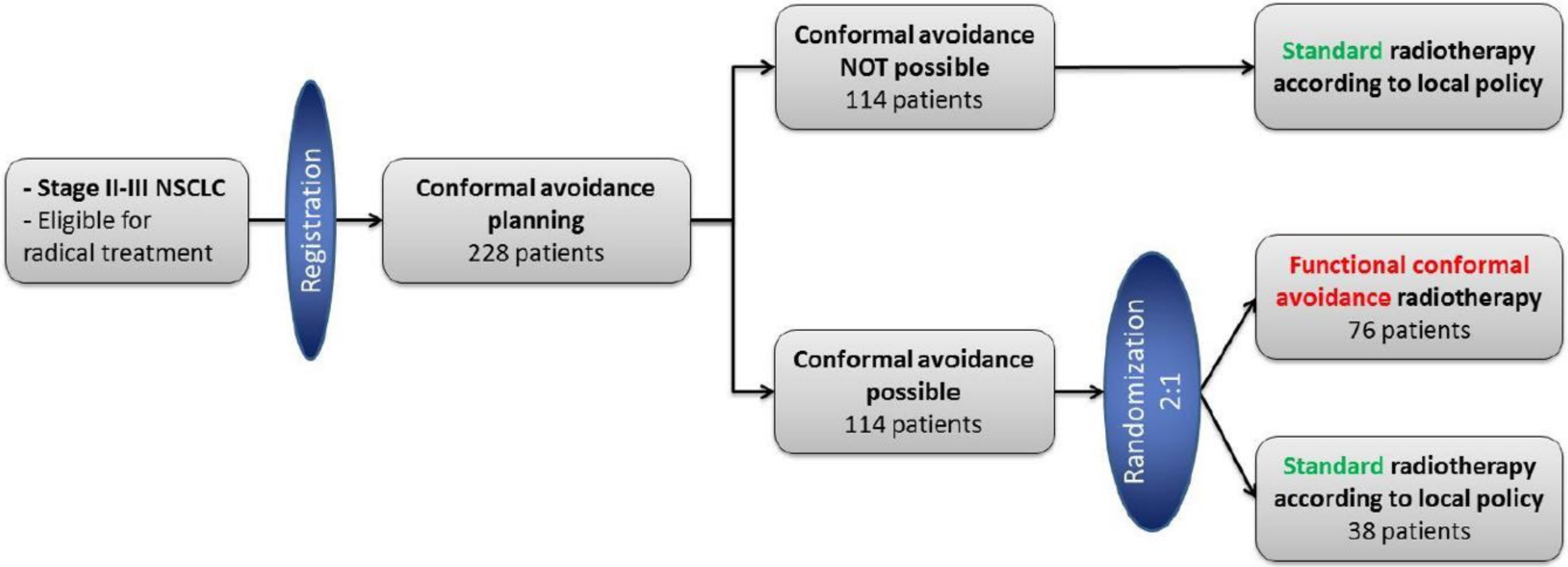
- Redistribution of radiation dose



Delivered IMRT plan

Redistribution IMRT plan: avoiding high density structure




- Stage II-III NSCLC
- Eligible for radical treatment
Registration
Conformal avoidance planning
228 patients
Conformal avoidance NOT possible
114 patients
Standard radiotherapy according to local policy
Conformal avoidance possible
114 patients
Randomization 2:1
Functional conformal avoidance radiotherapy
76 patients
Standard radiotherapy according to local policy
38 patients

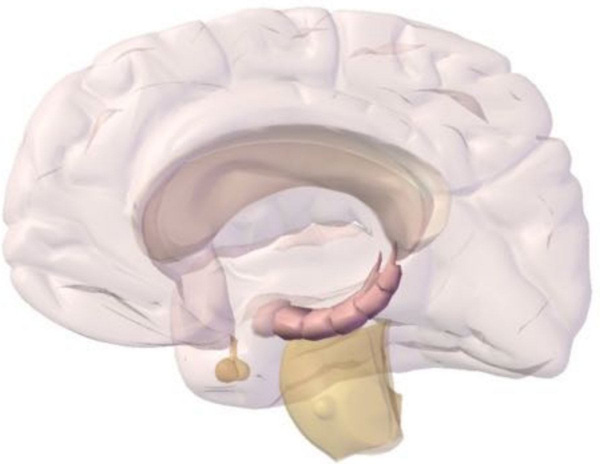
Heterogeneity in the brain

UZ LEUVEN

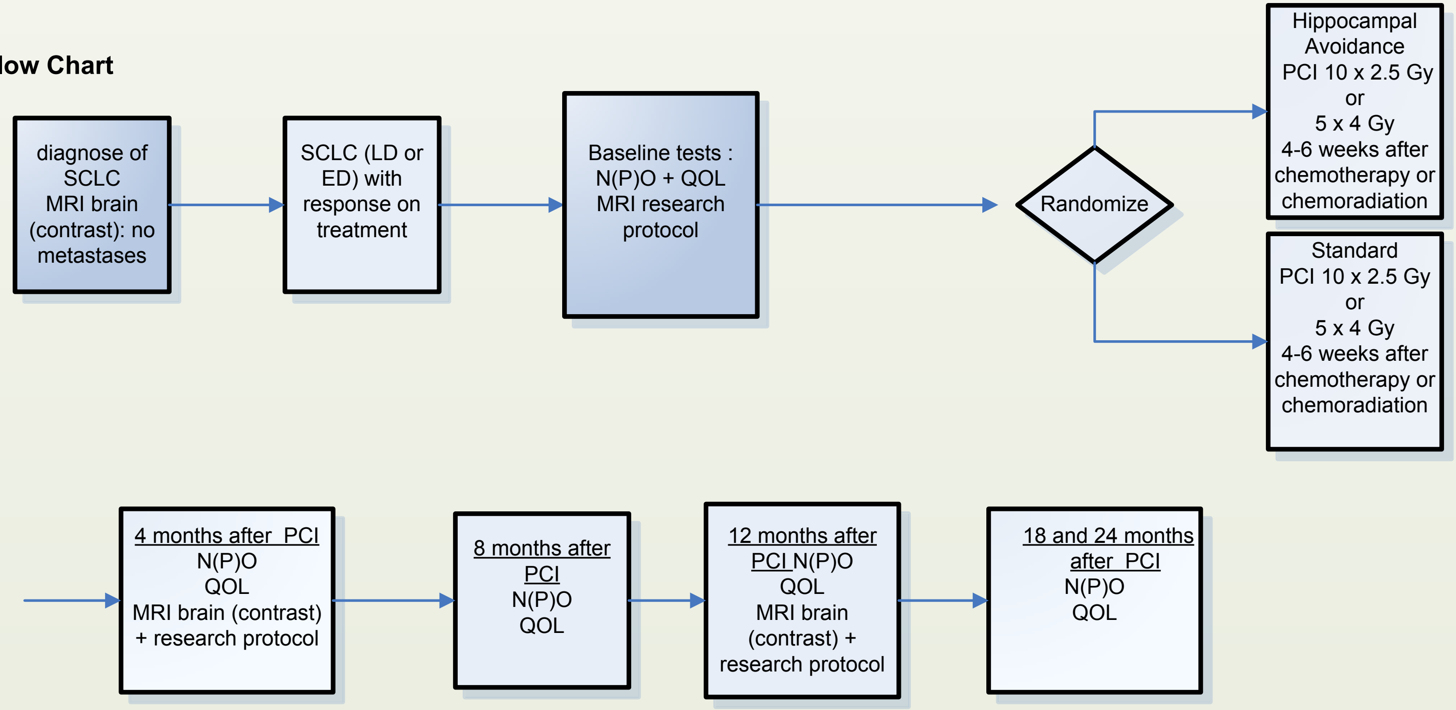
NKI-AVL
Het Nederlands Kanker Instituut
Antoni van Leeuwenhoek Ziekenhuis

Improvement of memory function after Prophylactic Cranial Irradiation (PCI) by avoidance of the hippocampus: A randomized phase III study in small cell lung cancer patients

Dirk De Ruysscher, MD, PhD, on behalf of the HA-PCI working group



Flow Chart



Inclusion criteria

- Patients with either limited disease (LD) or extensive disease (ED) small cell lung cancer (SCLC) candidate for PCI after a partial or complete response to chemotherapy or chemoradiation
- WHO-performance status ≤ 2 (see Appendix IV).
- Sufficient proficiency in Dutch language
- No evidence of progressive extracranial metastatic disease

Exclusion criteria

- Prior radiotherapy to the brain
- Patients receiving any systemic anticancer treatment during PCI
- Pregnancy or lactation

Randomization

- ♦ The patient had chemoradiation or chemotherapy less than 6 weeks prior the randomization
  The patient wil receive PCI within 2 weeks after randomization
- ♦ No signs of progressive disease after chemotherapy♦
- ♦ Signed informed consent

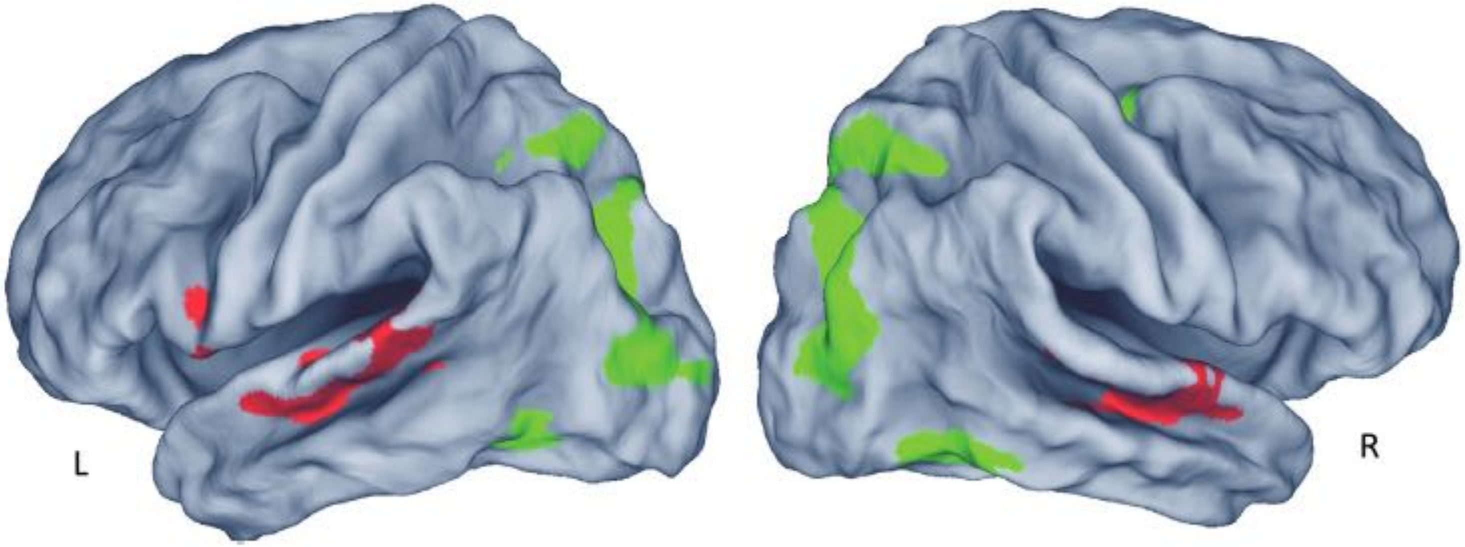
- **Primary Endpoint**

- The total recall score of the Hopkins Verbal Learning Test–Revised (HVLT–R), assessed at 4 months after PCI. A decline in the total recall score of 5 points or greater compared with baseline will be considered a failure.

- **Secondary Endpoints**

- Neurocognitive functioning and QoL, motor function
- Assessment of structural and functional brain abnormalities
- Incidence and location of brain metastases
- Overall survival
- Progression free survival
- Bio-markers (neuro-inflammation)

Single task imaging

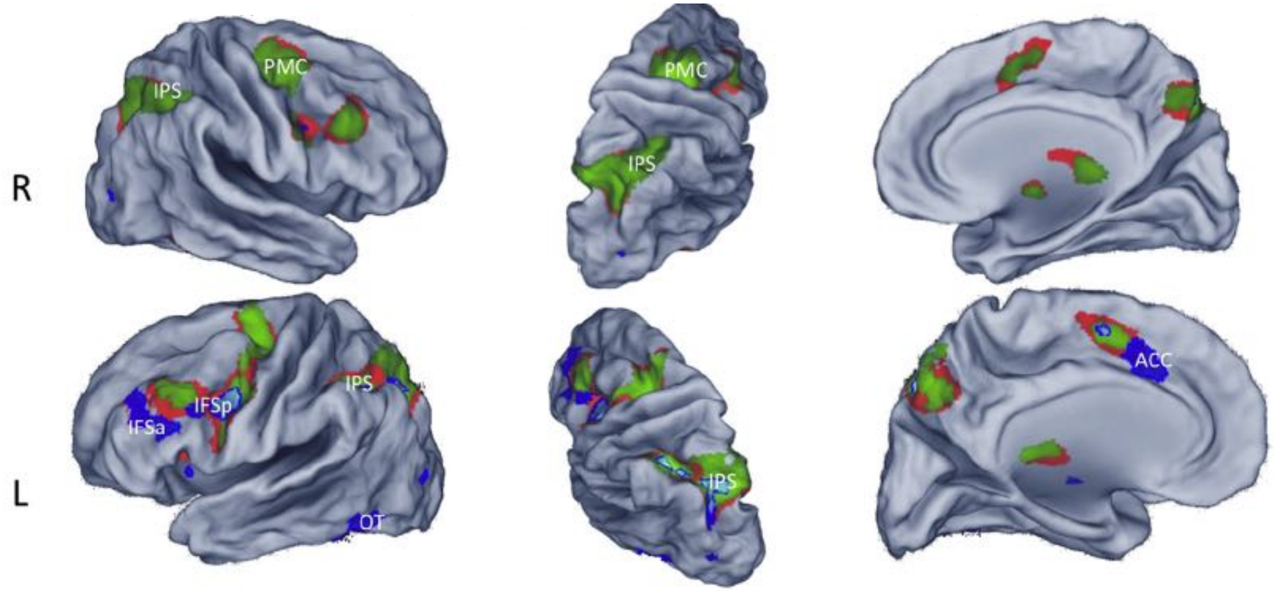


Red significance map: increased activity during the auditory relative to the visual task.

Green significance map: higher activity during the visual relative to the auditory task

Deprez S et al. Neuropsychologia 2013

Dual and multi-task imaging: Significance maps



Green: Higher activity during dual task compared to both single tasks

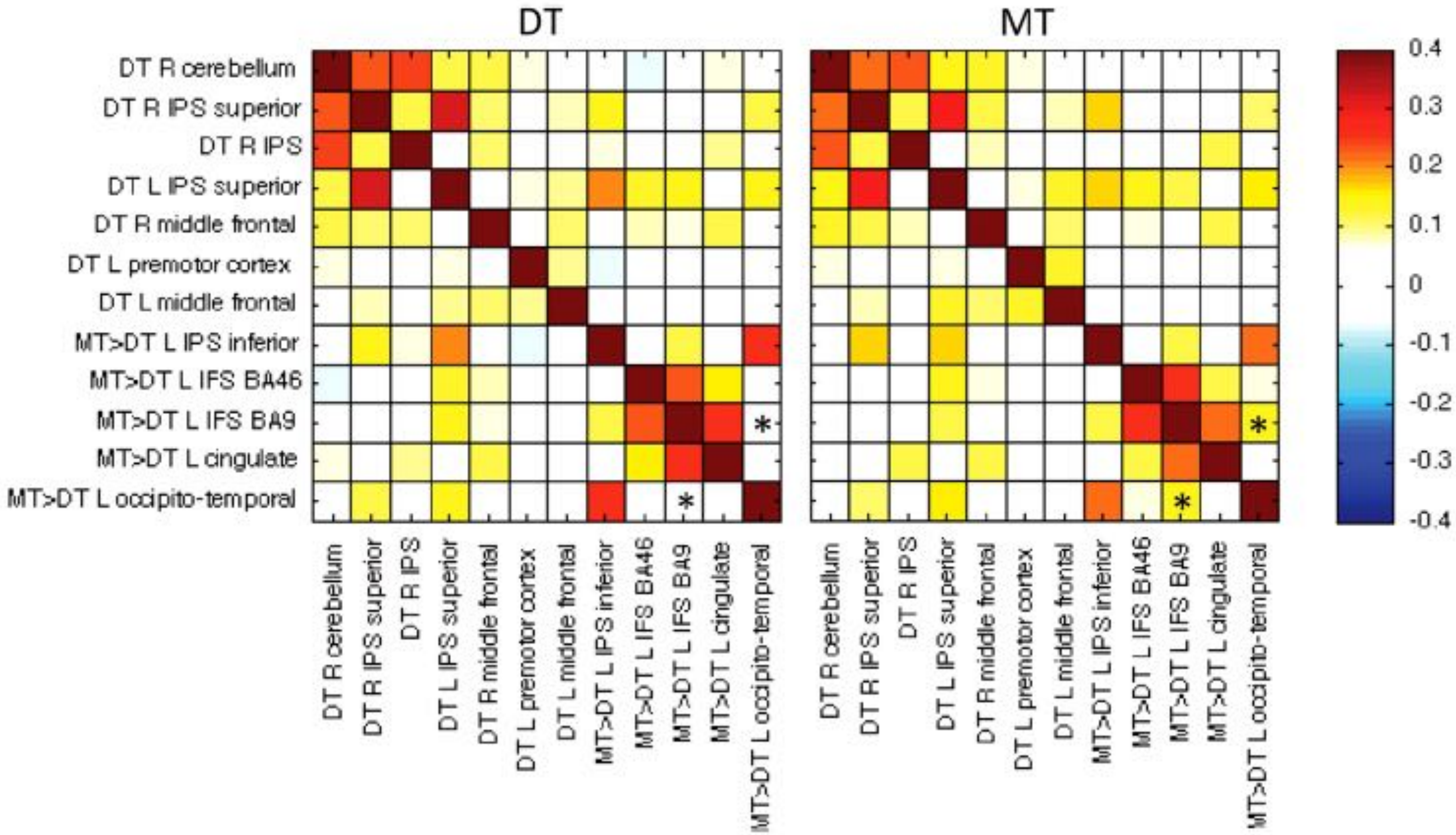
Red: Higher activation during multitask compared to both single tasks

Blue: Higher activation during multitask compared to dual-task

IPS: intra-parietal sulcus; PMC: premotor cortex; ACC: anterior cingulate cortex; OT: occipito-temporal; IFSa: activation in more anterior part of inferior frontal sulcus; IFSp: activation in more posterior part of inferior frontal

Deprez S et al. Neuropsychologia 2013

Functional connectivity maps

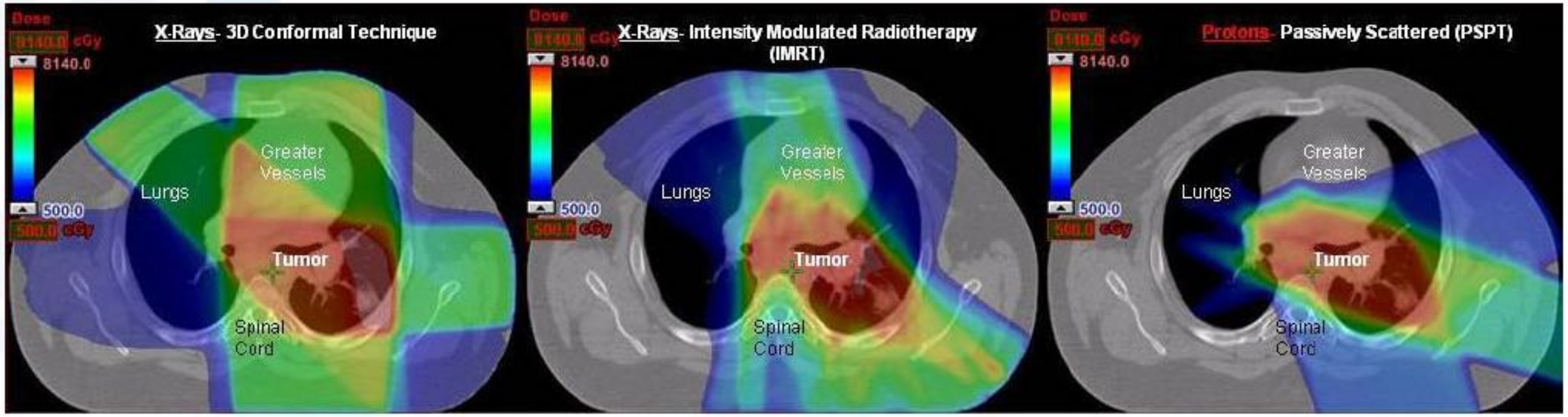


Deprez S et al. Neuropsychologia 2013

Applicable in proton therapy?

Applicable in proton therapy?

Applicable in proton therapy?



MASSACHUSETTS GENERAL HOSPITAL

HARVARD MEDICAL SCHOOL

Dr. Dirk De Ruysscher
IBA visiting professor

De Ruysscher D, Chang J. Sem Radiat Oncol 2013

	PD = 70 Gy		
	Photons		Protons
	3DCRT	IMRT	PSPT
Organs at risk			
Lung			
MLD	18.9 (7.3)[a]	16.4 (5.5)[a]	13.5 (6.2)
Esophagus			
D_{mean}	28.3 (13.9)[a]	26.0 (12.1)	24.4 (13.7)
Heart			
D_{mean}	15.3 (11.6)[a]	14.3 (10.3)[a]	7.6 (7.2)
Patient			
ID	11.0 (5.4)[a]	9.9 (4.4)[a]	6.9 (3.9)

Roelofs E et al. J Thor Oncol 2012

Combining with genetics of the patient and of the tumour

Correlation with genetics?

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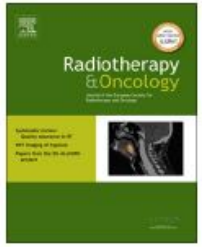

Review

STROGAR – STrengthening the Reporting Of Genetic Association studies in Radiogenomics

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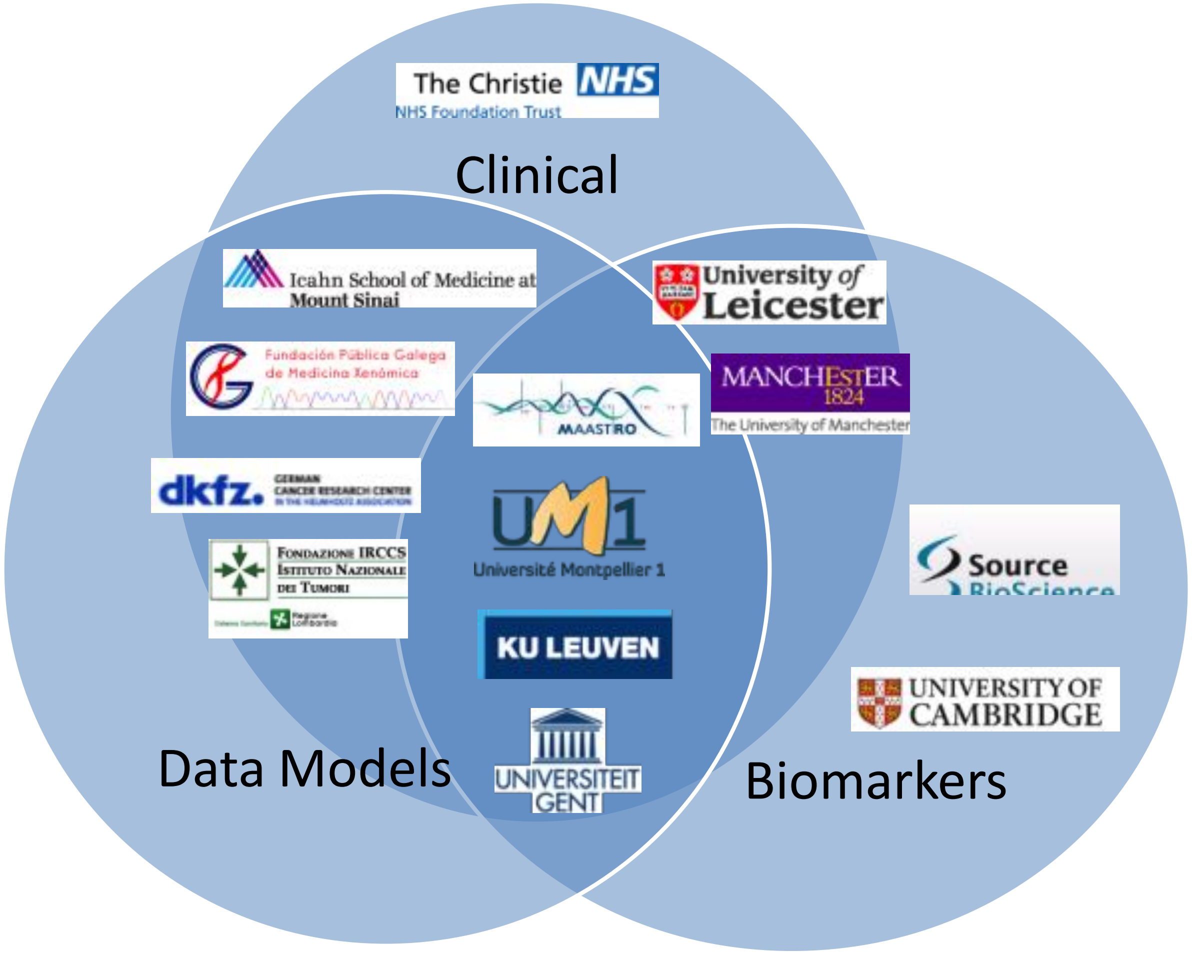
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Data Models
Biomarkers

Correlation of delta HU/ Gy (less multi-factorial than dyspnoea) and genetics

rs2252070 (p=0.006, *MMP13*)
rs2230588 (p=0.009, *JAK1*)
rs12901071 (p=0.009, *SMAD3*)

MMP13 gene= matrix metalloproteinase 13, encoding for collagenase 6; implied in COPD (tissue destruction).

JAK1 gene = essential for signal transduction of many cytokines and cell adhesion; implied in COPD (increased inflammation).

SMAD3 gene = member of the TGF-β superfamily; multifunctional; implied in COPD (inflammation regulation).

De Ruyck, De Ruysscher et al. 2013, work in progress

RADIOSCAPE

A Project of the European Thoracic Oncology Platform (ETOP)

Dirk De Ruysscher, Suresh Senan, Rafal Dziadziuszko, Cecile Le Pechoux, Corinne Faivre-Finn, Solange Peters, Rolf Stahel
on behalf of ETOP collaborators

Applicable in proton therapy?

Great future …