



Phase II study of the efficacy and safety of a radiotherapy dose increase in the treatment of hypoxic lesions identified by F-miso PET/CT in patients with curative non-small cell lung carcinoma [RTEP5 study - *NCT01576796* – PHRC 2011].

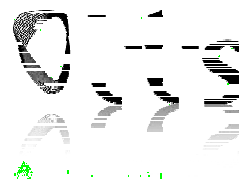
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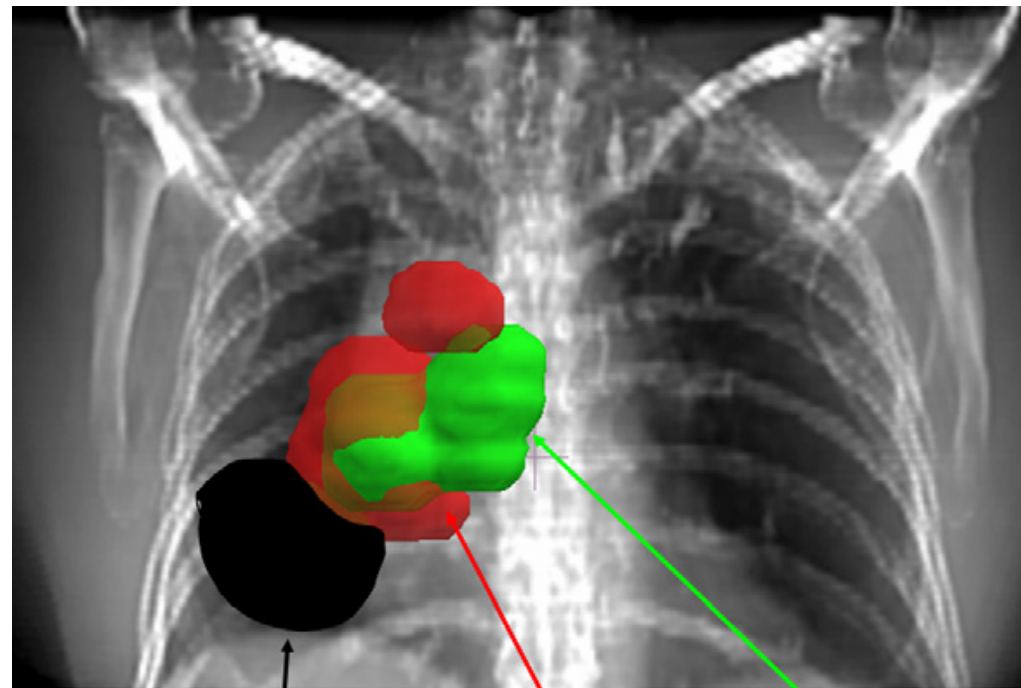
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Computing & data transfert : Romain Modzelewski, PhD



Planning FDG - PET (selective nodal irradiation)

- Reduction of radiation fields
 - ✓ Possibility to **boost** (increase LCR)
 - ✓ Decrease dose in oesophagus, normal lung and myocardium

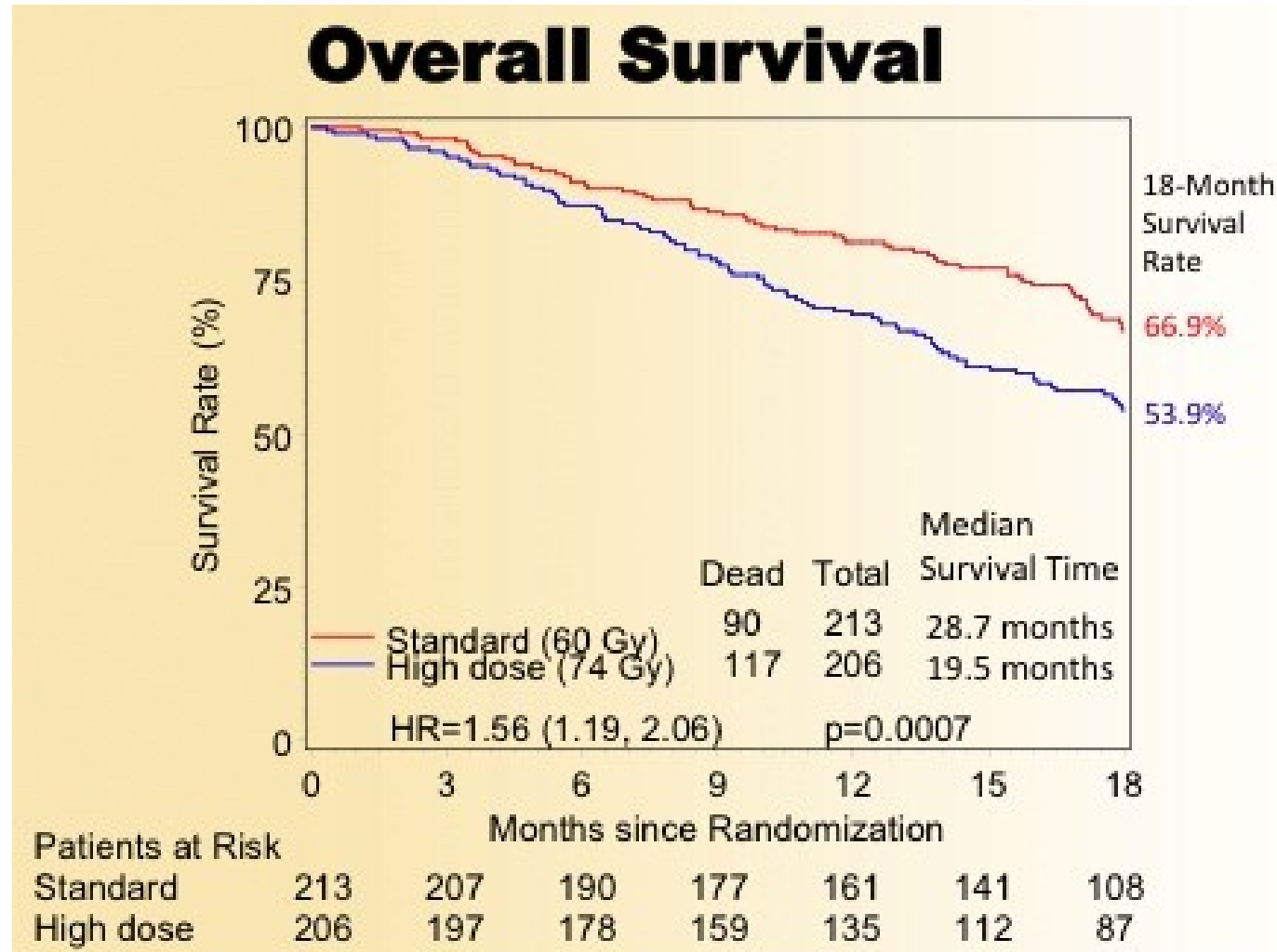


PTV prim. tumour

PTV CT N+

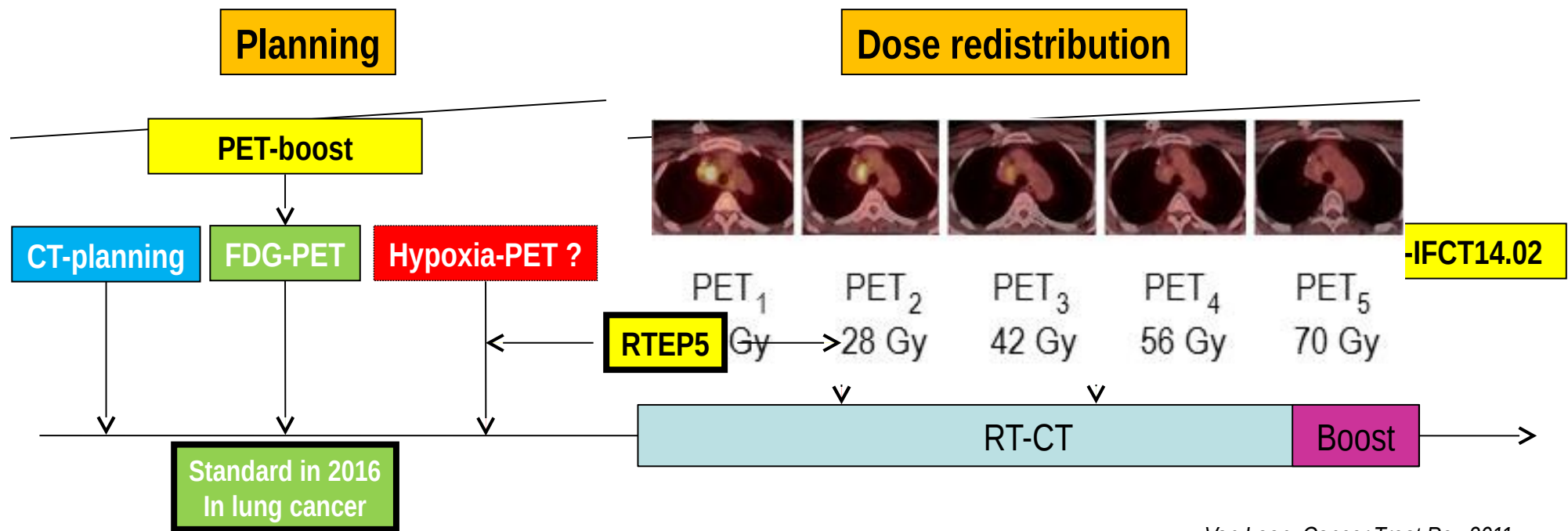
PTV PET N+

Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study

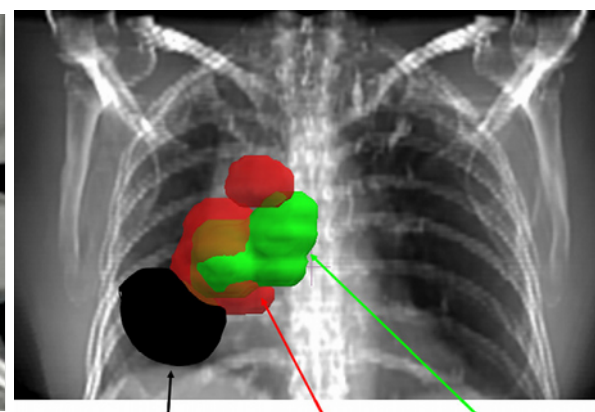
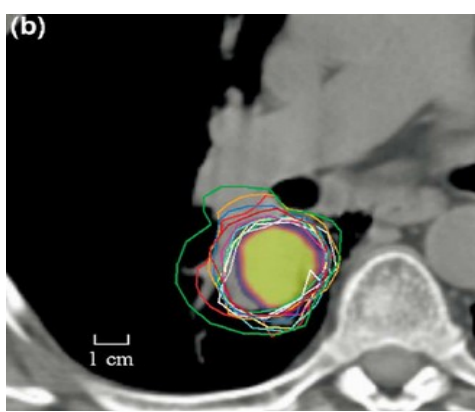
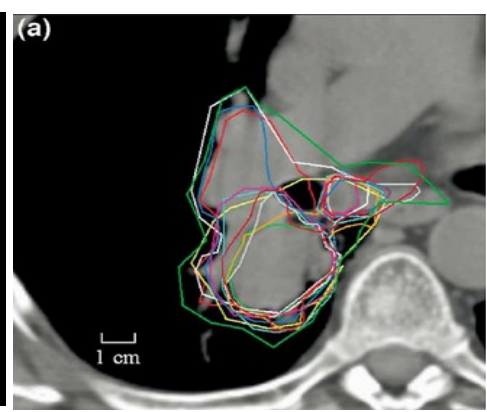
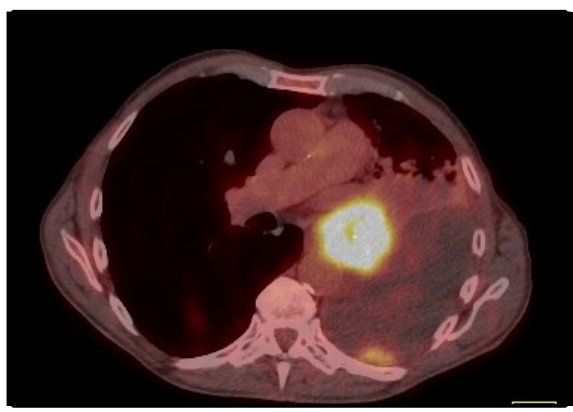


RT-CT standard treatment for stage III NSCLC

Auperin, JCO 2010

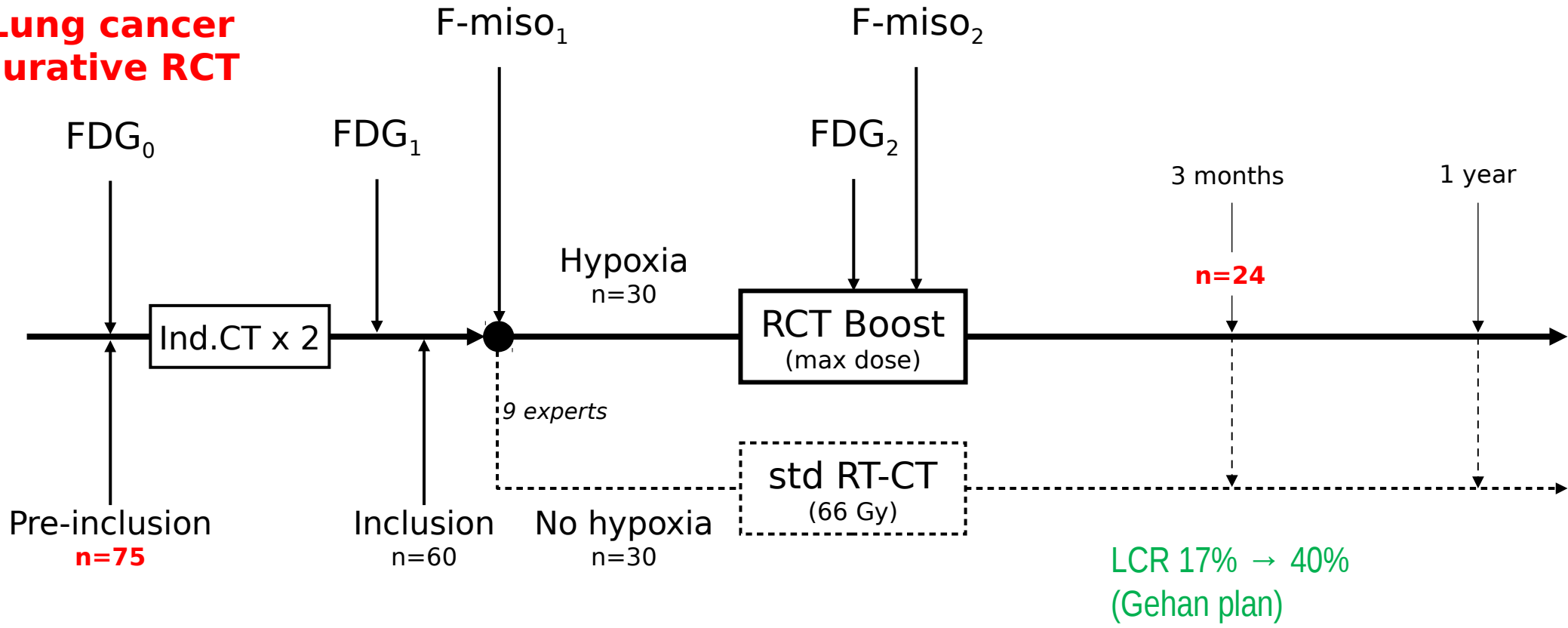


Van Loon, Cancer Treat Rev 2011



PTV prim. tumour PTV CT N+ PTV PET N+

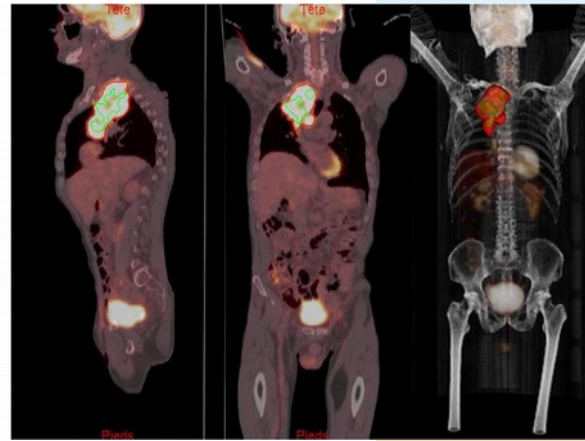
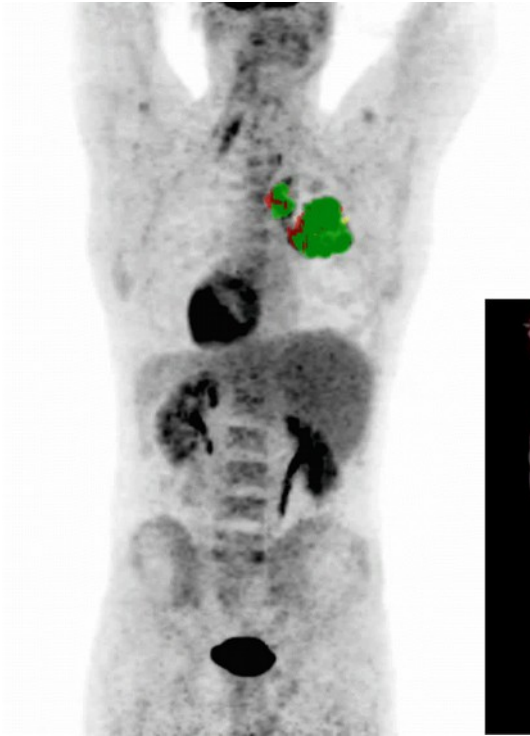
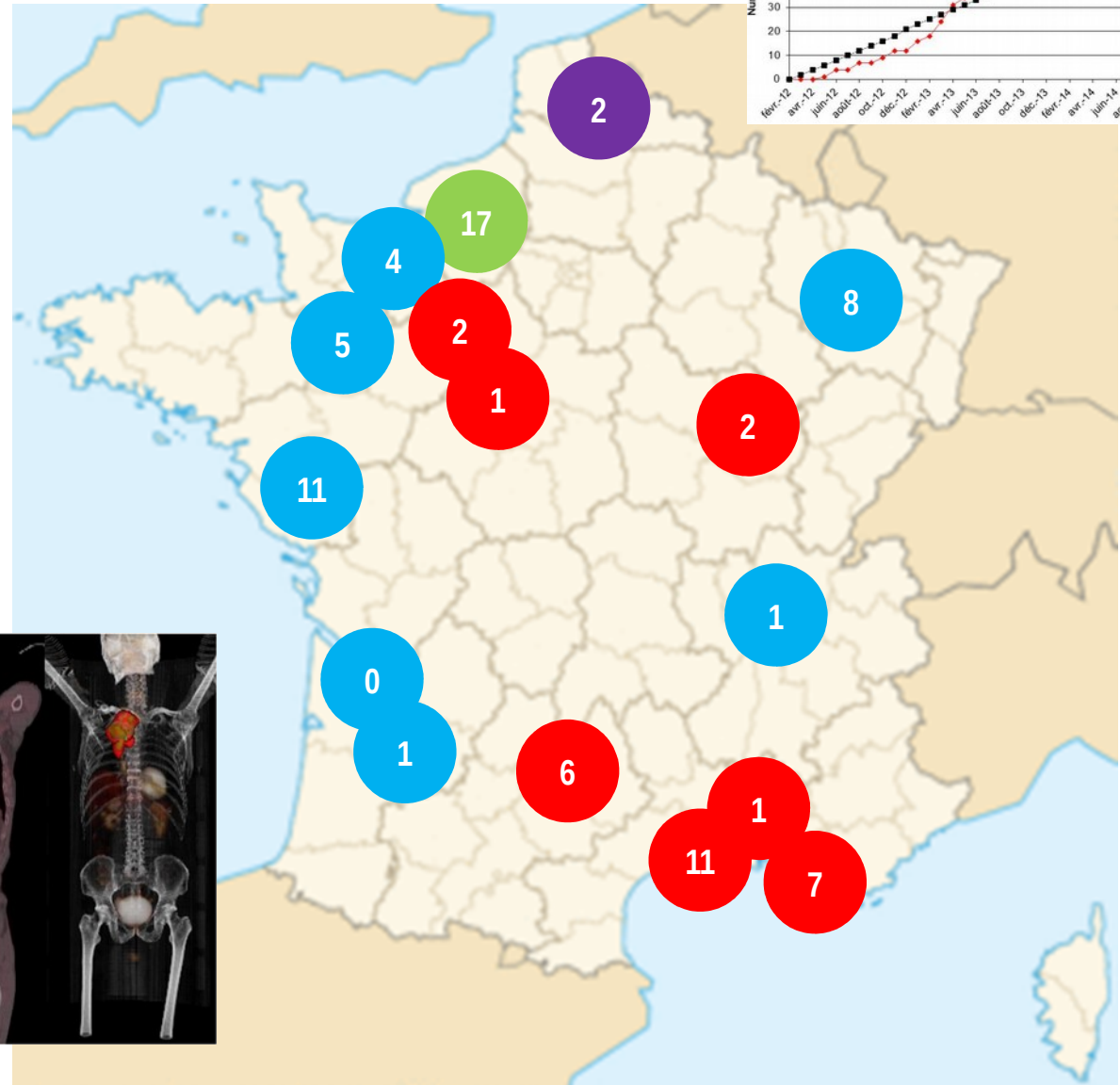
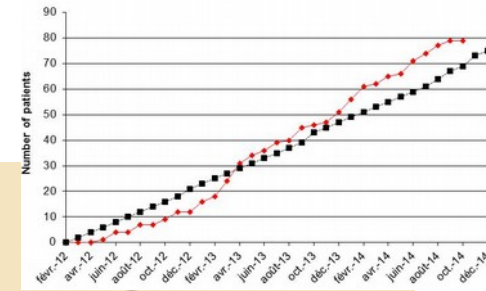
Lung cancer curative RCT



- PHRC 2011
- Multicentric **phase II** study (22 centers open)
- Centralized quality control
- Centralized and validated F-miso analysis and BTV delineation*

79 inclusions in 15/22 french centres

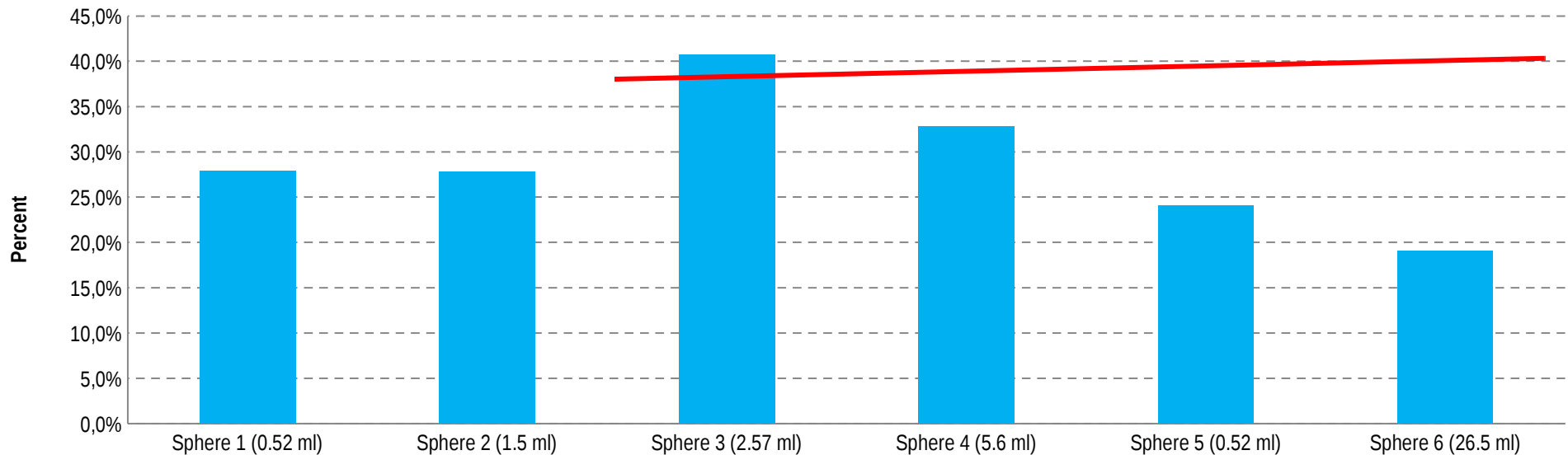
- PET quality control
- BTV delineation
- 9 experts centers
- 15/22 inclusion centers



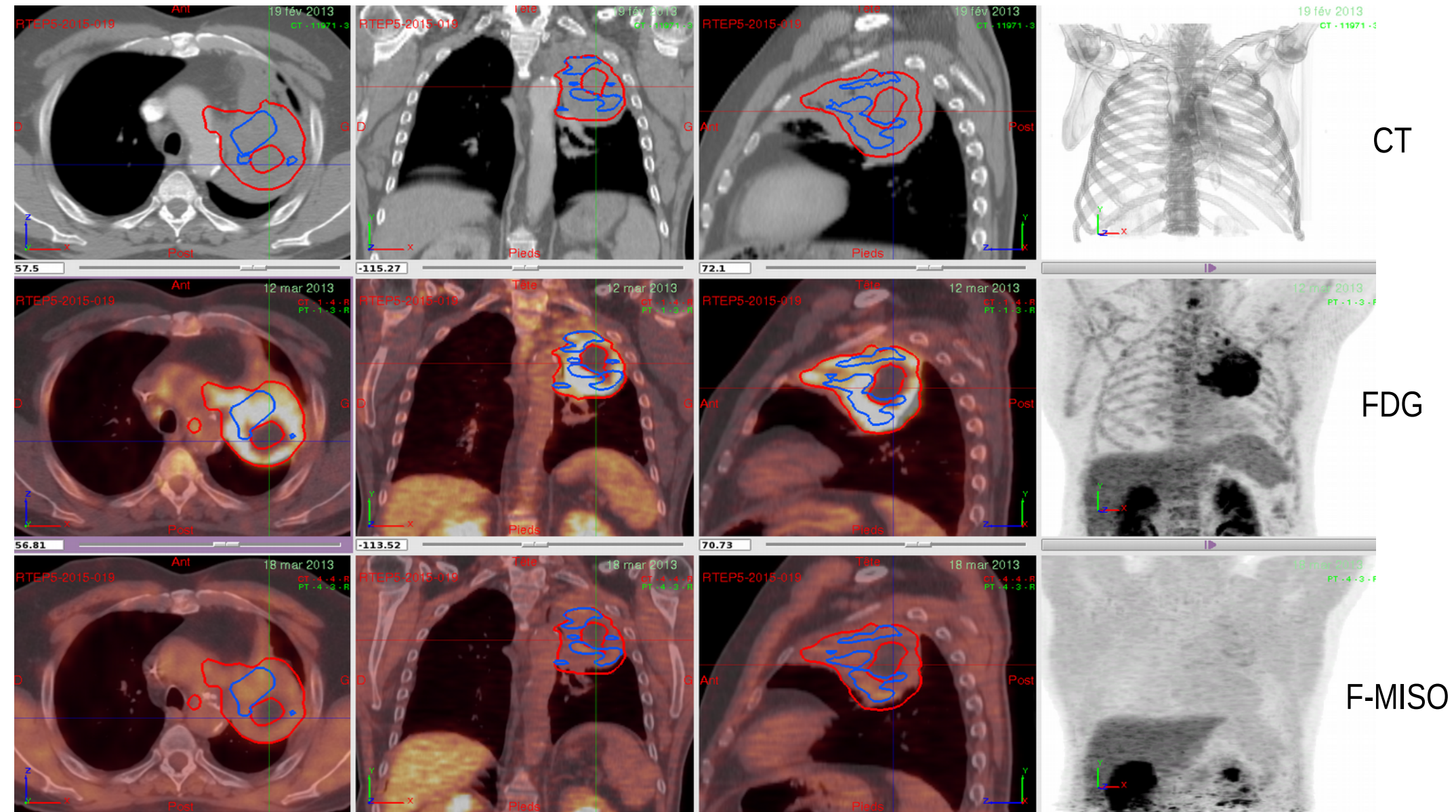
Quality controls of 15/22 PET centers

Test	Frequency	Modality
• Quality controls required by the manufacturer	• Baseline	PET
• Image uniformity	• Quaterly	
• Cross-calibration	• Quaterly	
• Image quality control	• Baseline – After manufacturer maintenance	
• Hounsfield units	• Quaterly	CT

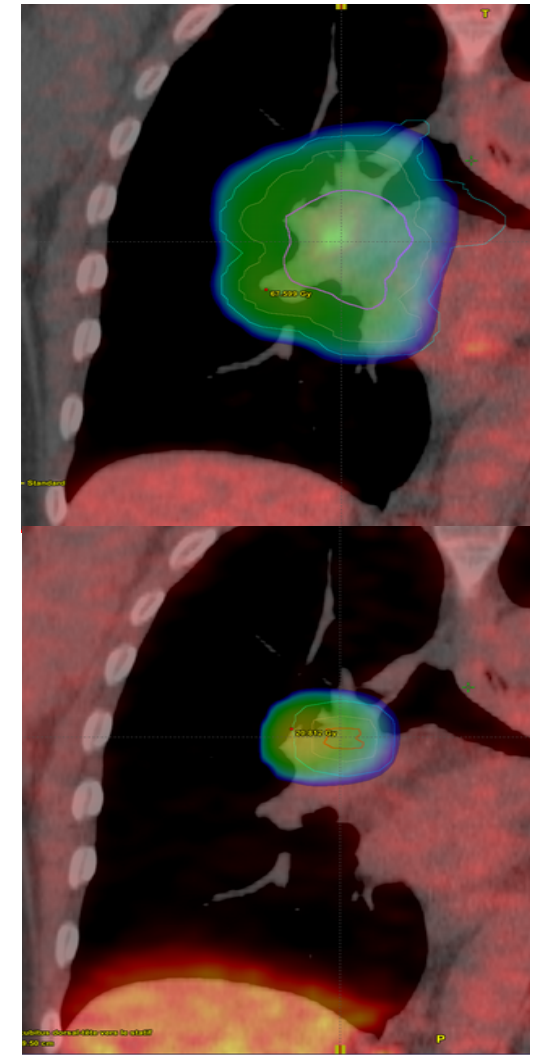
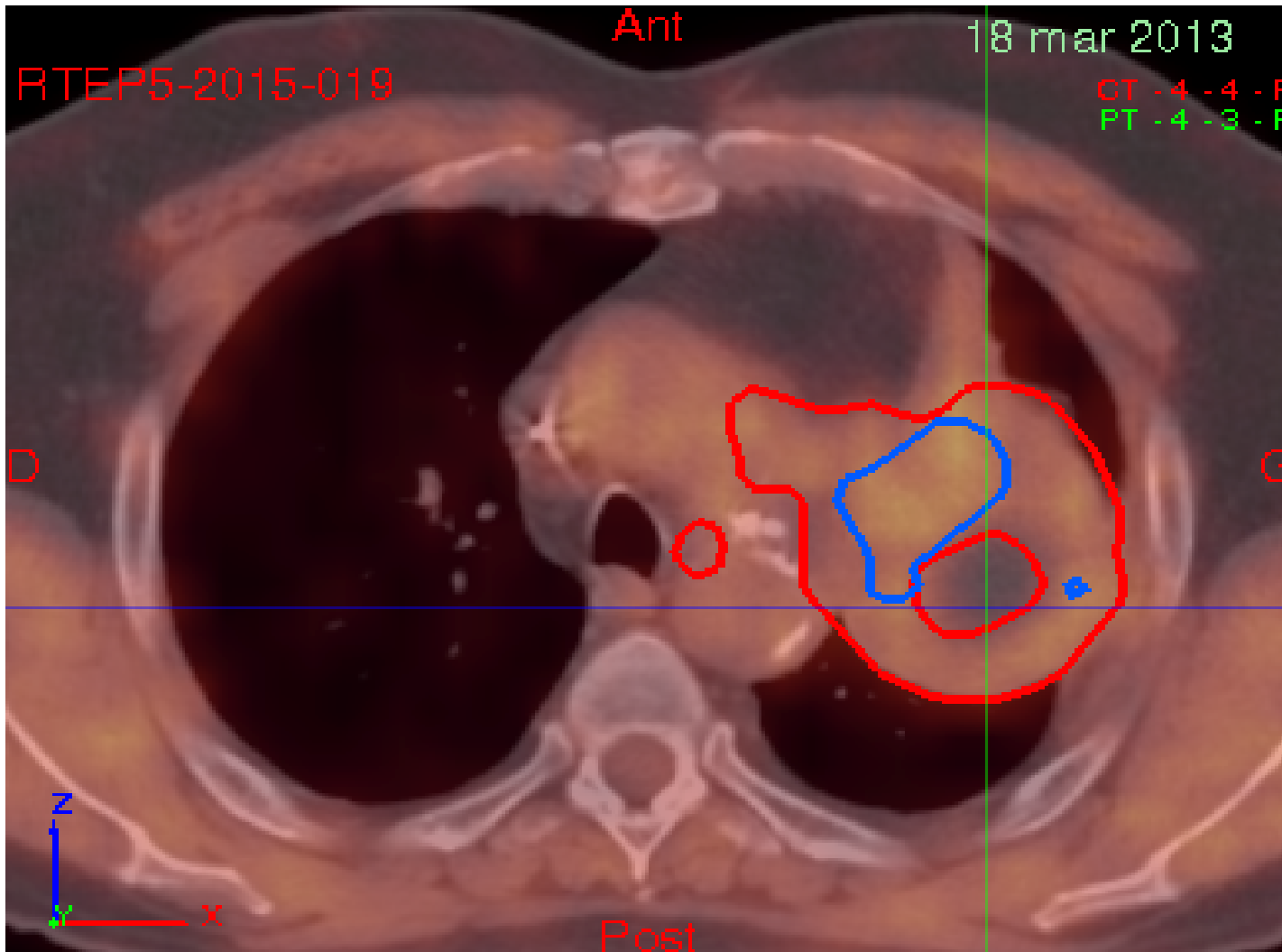
Segmentation relative error for each sphere



Centralized : BTV_{metabolism} (FDG) - BTV_{hypoxia} (f-miso)

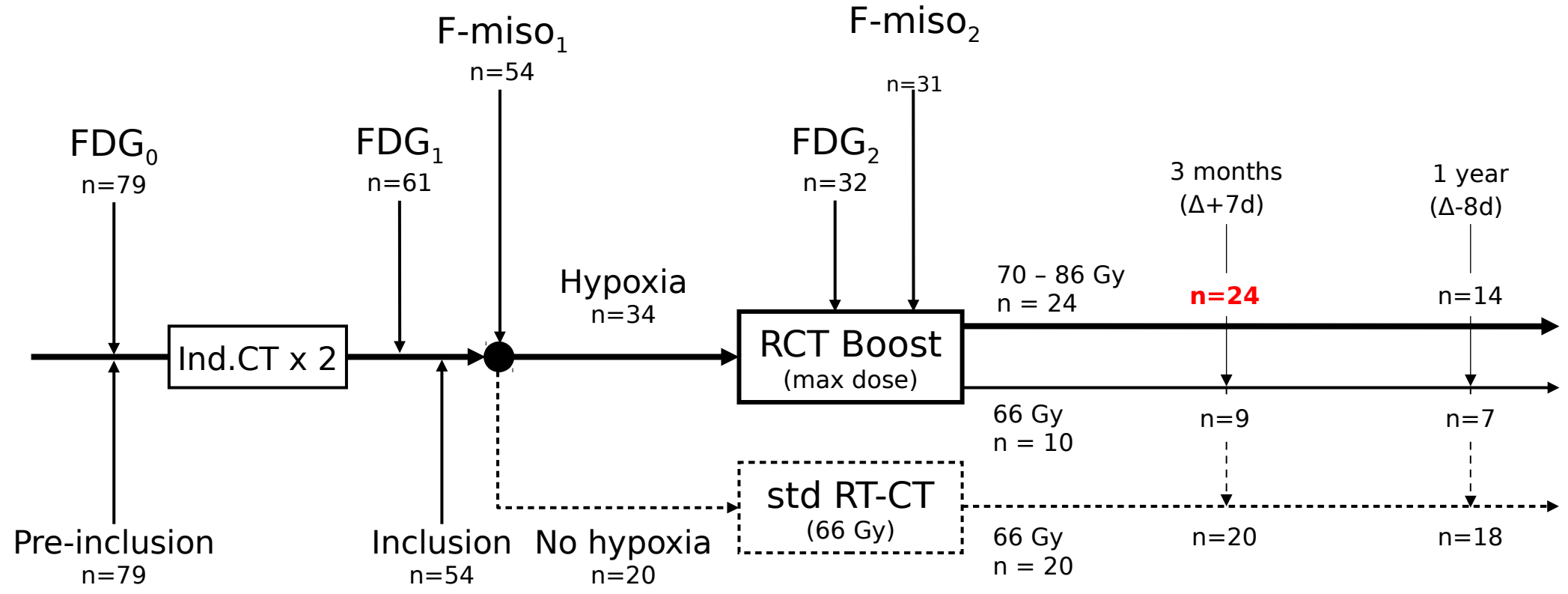


RTEP5 : Boost on pre-treatment F-miso PET

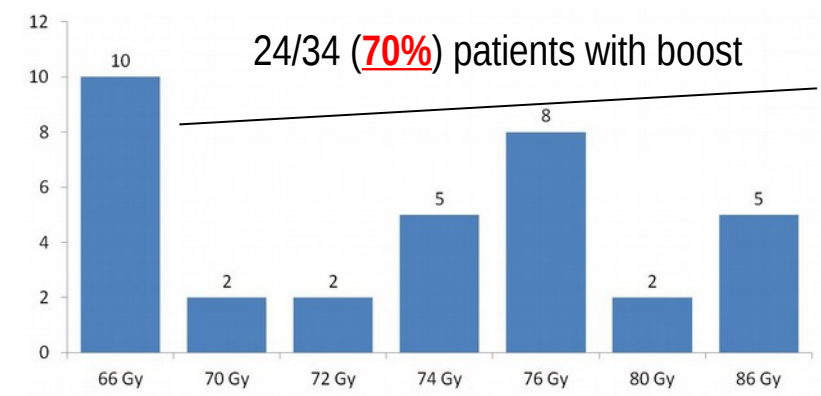


66 Gy + boost 20 Gy

Flowchart



-inclusions
 eligibility regarding FDG₁ (**including 9 M+ [11%] on FDG₁**)
 procedures (inadapted induction CT, technical or logistic problems)
 ent decision
 estigator decision



Descriptive data

	Hypoxia (n=34) - Trial arm			No hypoxia	Total
	Total	Boost	66 Gy	66 Gy	
	n=34	n=24	n=10	n=20	n=54
Sex F/M (n)	6/28	4/20	2/8	1/19	7/47
Age mean \pm SD	59.5 \pm 8.6	60.5 \pm 8.4	57.2 \pm 9.2	61.4 \pm 5.7	60.3 \pm 7.7
Height (cm \pm SD)	169.7 \pm 9.3	171.1 \pm 10.1	166.6 \pm 6.1	170.3 \pm 8.1	170.0 \pm 8.8
Weight (Kg \pm SD)	73.2 \pm 14.6	71.5 \pm 12.3	77.2 \pm 19.2	76.5 \pm 12.1	74.4 \pm 13.7
Histology (n)					
SCC	17	14	3	9	26 (48)
ADC	11	6	5	10	21 (39)
Undifferentiated	4	4	2	1	7 (13)
Tumour stage (n)					
IB	1	1	-	1	2
IIA	-	-	-	1	1
IIB	2	1	1	0	2
IIIA	17	13	4	7	24
IIIB	13	8	5	11	24
IV	1	1	-	-	1
RT Dose (Gy \pm SD)	73.9 \pm 6.7	77.1 \pm 5.2 *	66 \pm 0	66 \pm 0.4	71 \pm 6.5

* $p < 0.001$ vs 66 Gy arms

PET data

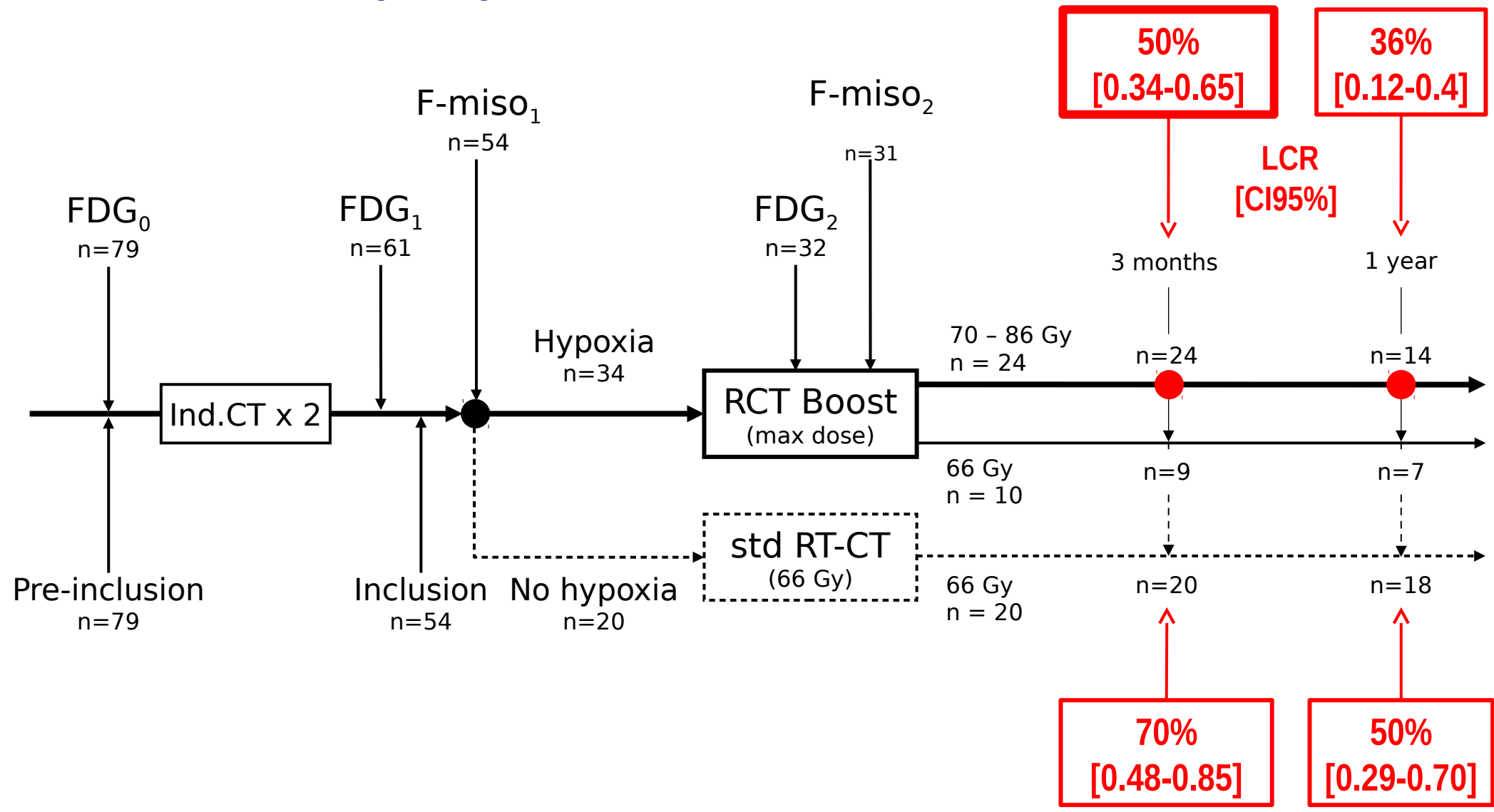
	Hypoxia (n=34) - Trial arm			No hypoxia		
	Total	Boost	66 Gy	66 Gy	Total	
	n=34	n=24	n=10	n=20	n=54	p
FDG-SUV_{max}						
PET1 (n=54)	14.5 ± 9.3	13.8 ± 7.8	16.4 ± 12.4	8.4 ± 9.0	10.0 ± 0.7	0.021
PET2 (n=32)	9.4 ± 6.1	10 ± 7.1	8.1 ± 4.0)	-	-	
Δ(%)	-32 ± 26	-27 ± 29	-44 ± 17	-	-	
FDG_{BTV} @ 40% SUV_{max} (cc)*						
PET1 (n=54)	55.4 ± 72.2	58.9 ± 84.8	46.8 ± 24.9	27.3 ± 23.9	45.0 ± 60.3	0.026
PET2 (n=32)	36.1 ± 44.6	39.9 ± 52.5	27.4 ± 17.6	-	-	
Δ(%)	-10 ± 226	-27 ± 271	-26 ± 41	-	-	
F-miso-SUV_{max}						
PET1 (n=54)	2.5 ± 0.7	2.4 ± 0.6	2.7 ± 0.9	1.4 ± 0.5	2.1 ± 0.8	<0.001
PET2 (n=31)	1.9 ± 0.5	1.8 ± 0.4	2.2 ± 0.6	-	-	
Δ(%)	-17 ± 24	-21 ± 20	-8 ± 39	-	-	
F-miso_{BTV} @ 1.4 SUV (cc)*						
PET1 (n=54)	33.5 ± 52.2	34.1 ± 58.1	31.9 ± 37.9	-	-	
PET2 (n=31)	20.9 ± 34.6	18.9 ± 37.4	25.4 ± 28.9	-	-	
Δ(%)	-24 ± 75	-20 ± 84	-34 ± 44	-	-	

* Methodology of BTV measurement validated (Thureau, JNM 2013)

Toxicity

Acute Adverse events [3 months (+7d)]	Hypoxia (n=34) - Trial arm						No hypoxia		
	Boost (n=24)			66 Gy (n=10)			66 Gy (n=20)		
	G1&2	G3	G4&5	G1&2	G3	G4&5	G1&2	G3	G4&5
Asthenia	5			6	1		10		
Pain	2			1			4		
Thoracic pain	5			2					
Dysphagia	17	1		6	3	1	11	4	
Dyspnea	10			3	1		6		
Hemoptysis	1					1	1		
Dry skin or pruritus	15			1	1		9		
Anorexia	3			2			3		
Pneumonitis		2	1				3		
Cough or expectoration	16			6			11		
Hematologic toxicities	2	1		1	1		4	2	1
Chemotherapy toxicities	25	3		7	5		12	2	1
Others toxicities	10						5		
Late Adverse events [1 year (-8d)]	Hypoxia (n=34) - Trial arm						No hypoxia		
	Boost (n=24)			66 Gy (n=10)			66 Gy (n=20)		
	G1&2	G3	G4&5	G1&2	G3	G4&5	G1&2	G3	G4&5
Asthenia	2			1			2		
Pain	1			1	1				
Thoracic pain	1			1					
Dysphagia									
Dyspnoea	5			3			4		
Dry skin or pruritus	1						1		
Pneumonitis							1		
Peripheral neuropathy							1		
Cough or expectoration	5			5			1		
Chemotherapy Toxicities	3						1		
Others toxicities	2						1		

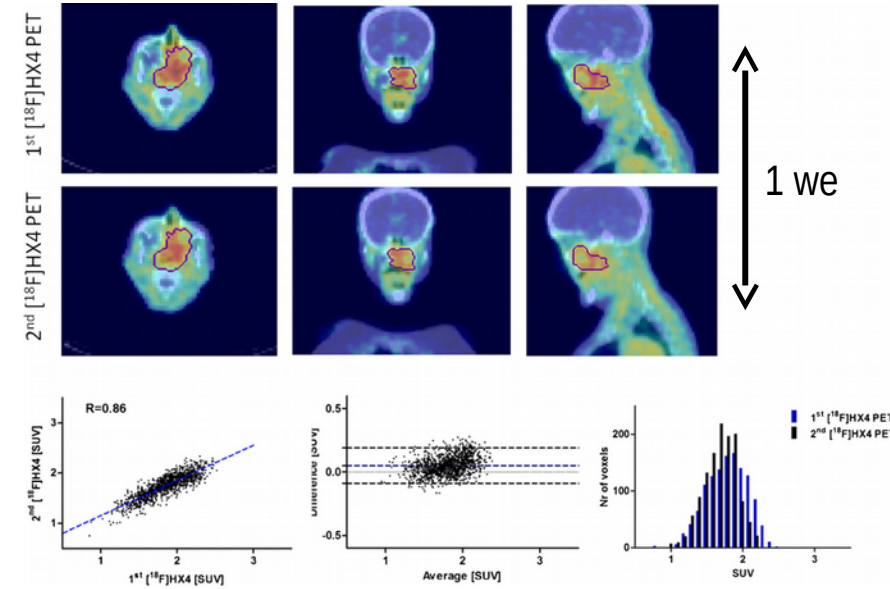
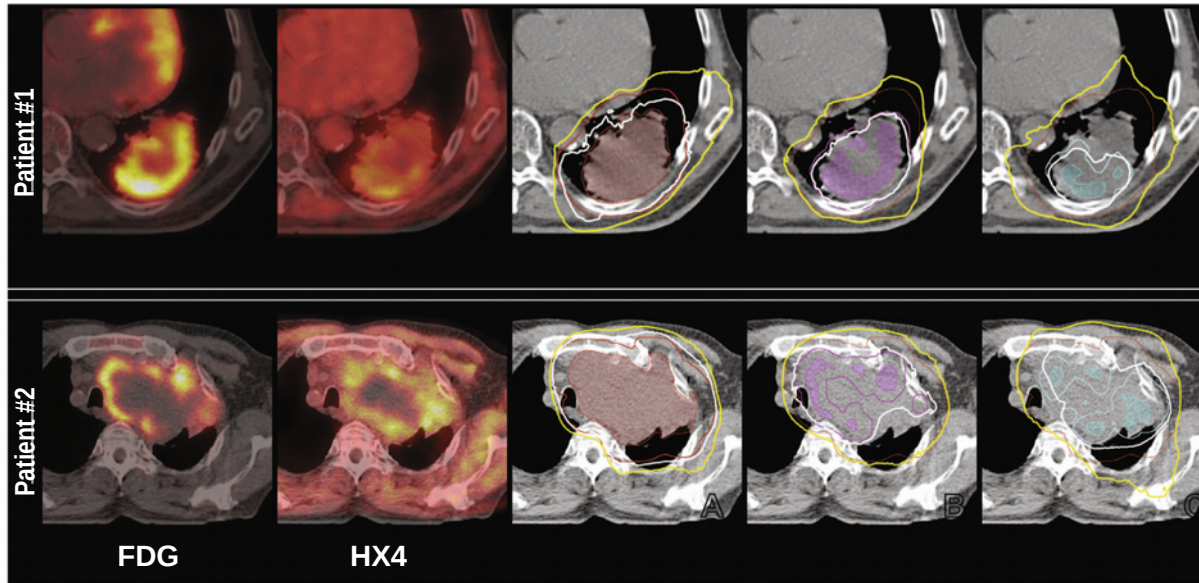
LCR - Primary objective



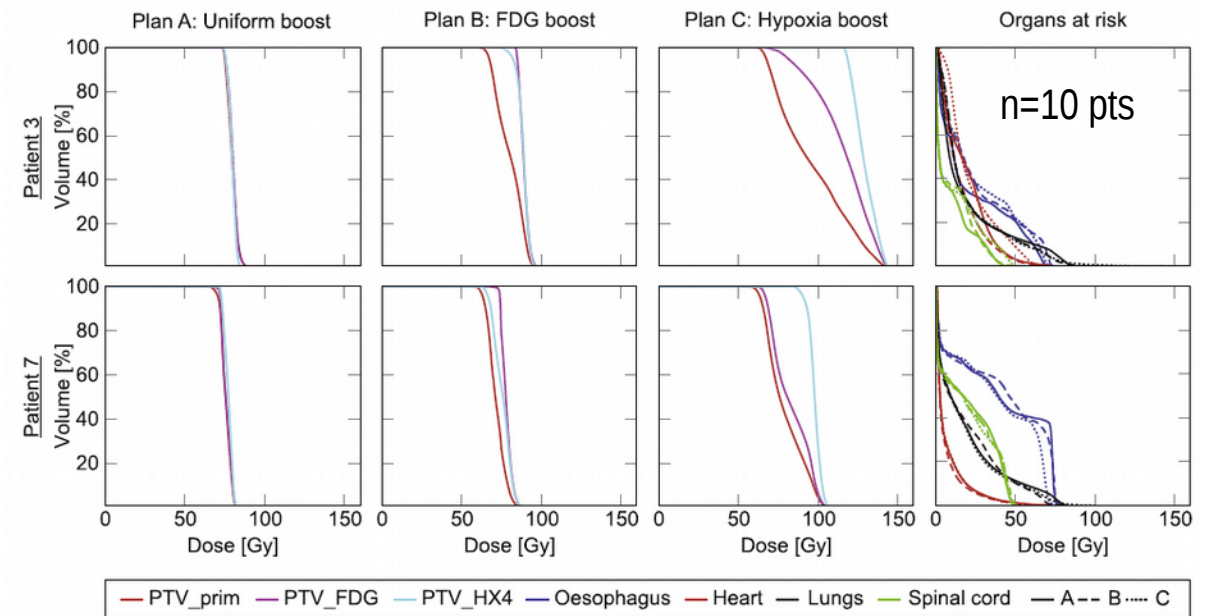
FDG & HX4 PET for RT planning in lung cancer

n=19 pts

1 we



A : Uniform boost
B : FDG boost
C : Hypoxic boost



RTEP5 – Lung RT-boost based on F-miso PET

- Largest series of RT-boost based on F-miso PET
 - ✓ Ongoing phase II-III RTOG1106 / AFRINN6697
- Could be done in multicentric with validated methodology
- Feasible
- Safe: no grade 4&5 toxicity
- LCR
 - ✓ 50% @ 3 months
 - ✓ 36% @ 1 year

- Phase III study (~300 pts) ?

Acknowledgements



QuantIF (EA4108 – FR CNRS)

- ✓ **Dr S.Thureau**
- ✓ **R.Modzelewski**
- ✓ Pr B.Dubray
- ✓ Mme I.Gardin
- ✓ Pr S.Ruan
- ✓ Dr P.Bohn
- ✓ Mr S.Hapdey
- ✓ Mr JF.Ménard
- ✓ Mme C.Petitjean
- ✓ Dr S.Becker
- ✓ Dr A.Edet-Sanson
- ✓ Pr C.Savoie-Collet
- ✓ Dr M.Salaun
- ✓ Pr L.Thiberville
- ✓ Mr J.Lapuyade-Lahorgue

Readers

- ✓ Claire Houzard
- ✓ Philippe Fernandez
- ✓ Pierre Olivier
- ✓ Amandine Pallardy
- ✓ Hélène Gauthier
- ✓ Anne Devillers
- ✓ Frederic Courbon
- ✓ Nicolas Aide
- ✓ Pierre Vera

Quality control

- ✓ **Sebastien Hapdey**
- ✓ **Maximilien Vermandel**

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Statistics - Methodology

- ✓ **Pr Ph.Chaumet-Riffaud**

Clinical research Unit

- ✓ **Mr O.Rastelli, Mme L.Burel**
- ✓ Mme D.Richard
- ✓ Dr LF.Pepin

