Place de l'imagerie fonctionnelle en radiothérapie thoracique

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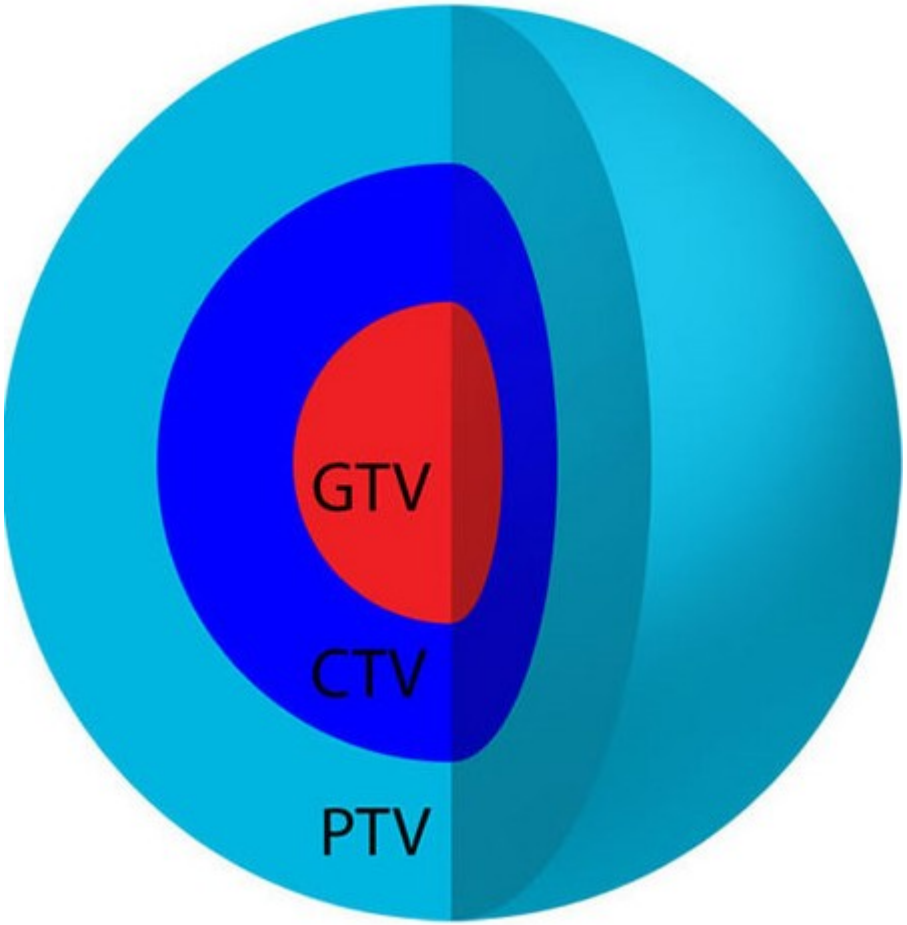
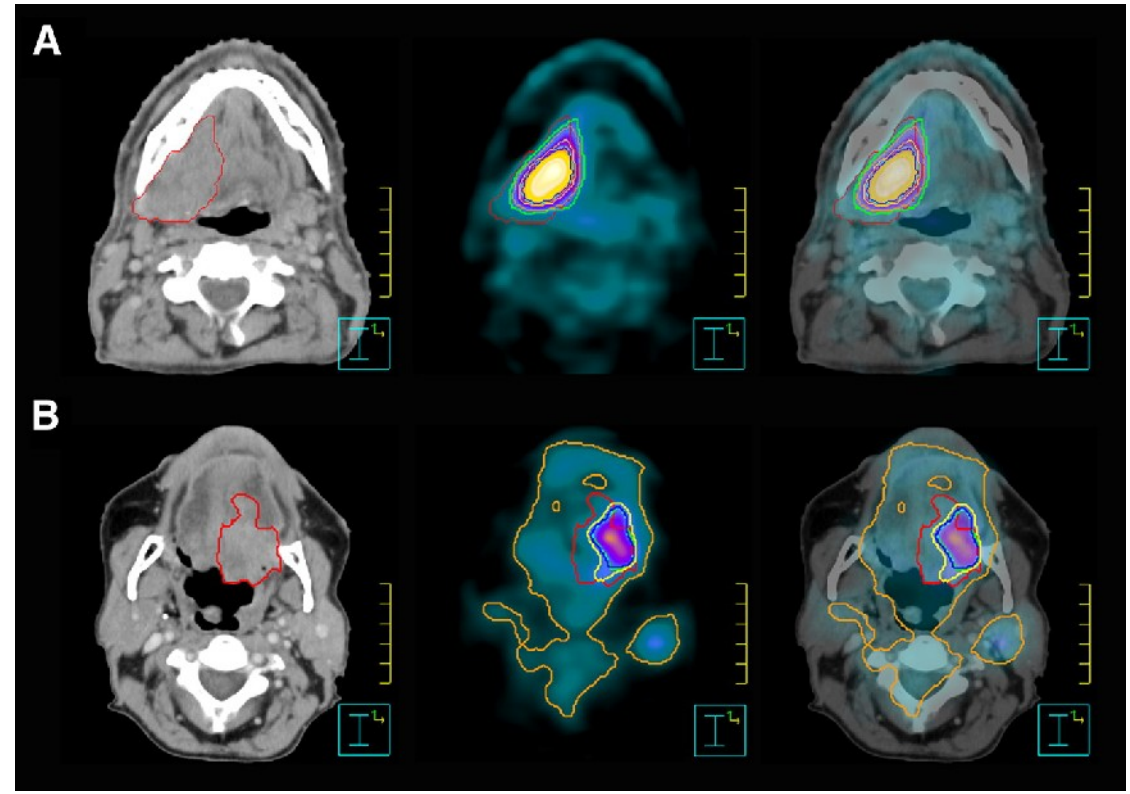
Quant.IF (EA4108 – FR CNRS 3638)

Study	Organ	Pts	PET	State	Center	Tracers	Publications
TEP-TDM+	Lymphoma (model)	30	60	Closed	Rouen	FDG	EJNMMI 2008 QJNM 2011 R&O 2013
RTEP1	Lung	12	72	Closed	Rouen	FDG	R&O 2012
RTEP2	Lung	77	266	Closed	Multicentric	FDG	EJNMMI 2014
RTEP3	Oesophagus	90	180	Closed	Multicentric	FDG	EJNMMI 2013 EJNMMIr 2014
RTEP4	Lung	5	30	Closed	Rouen	FDG/FLT/Miso	R&O 2012
VoSeTep	Breast (lung model)	30	30	Closed	Rouen	FDG	R&O 2014
RTEP5	Lung	75	195	Recruiting	Multicentric	FDG/Miso	JNM 2013
Calmette	Lung	100	300	Recruiting	Rouen	FDG	
RTEP6	*Lung*	*20*	*60*	*Project*	*Rouen-Bxl*	*Miso/Faza*	
RTEP7	*Lung*	*150*	*300*	*Project*	*Multicentric*	*FDG*	
Mosart	*Lung – H&N*	*700*	*2000*	*Project*	*European*	*FDG/Faza*	
Total		**419**	**1133**				

J John, peintre américain

ICRU 83





GTV **BTV** **?**

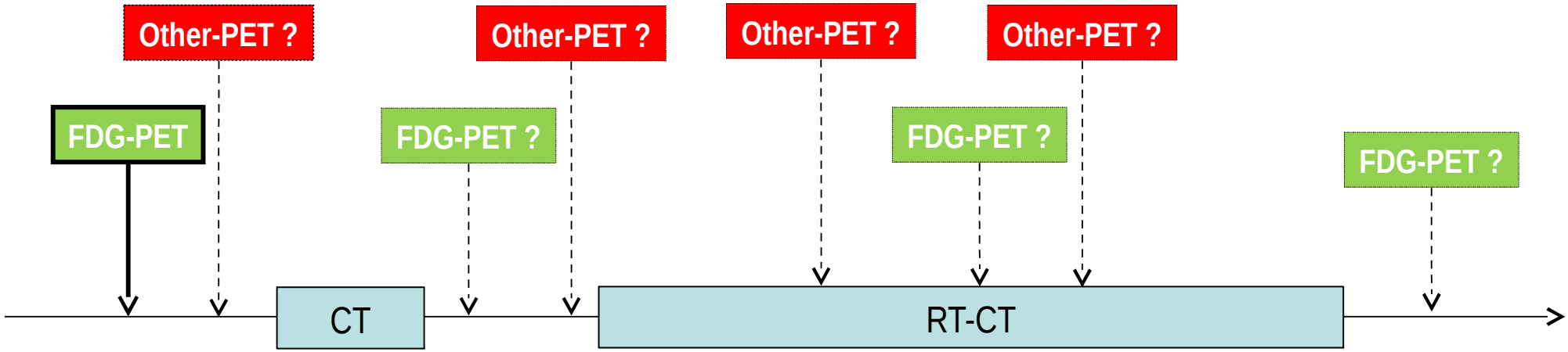
Troost, JNM, 2010

TDM

TEP

PET/CT for therapy planning in **lung** cancer

- RCT standard for stage III NSCLC (Auperin, JCO 2010)
- FDG-PET is a **standard** for therapy planning in 2015



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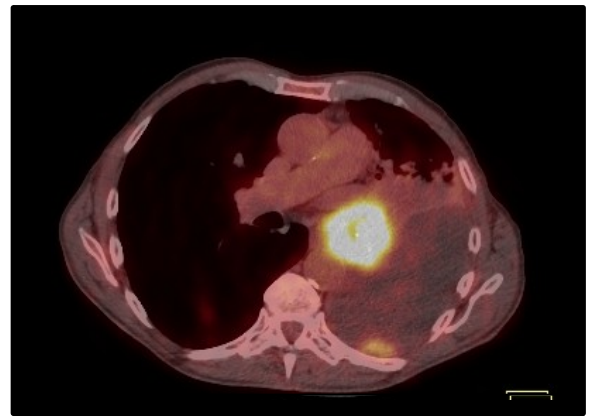
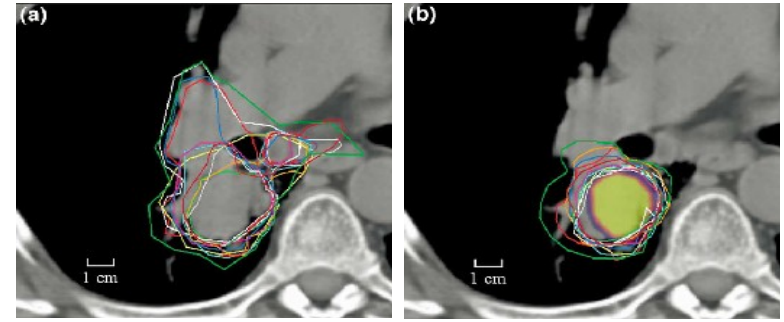


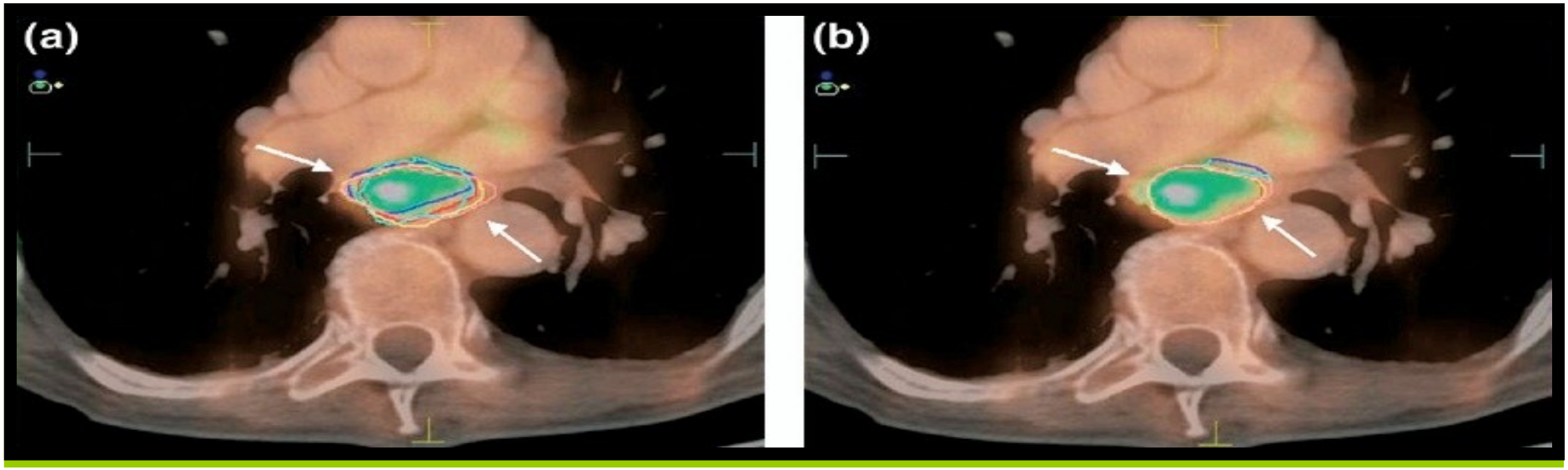


Caldwell, IJROBP 2001 ; Van Baardwijk, IJROBP 2007 ; Roel IJROBP 2006

Nestle, Radioth & Oncol 2006 ; Gerbaudo Eur J Radiol 2007

Rôle de la TEP-FDG dans le planification de la RT

- Comparaison délinéation selon CT ou TEP
  - ✓ GTVCT: 2.31 [1.06 – 7.66]
  - ✓ GTVFDG: 1.56 [1.09 – 2.77]



Caldwell, IJROBP 2001 *Van Baardwijk, IJROBP 2007*

Irradiation des aires ganglionnaires suspectes (IFI) ou irradiation prophylactique(ENI)

N = 200	IFI (68 - 74 Gy)	ENI (60 – 64 Gy)	p
Pneumopathie	17 %	29 %	0.04
contrôle local à 5 ans	51 %	36 %	0.03
Rechute ganglionnaire à distance	7 %	4 %	0.35
Rechute des aires initialement envahies	38%	55 %	0.02
Survie global à 2 ans	39 %	26 %	
à 5 ans	25 %	18 %	0.2

- ✓ Stade III inoperable, sans TEP, ∅ ≤ 6 cm, SC -, pleura –
- ✓ IK ≥ 80, perte de poids < 10 %
- ✓ 4 – 6 cyclesCT concomitante à base de CDDP

Yuan AJCO 2007

Volumes déterminés par le TEP-FDG

- 44 pts, CPNPC I-III, 10/44 down-staging par la TEP
  - ✓ Dose à 64.8 Gy (1.8/j)
  - ✓ GTV = tumeur + ganglions en TEP-FDG
  - ✓ Récidive ganglionnaire
  - ✓ Récidive en dehors du CTV (sans récidive locale)

- 18 récidives locales (41%) à 16 mois
- 1 seule récidive en dehors du champ initial chez un pt N0 en TEP et CT

Recurrences	No. of patients (%)
None	26 (59)
In-field	10 (23)
Exclusively in-field	5
In-field and distant	5
Isolated nodal	1 (2)
Nodal (outside of CTV) along with local or distant failure	2 (4.5)
Distant only	7 (16)
Brain only	1

De Ruysscher, IJROBP , 2005; Belderbos IJROBP 2006

Which data?

Table 1
Studies included in the review that reported on the risk of ENF (elective nodal failure) in patients staged with or without PET.

Study: First author [Ref.]; type of the study	Number of patients evaluated	Number of ENF (%)	Details on treatment	Patient/tumor characteristics	Median follow-up [in months]; unless otherwise stated
Patients staged without PET					
Lao [23]; prospective	23*	0 (0)	SBRT**	T1–T2N0	20 months
Sloman [24]; retrospective	31	1 (3.2)	12 × 4 Gy;	T1–T2N0	Not specified
Krol [25]; retrospective	108	2 (1.9)	2.5–3.0 Gy/fraction to 60–65 Gy	Peripheral tumors	Not specified
Robertson [26]; prospective	30	1 (3.3)	Dose escalation up to 92.4 Gy	Stage II and III	Not specified
Hayakawa [27]; retrospective	26	1 (3.8)	60–81 Gy	Stage I	Range: 3–18 years
Cheung [28]; retrospective	103	4 (3.8)	52.5 Gy in 20 fr	T1–T4N0 (5 × N1)	86
Rosenzweig [29]; retrospective	171	11 (6.4)	Dose escalation up to 81 Gy	85% stage III; 14% stage I and II	21
Hayman [30]; prospective	63	2 (3.2)	Dose escalation up to 102.9 Gy	All stages	9.4
Cheung [31]; retrospective	33	2 (6.1)	48 Gy in 12 fractions	T1T2N0	22.5
Senan [32]; prospective	43	0 (0)	Sequential CHT-RT	Stage III; only patients who received at least 50 Gy	16
Hof [33]; retrospective	19	0 (0)	SBRT	Stage I	14.9
Bradley [34]; prospective	61	0 (0)	Dose escalation up to 60 Gy	Stage I–II	20
Onishi [35]; prospective	32	0 (0)	SBRT	Stage I	13
Bradley [36]; prospective	179	14 (8)	Dose escalation up to 70–90 Gy; in stage III combined with sequential CHT	Stage I–III	Range of median for subgroups: 13.3–18.7
Belderbos [37]; prospective	21	0 (0)	50 to 91 Gy; induction in CHT	Stage I	17
Baumann [38]; retrospective	135	6 (4.4)	SBRT	Stage I	33
Ohtsuka [39]	35	0 (0)	80.5 Gy in 35 fractions	Stage I and II	33
Yuan [40]; prospective	100	0 (0)	Dose escalation with sequential CHT	Stage III	27
Mostafa [41]; prospective	32	0 (0)	Concurrent CHT	Stage III	13.5
Yu [42]; prospective	80	0 (0)	SBRT	Stage I and II	72
Suzuki [43]; retrospective	29	0 (0)	Most concurrent RT (64 Gy)-CHT	All stages	18
Nakayama [44]; retrospective	45	2 (4.4)	66–84 Gy with sequential or concomitant CHT	Stage III	Not specified
Onishi [45]; retrospective	87	11(12.6)	SBRT	Stage I	55
Chen [46]; prospective	32	0 (0)	Median RT dose of 60 Gy with induction and concomitant CHT	Stage III	33
Patients staged with PET					
Lao [23]; prospective	155*	19 (12.2)	SBRT	Stage I	20
Zimmermann [47]; retrospective	30	2 (6.7)	SBRT	Stage I	18
De Ruysscher [48]; prospective	44	1 (2.3)	61.2–64.7 Gy in 34/37 fractions	All stages	16
Belderbos [37]; prospective	67	2 (3)	Dose escalation from 50 to 94 Gy (median: 80 Gy); 18% induction CHT	All stages	17
Hoopes [49]; prospective	57	6 (10.5)	SBRT	Stage I	42.5
Klopp [50]; retrospective	35	3 (8.5)	60–70 Gy; 70% with concurrent CHT	All stages	13
Chang [51]; retrospective	13	1 (7.7)	SBRT	Stage I	17
Sulman [43]; retrospective	86	2 (2.3)	Most concurrent RT (mean: 64 Gy)-CHT	All stages	18
Stephans [52]; retrospective	88	7 (8.1)	SBRT	Stage I	15.3
Collins [53]; retrospective	20	0 (0)	SBRT (cyberknife)	Stage I ("small, peripheral")	25
Baldris [54]; prospective	70	4 (5.7)	SBRT	Stage I	60.2
Bradley [55]; retrospective	91	4 (4.4)	SBRT	Stage I and II (+6 T1N0M1)	18
Fernandes [56]; retrospective	48	6 (12.5)	60–84 Gy with concurrent or sequential CHT	Stage III (including 3 oligometastatic)	16.2
Kimura [57]; retrospective	50	4 (8)	60–80 Gy; in 72% with sequential or concurrent CHT	Stage II – 28% Stage III – 72%	Not specified
Ricardi [58]; prospective	62	7 (11.3)	SBRT	Stage I	28
Timmerman [59]; prospective	55	2 (3.6)	SBRT	Stage I	34.4
Grills [60]; retrospective	55	4 (7.3)	SBRT	Stage I	30
Fleckenstein [61]; prospective	23	1 (4.3)	66.6 Gy with concurrent CHT	Stages II and III	27.2
Bral [62]; prospective	40	2 (5)	SBRT	T1–T3N0	16
Kolodziejczyk [63]; prospective	50	3 (6)	RT 58.7 – 66 Gy with or without sequential CHT	All stages	32
Bradley [64]; prospective	47	1 (2)	Different curative doses with or without CHT	Stages II (6%) and III (94%)	12.6
Tada [65]; prospective	22	1 (4.5)	Hyperfractionated dose escalation concurrent CHT	Stage III	Not specified
Senthi [66]; retrospective	676	37 (5.5)	SBRT	Stage I and II	32.9
Van Baardwijk [67]; prospective	132	6 (4.5)	Concurrent RT-CHT	Stage III	30.9
Zhang [68]; retrospective	68	6 (8.8)	SBRT	Stage I	31
Chen [46]; prospective	13	0 (0)	Median RT dose of 60 Gy with induction and concomitant CHT	Stage III	33
Samuels [69]; retrospective	46	4 (8.7)	SBRT	Stage I	17.4
Kim [70]; retrospective	16	1 (6)	SBRT	Stage I	14

* Numbers provided by personal communication of Dr. Cho [23].
** SBRT – Stereotactic-body Radiotherapy.

Etudes de faibles effectifs
Des stades 1 et 2
Stéréotaxie

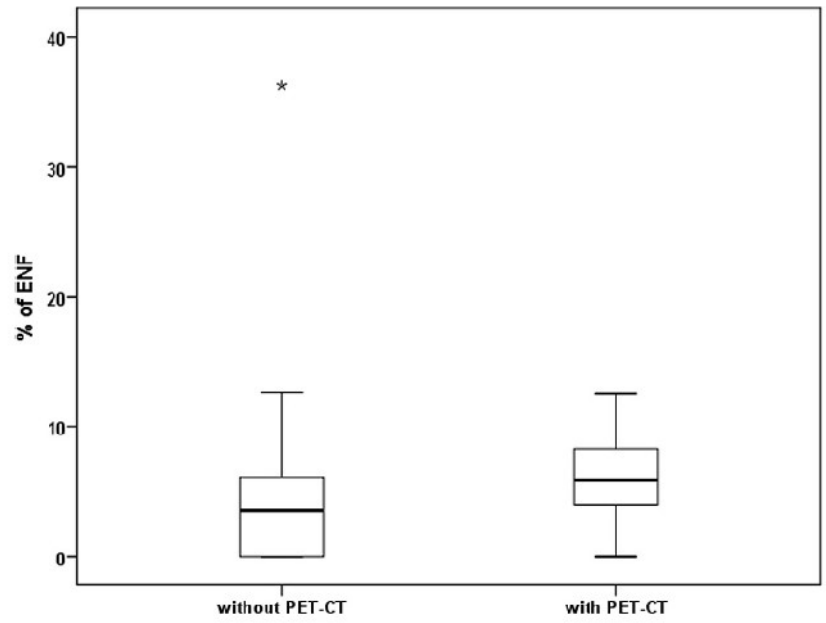
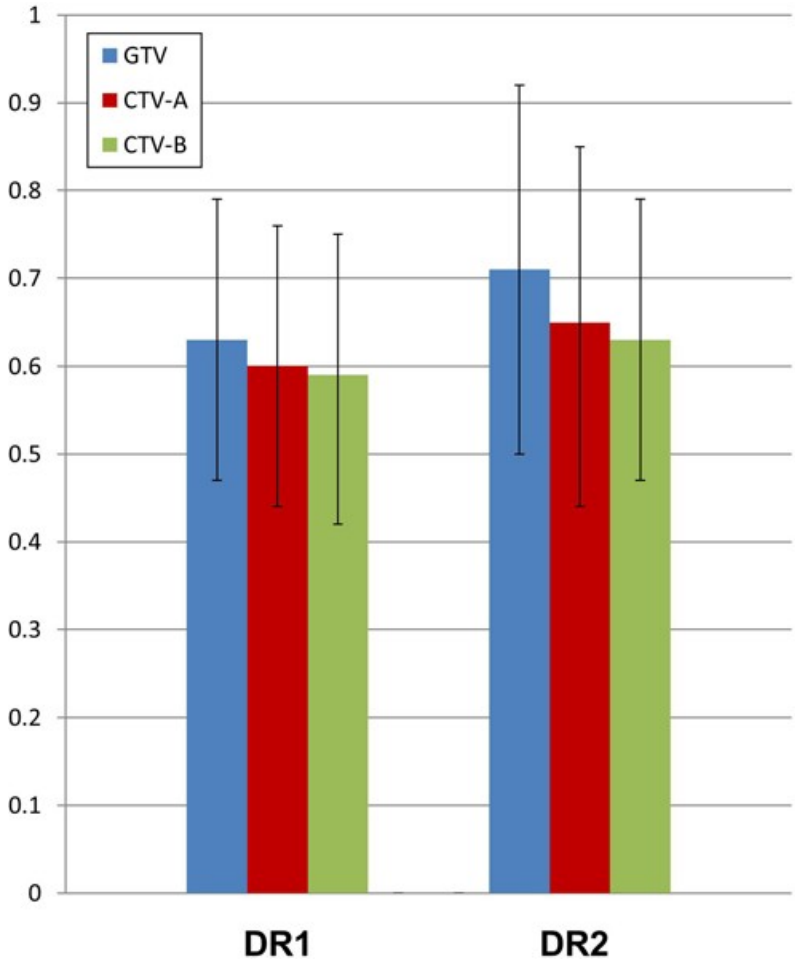
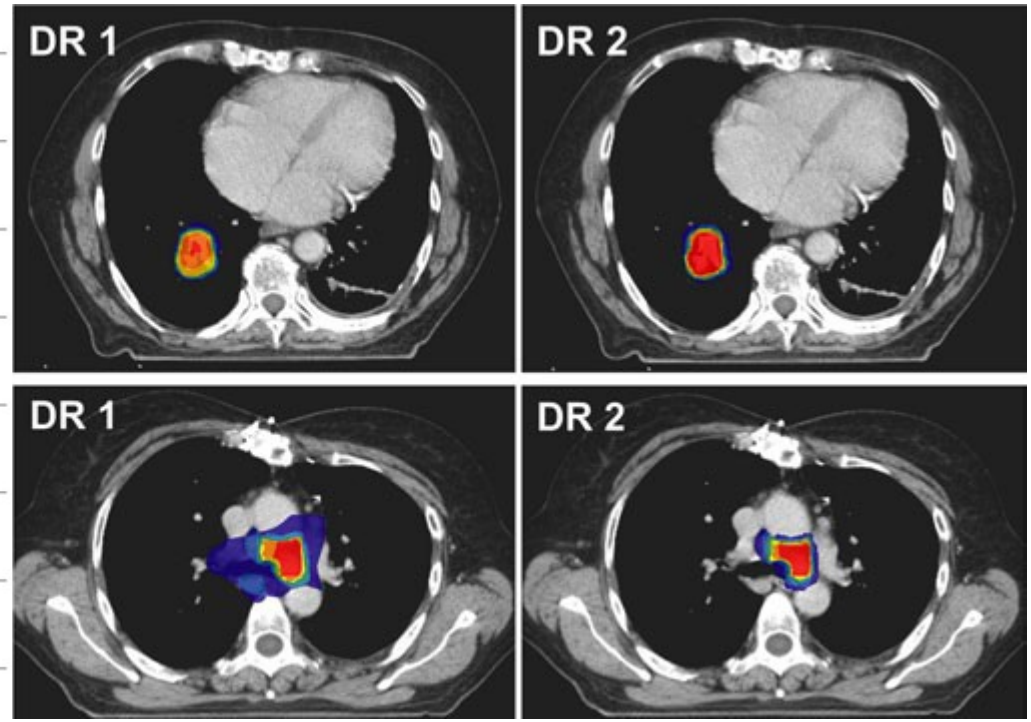


Fig. 1. Median and range values of the rate of elective nodal failures (ENF) in 28 groups (2158 patients) with PET-CT and in 24 groups (1487 patients) without PET-CT performed before radiotherapy.

Kepka, Radiother Oncology, 2015

Lung

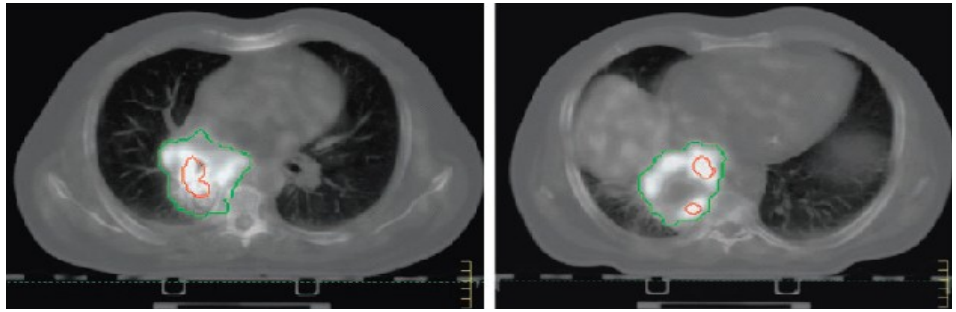


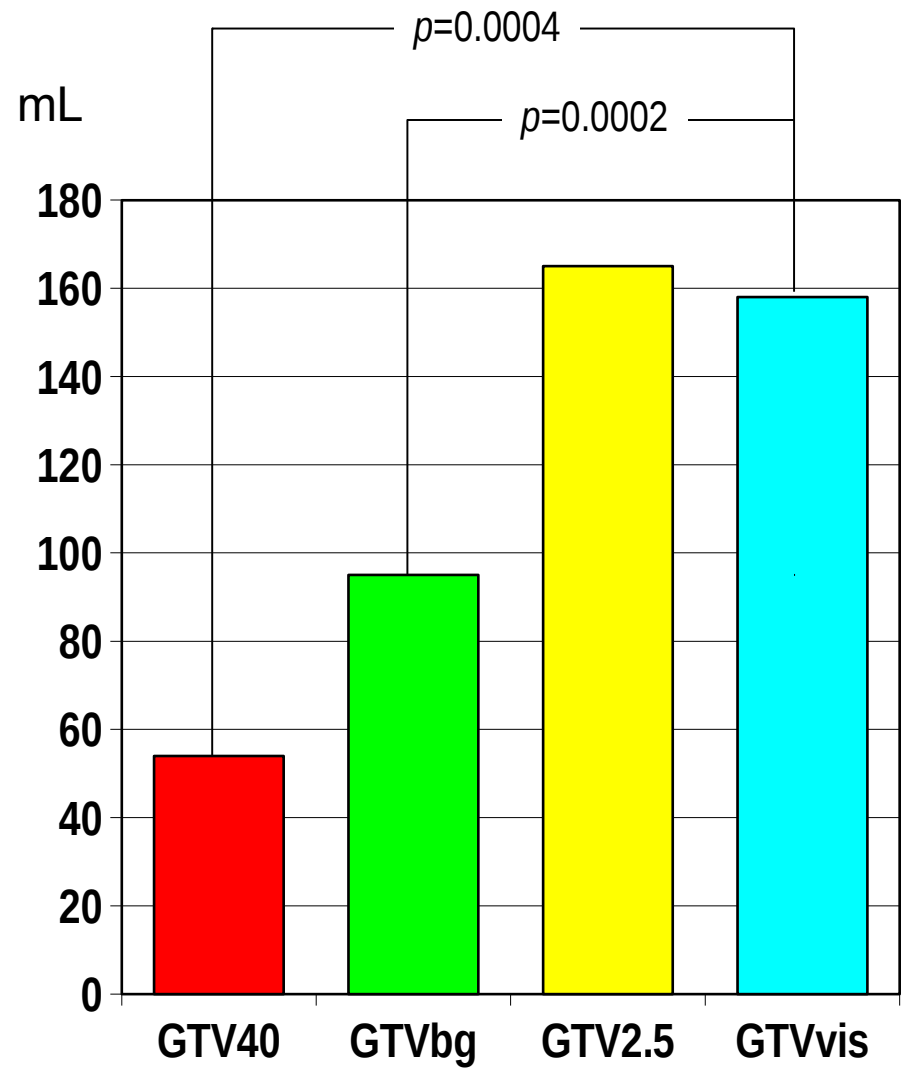


Schimek-Jasch T, Strahlenther Oncol, 2015
Dummy run PET-Plan

GTV influenced by delineation method

- GTV based on **FDG**-PET
- Significant difference correlated with
  - ✓ SUVmax
  - ✓ Lesion size
  - ✓ Heterogeneity
- Best method not defined in 2014





Nestle, J Nucl Med, 2005

Impact de la TEP sur le volume cible

Consequences of additional use of PET information for target volume delineation and radiotherapy dose distribution for esophageal cancer

Christina T. Muijs [a,*], Liesbeth M. Schreurs [b], Dianne M. Busz [a], Jannet C. Beukema [a], Arnout J. van der Borden [a], Jan Pruim [c], Eric J. Van der Jagt [d], John Th. Plukker [b], Johannes A. Langendijk [a]

- Modification du volume cible de plus de 10% chez 61% des patients

Estimated NTCP, comparing CT- and PET/CT-based treatment plans, for symptomatic pneumonitis and cardiac mortality after 10–15 years resulting from irradiation.

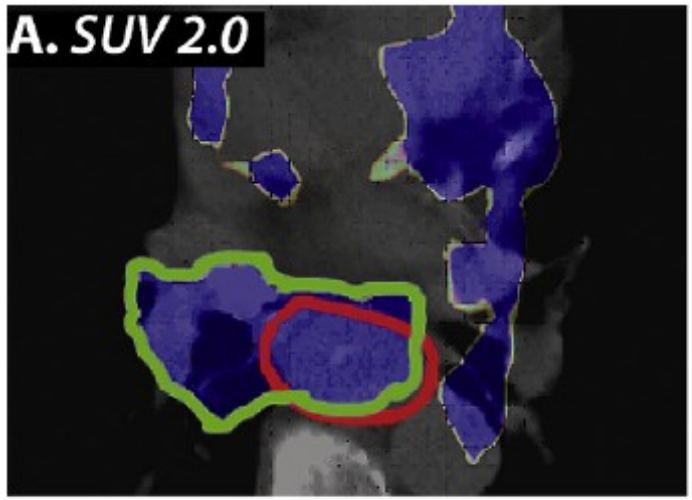
Endpoint	CT-based (mean ± SD)	PET/CT-based (mean ± SD)	*p*-Value[a]
Normal tissue complication probability			
Symptomatic pneumonitis (%)			
Overall	6.4 (±2.6)	5.7 (±2.0)	0.03
Increased lung dose	4.5 (±2.2)	5.1 (±2.4)	0.03
Decreased lung dose	6.9 (±2.2)	5.5 (±1.6)	0.00
Cardiac mortality (%)			
Overall	2.8 (±1,4)	2,5 (±1.3)	0.01
Increased heart dose	1.9 (±1.0)	2.0 (±1.0)	0.22
Decreased heart dose	3.4 (±1.3)	2.9 (±1.4)	0.00

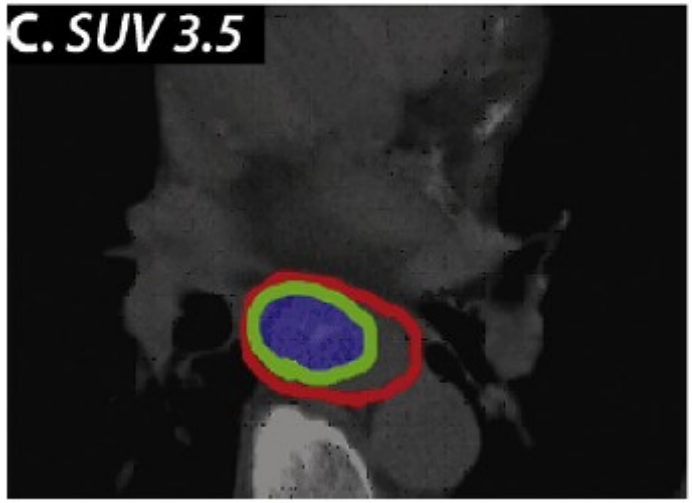
Abbreviations: NTCP, normal tissue complication probability; CT, computer tomography; PET, positron emission tomography. Data presented as mean values, with standard deviation in parentheses.

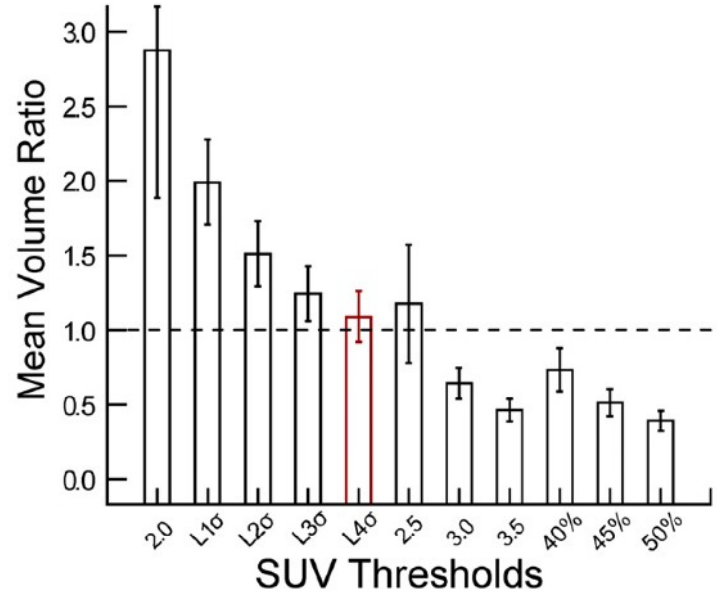
[a] Wilcoxon signed rank test.

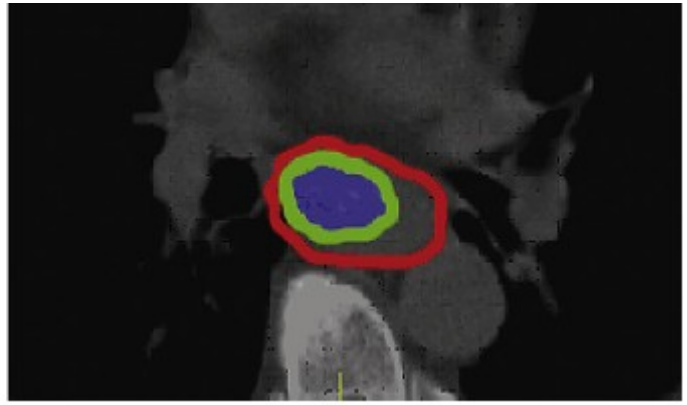
Muijs, Rad and Oncol, 2009

GTV influencée par la méthode de contourage









Vali, IJROBP, 2009

Which Target?

Table 2. Pathologic length compared with lengths detected by different methods using CT, FLT, and FDG PET/CT

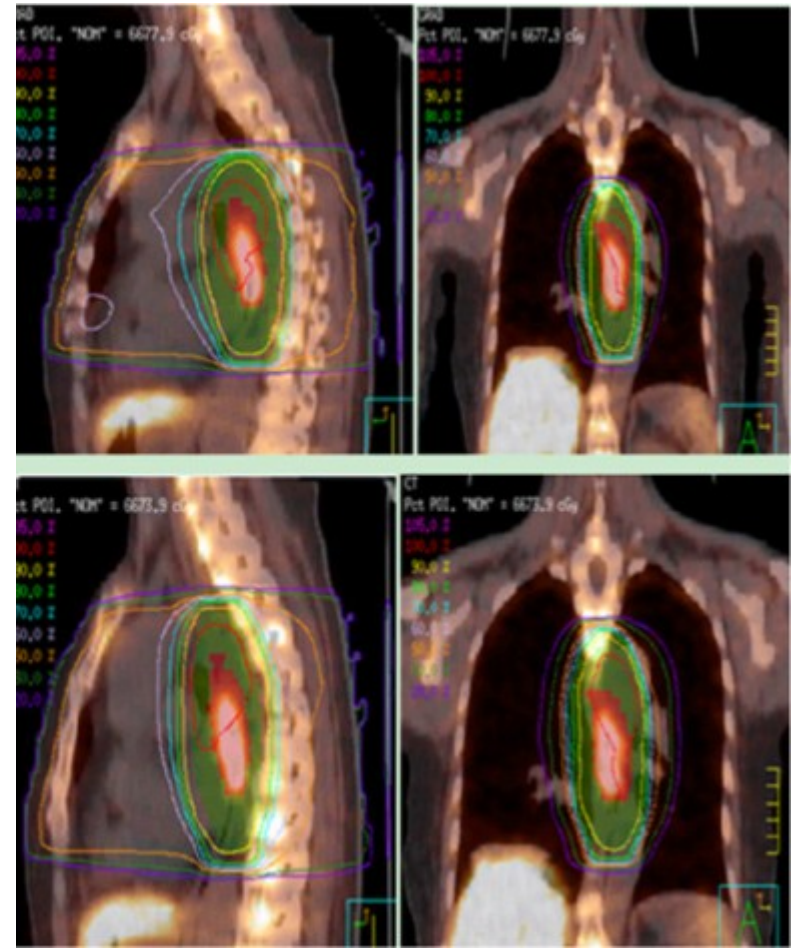
Group	Median	Mean ± SD	R	*p*	Mean difference	95% CI difference	*t*	*p*
L_{Path}	4.65	4.94 ± 2.21	—	—	—	—	—	—
L_{CT}	4.75	4.71 ± 1.91	0.895	.000	−0.23 ± 0.99	−0.67 to 0.21	−1.084	.290
L_{FDGvis}	5.10	5.10 ± 2.22	0.985	.000	0.17 ± 0.39	−0.01 to 0.34	1.994	.059
$L_{FDG2.5}$	4.89	5.10 ± 2.18	0.991	.000	0.16 ± 0.29	0.03 to 0.29	2.532	.019
$L_{FDG40\%}$	3.83	3.85 ± 1.52	0.911	.000	−1.09 ± 1.04	−1.55 to −0.63	−4.914	.000
L_{FLTvis}	4.68	4.89 ± 2.41	0.956	.000	−0.05 ± 0.71	−0.36 to 0.27	−0.309	.761
$L_{FLT1.3}$	5.32	5.24 ± 2.48	0.950	.000	0.30 ± 0.79	−0.05 to 0.65	1.784	.089
$L_{FLT1.4}$	4.68	4.91 ± 2.43	0.964	.000	−0.03 ± 0.66	−0.32 to 0.27	−0.196	.847
$L_{FLT1.5}$	4.68	4.66 ± 2.47	0.954	.000	−0.28 ± 0.75	−0.61 to 0.06	−1.732	.098
$L_{FLT20\%}$	5.53	5.57 ± 2.23	0.784	.000	0.63 ± 1.46	−0.02 to 1.28	2.019	.056
$L_{FLT25\%}$	4.68	5.10 ± 2.25	0.790	.000	0.17 ± 1.45	−0.47 to 0.81	0.543	.593
$L_{FLT30\%}$	4.28	4.82 ± 2.24	0.808	.000	−0.12 ± 1.38	−0.73 to 0.49	−0.411	.685

Han, IJROBP, 2010

Which Target?

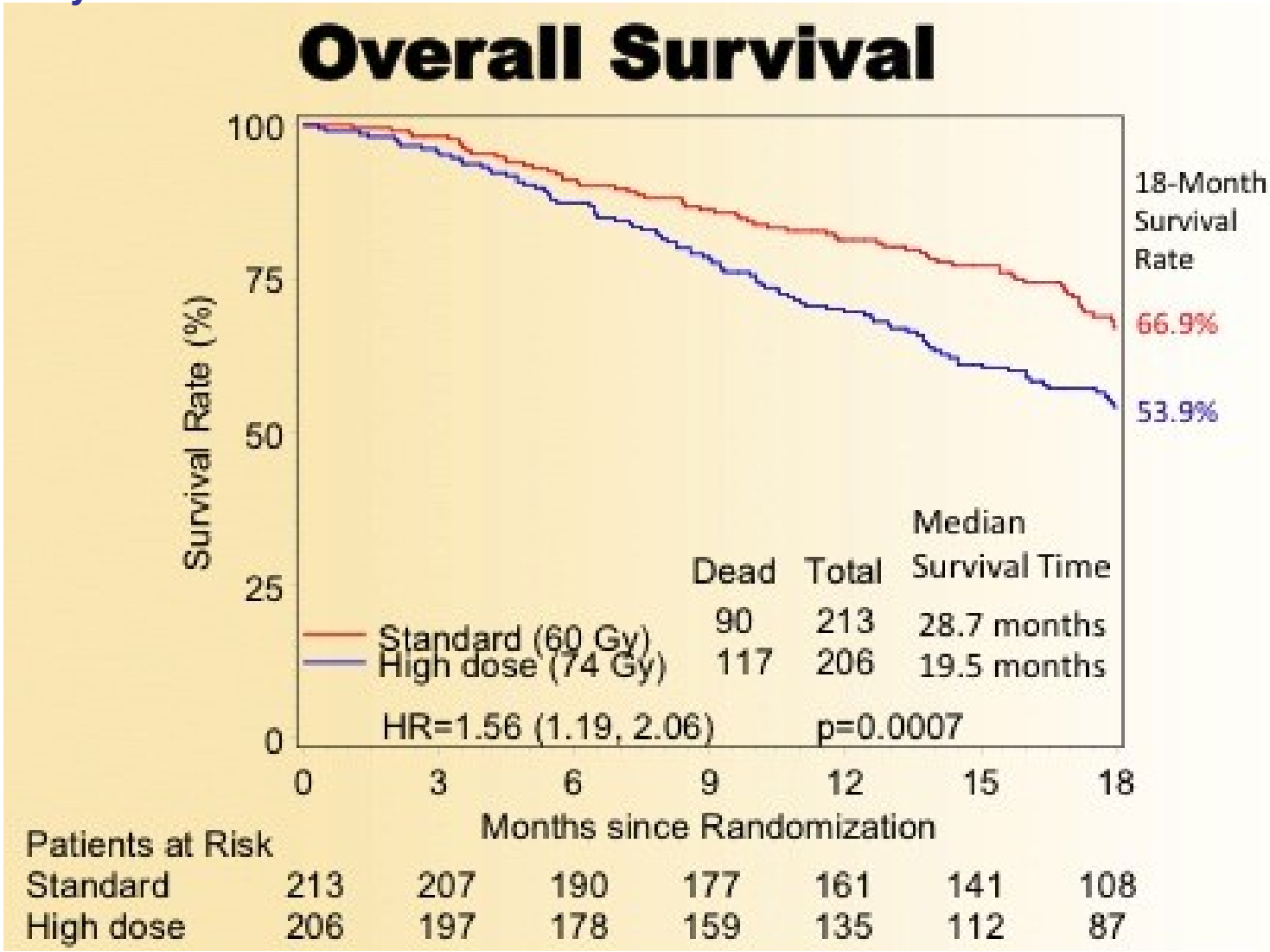
Table 2 Comparison of FLT and CT-based overall values of measured dose–volume histogram-based evaluation factors for esophageal cancer patients

Mean ± SD	$plan_{GRAD}$	$plan_{CT}$	*t*	*P*
Total-lung				
V_5 (%)	47.9 ± 15.30	56.1 ± 13.80	−6.31	0.000
V_{10} (%)	33.8 ± 8.90	40.1 ± 9.10	−6.78	0.000
V_{20} (%)	18.2 ± 10.00	23.8 ± 9.70	−4.36	0.003
V_{30} (%)	5.49 ± 4.40	8.9 ± 4.70	−3.17	0.016
MLD (Gy)	9.82. ± 319.50	10.96 ± 3.02	−4.70	0.002
Heart				
V_{30} (%)	37.6 ± 19.30	44.1 ± 20.80	−5.97	0.000
V_{40} (%)	20.8 ± 13.50	22.8 ± 14.10	−1.19	0.272
MHD (Gy)	22.63 ± 10.25	25.37 ± 10.71	−5.92	0.000
D_{max} of spinal cord (Gy)	44.26 ± 1.36	44.69 ± 0.29	−0.94	0.380



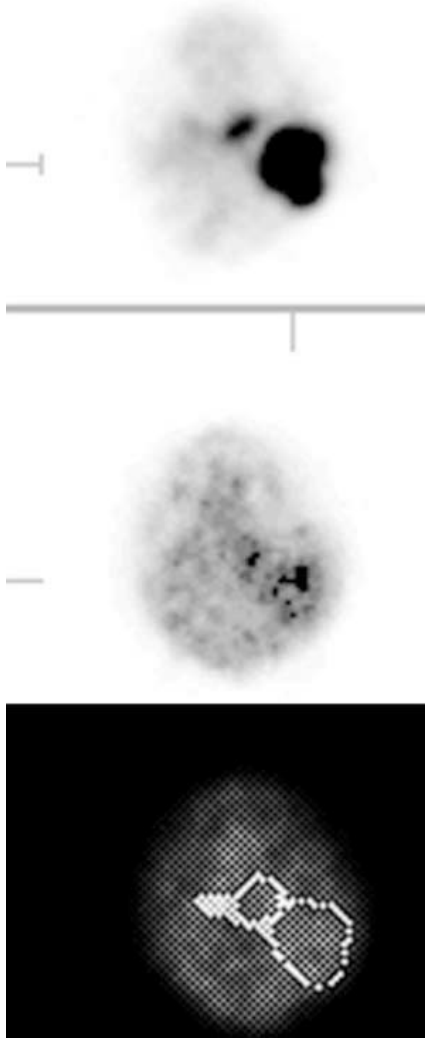
Han, IJROBP, 2015

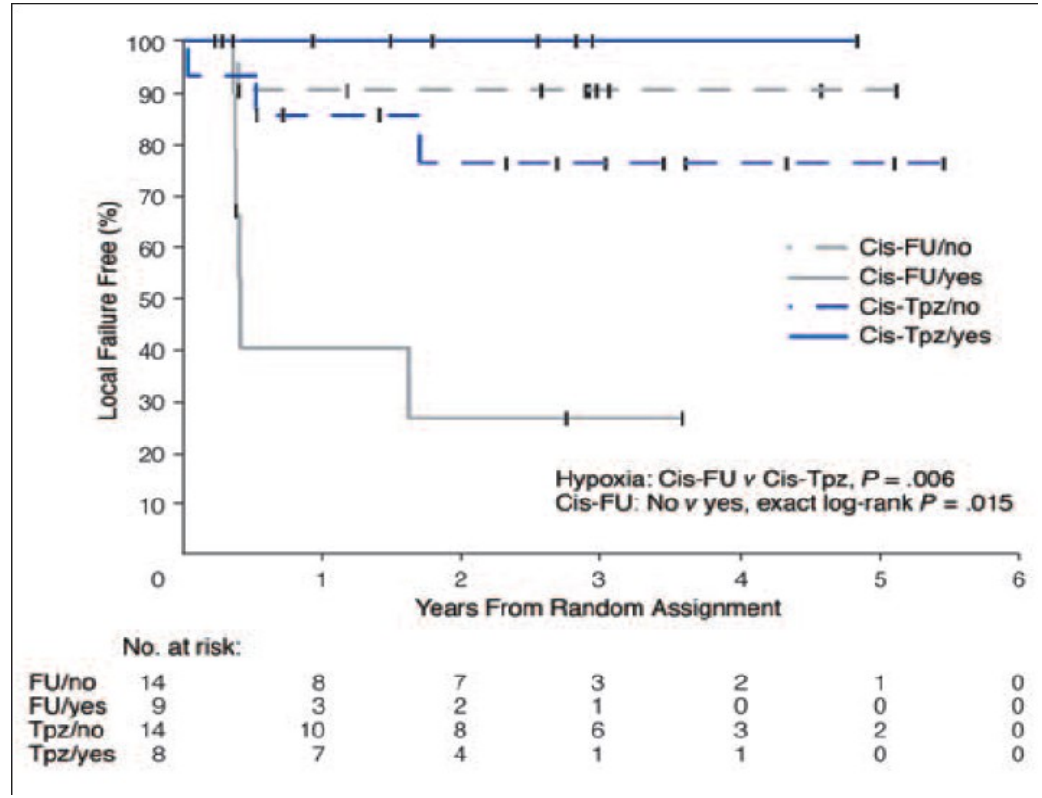
Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study



Bradley, Lancet Oncol 2015

Patient selection





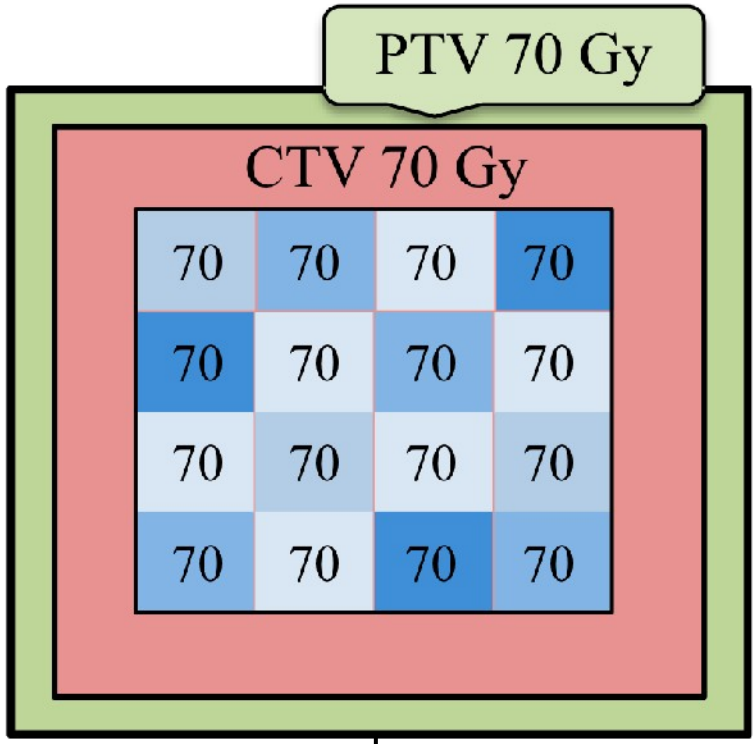
Rischin, JCO, 2006, 2010
Hicks, EJNMMI, 2005

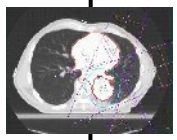
Fletcher GH, Radiology, 1974

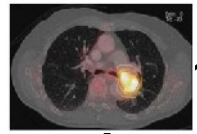
Il faut environ 100Gy pour stériliser un cancer épidermoide

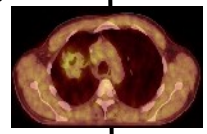
Dose painting

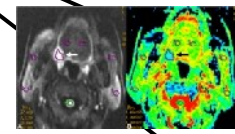
Prescription non uniforme dans le GTV
(**Hall**, *The Lancet Oncology 2005*)











CT
(1980…)

FDG-PET
(2005…)

Hypoxia-PET…
(2010…)

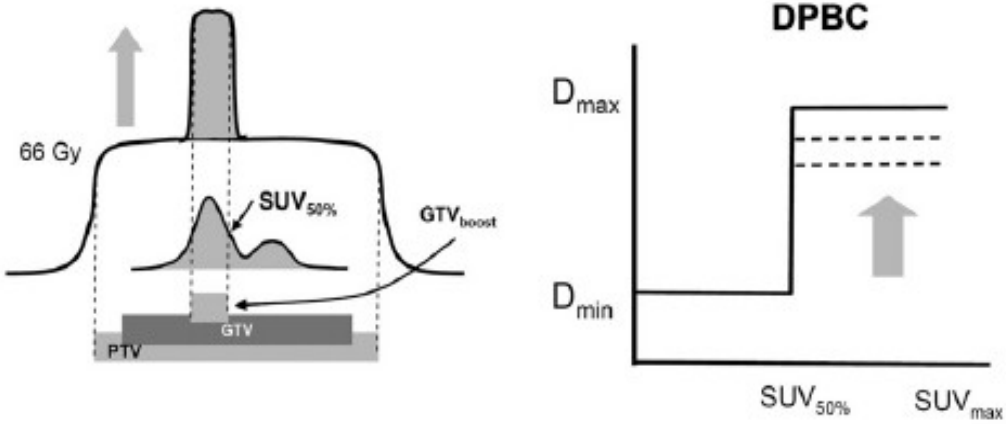
DW-MRI
PET-MR
(2014)

…
(2020)

Courtesy Prof V.Grégoire. MIRO Brussels

Dose painting

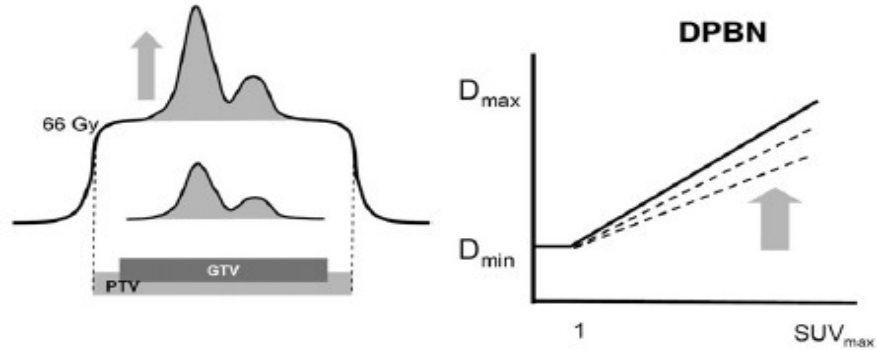
- **By Contour (DPBC)**
  - ✓ Boost dans le **BTV**, mais qui reste uniforme dans les volumes
  - ✓ Exemple avec un seuillage du BTV à 50% du SUVmax



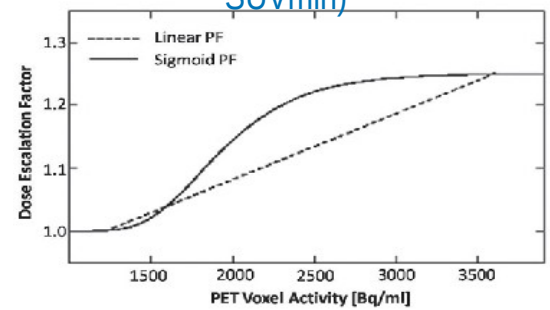
Comment segmenter le BTV ?

Meijer Radiother Oncol 2011

- **By numbers (DPBN)**
  - ✓ Prescription fonction de la valeur du SUV : La dose est ajustée à l'échelle du **voxel**



D(SUV)= Dmin + (Dmax-Dmin)*(SUV-SUVmin)/(SUVmax-SUVmin)



Quelle fonction de prescription choisir ?

Bentzen, R&O 2011; Thorwarth Nucl Med Review 2012

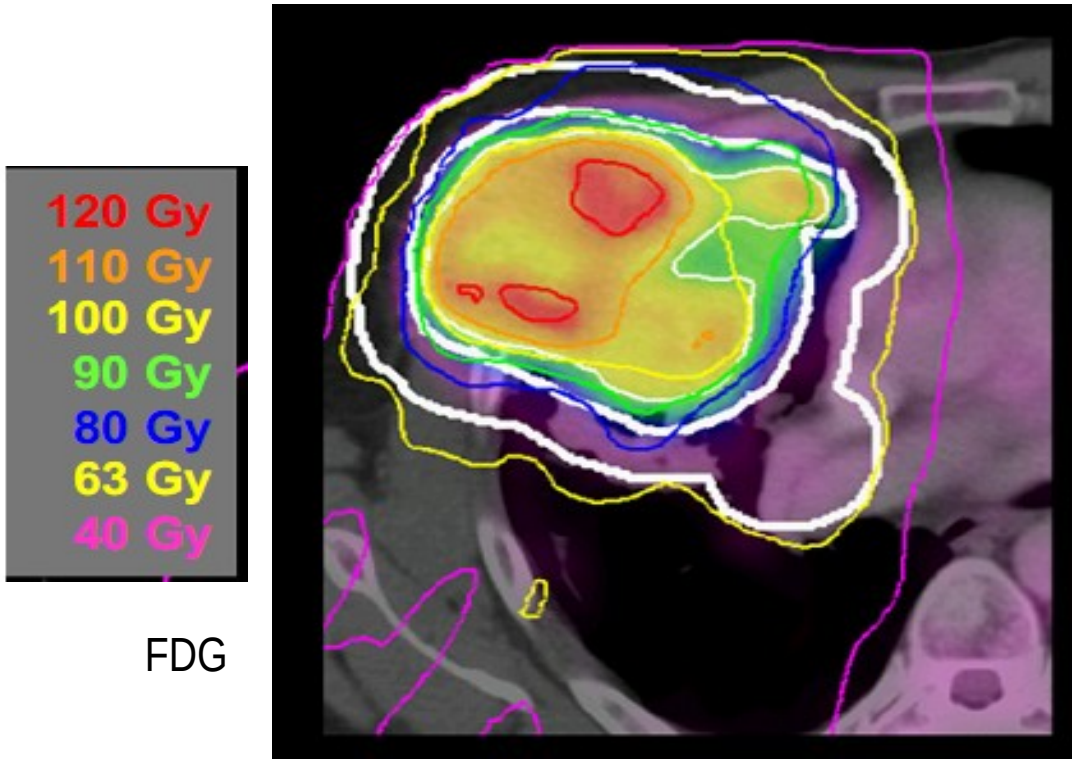
Dose painting: DPBN

☹ TPS manipule des volumes (RT structures) et pas des voxels

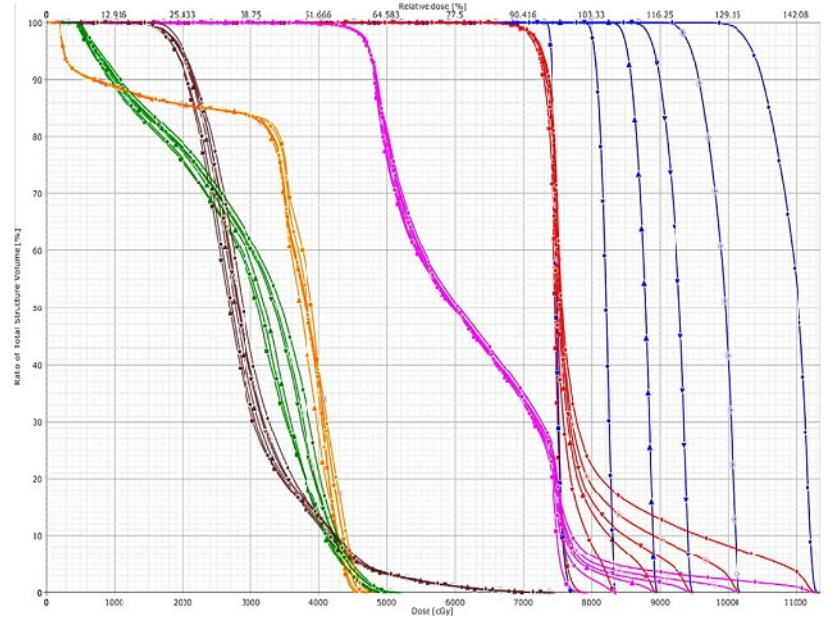
☹ Il faut opérer une conversion du DPBN en isocontours compatibles avec le TPS

☹ Isocontours doivent être compatibles avec les contraintes technologiques de l'IMRT

☹ Performances des LINAC : Gradients de dose IMRT < à 20 Gy/cm (VARiAN)



FDG



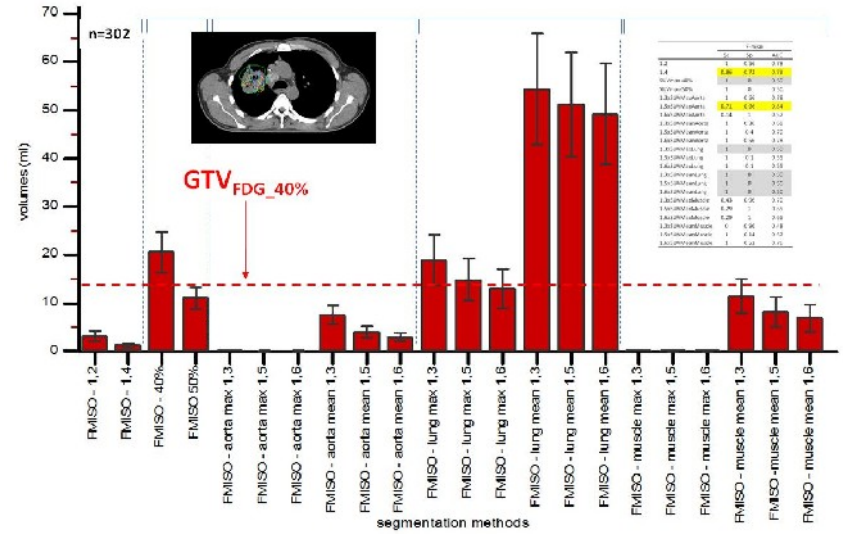
Meijer R&O 2011

Choi Radioth Oncol 2010

BTVm et BTV(h) delineation

- Pre-RCT
  - ✓ **BTVm**
  - ✓ Best method not defined in 2015
  - ✓ *40% SUVmax*
  - ✓ Possible on injected PET/CT
  - ✓ BTV(h)
- Per-RCT
  - ✓ BTVm et BTV(h)

Authors	Organ	Tracer	Method	Background	Reprod.
Souvatzoglou EJNMMI2007	H&N	Faza	– 1.5 x SUV T/M	SUV_{mean_muscle} (what muscle ?)	Not tested
Mortensen RO2012	H&N	Faza	– 1.4 x SUV_{max} T/M – 1.4 x SUV_{mean} T/M	Mean ± 3 SD	Not tested
Thureau JNM2013	Lung	Miso	– 1.5 x SUV_{max_aorta} – 1.4		Very poor
Tachibana JRR2013	H&N	Miso	– 1.6 x SUV_{max} T/M	$SUV_{mean\_postneckmuscles}$	Not tested
Bittner RO2013	H&N	Faza	– 1.5 x T/B	$SUV_{mean\ contraNormalTissu}$ with manual correction	Not tested
Servagi EJNMMI2014	H&N	Faza	– SUV_{mean} + 3 SD of BG	$SUV_{mean\ postneckmuscles}$	Not tested



Thureau, JNM 2013

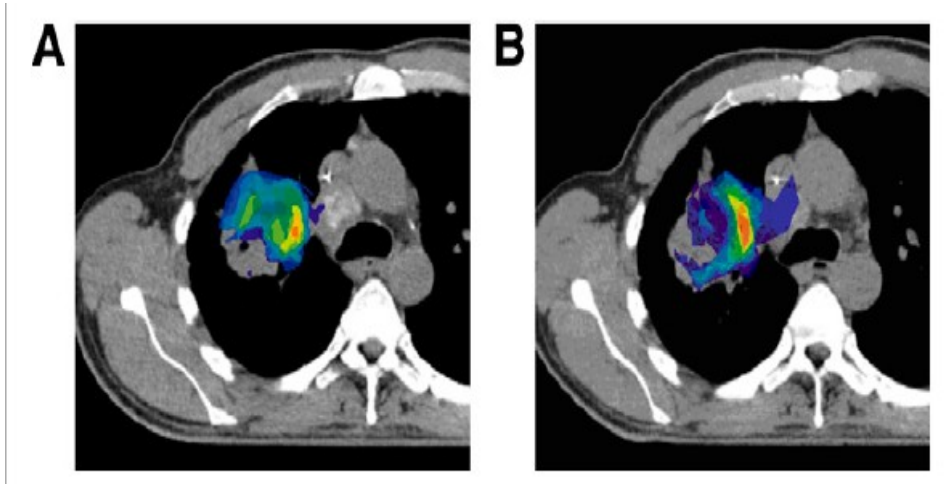
Analyse des traceurs à faible contraste

Global κ-Test for Visual Analysis of PET/CT Images for 18 Nuclear Medicine Physicians at 18 Centers

κ	^{18}F-FDG	^{18}F-FMISO	^{18}F-FLT
5 classes	0.59	0.43	0.44
2 classes	0.81	0.77	0.77

κ-Values for PET/CT Images Regarding Primary Tumors and Nodes

	^{18}F-FDG		^{18}F-FMISO		^{18}F-FLT	
κ	Tumor	Node	Tumor	Node	Tumor	Node
5 classes	0.84	0.51	0.45	0.44	0.49	0.41
2 classes	0.87	0.78	0.65	0.81	0.84	0.74

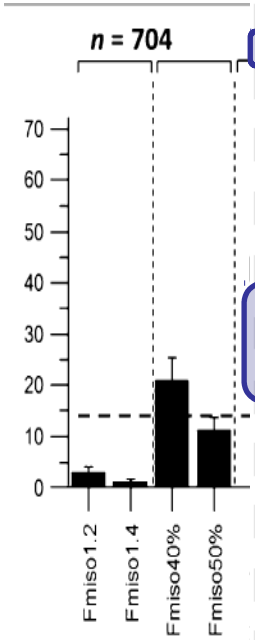


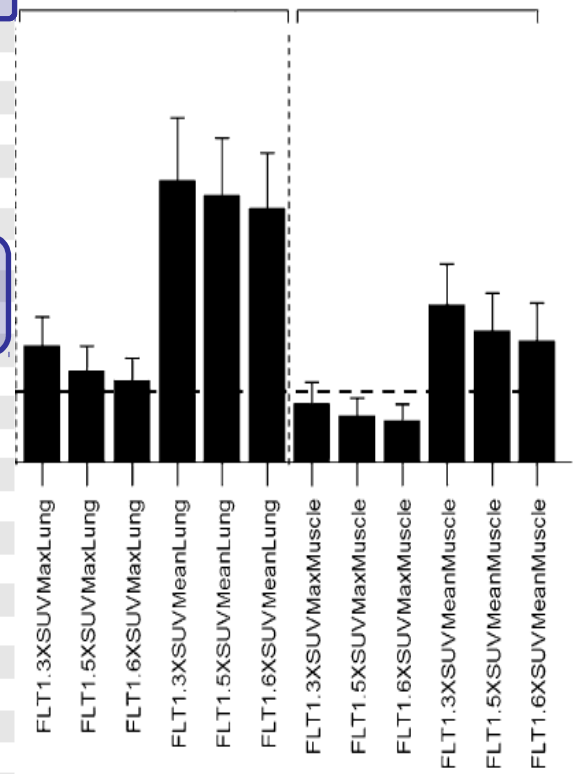
Thureau, JNM, 2013

Analyse des traceurs à faible contraste

Sensitivity and Specificity of Different Methods of Volume Delineation

	^{18}F-FMISO			^{18}F-FLT		
Segmentation	Sensitivity	Specificity	AUC	Sensitivity	Specificity	AUC
1.2	1	0.56	0.78	0.92	0.5	0.71
1.4	0.86	0.72	0.79	0.92	0.83	0.88
SUVmax						
40%	1	0	0.50	1	0	0.50
50%	1	0	0.50	1	0	0.50
SUVmaxAorta						
1.3 ×	1	0.56	0.78	0.96	0.5	0.73
1.5 ×	0.71	0.96	0.84	0.92	0.83	0.88
1.6 ×	0.14	1	0.57	0.92	0.83	0.88
SUVmeanAorta						
1.3 ×	1	0.36	0.68	1	0.33	0.67
1.5 ×	1	0.4	0.70	1	0	0.50
1.6 ×	1	0.56	0.78	1	0	0.50
SUVmaxLung						
1.3 ×	1	0	0.50	1	0	0.50
1.5 ×	1	0.1	0.55	1	0.33	0.67
1.6 ×	1	0.1	0.55	1	0.33	0.67
SUVmeanLung						
1.3 ×	1	0	0.50	1	0	0.50
1.5 ×	1	0	0.50	1	0	0.50
1.6 ×	1	0	0.50	1	0	0.50
SUVmaxMuscle						
1.3 ×	0.43	0.96	0.70	0.96	0.83	0.90
1.5 ×	0.29	1	0.65	0.92	0.83	0.88
1.6 ×	0.29	1	0.65	0.87	0.83	0.85
SUVmeanMuscle						
1.3 ×	0	0.96	0.48	1	0.17	0.59
1.5 ×	1	0.14	0.57	1	0.17	0.59
1.6 ×	1	0.52	0.76	0.96	0.17	0.57



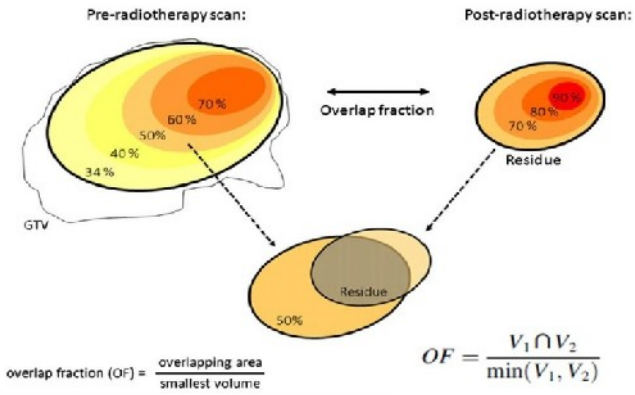


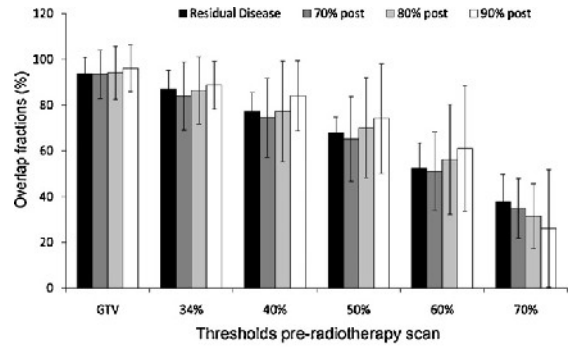
Thureau, JNM, 2013

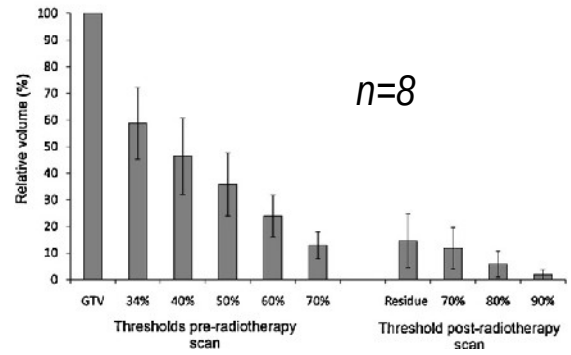
Pre-treatment PET/CT for RT in lung cancer

1. **FDG (standard in 2014)**
2. Hypoxia

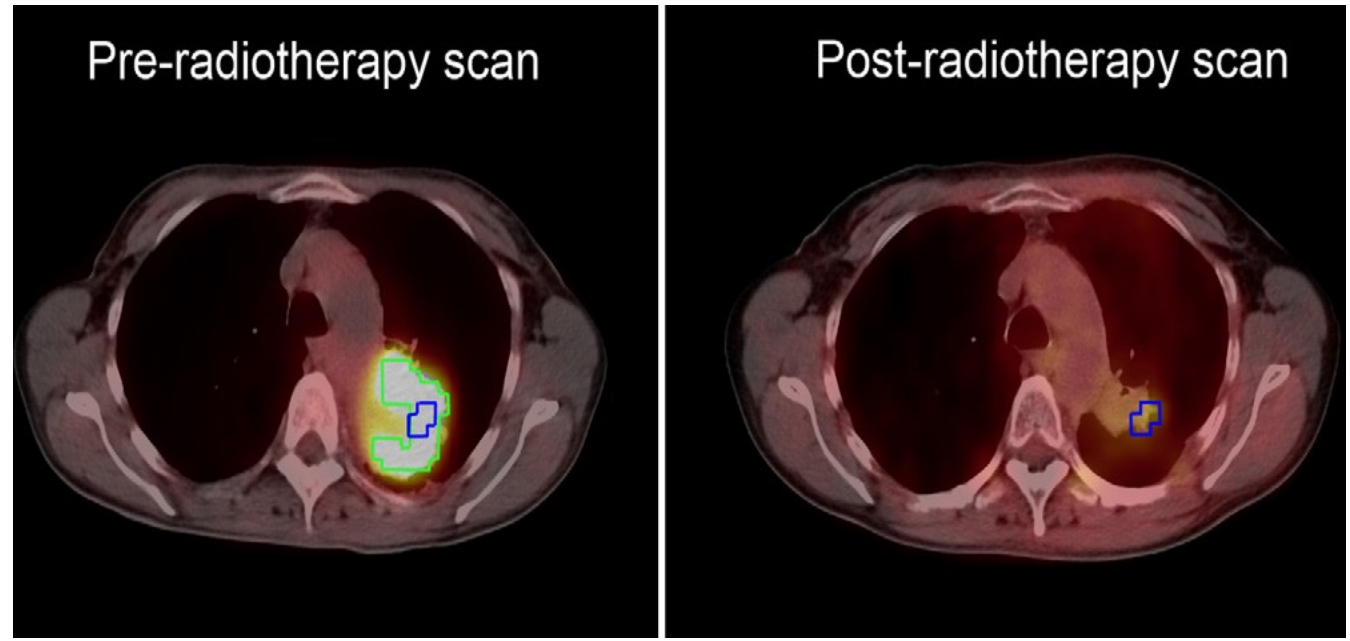
High uptake in pre-RT : recurrence or radioresistance







n=8

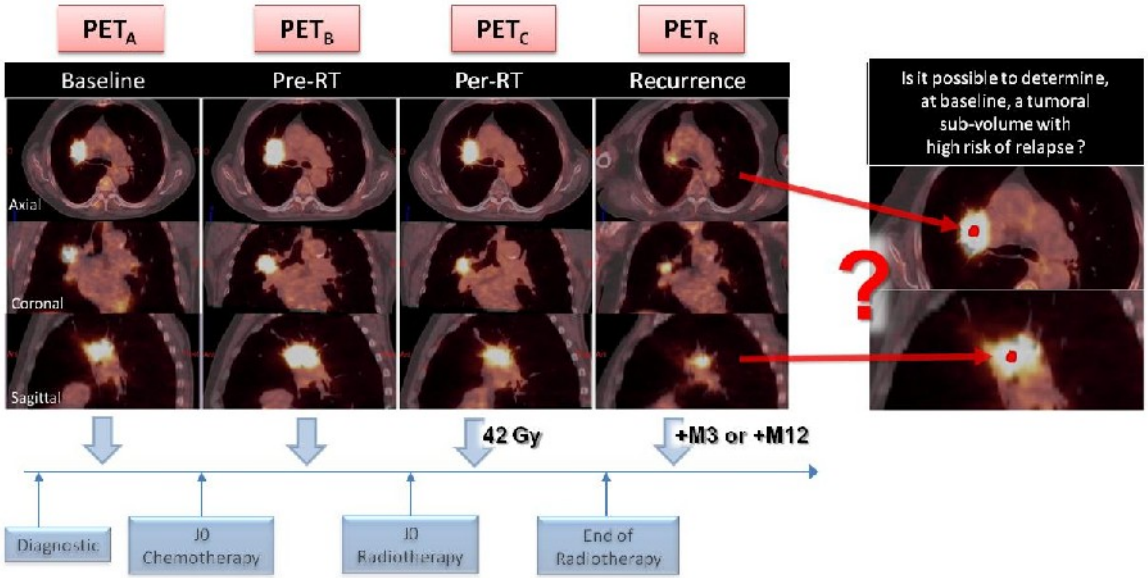


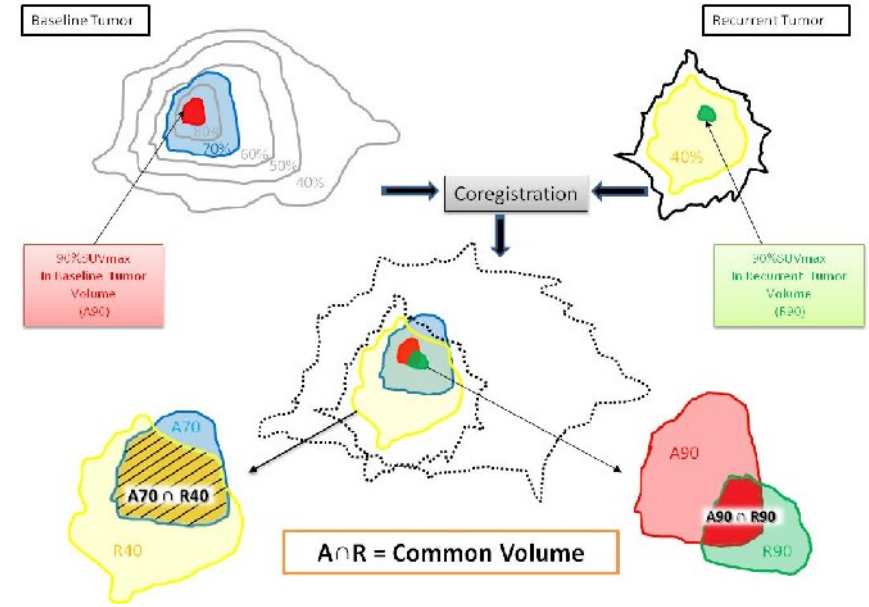
PET-Boost Phase II-III in progress
(Pr D.De Ruysscher, Leuven)

Aerts, IJROBP 2008; Aerts, R&O 2009; Abramyuk R&O 2009; Aerts Lung Cancer 2012

Calais, JNM2015

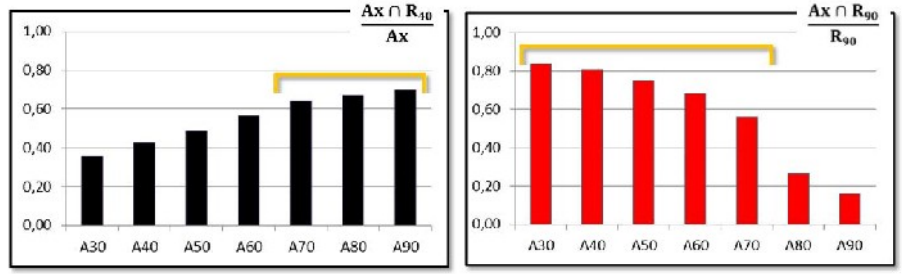
Lung « Hotspot » study

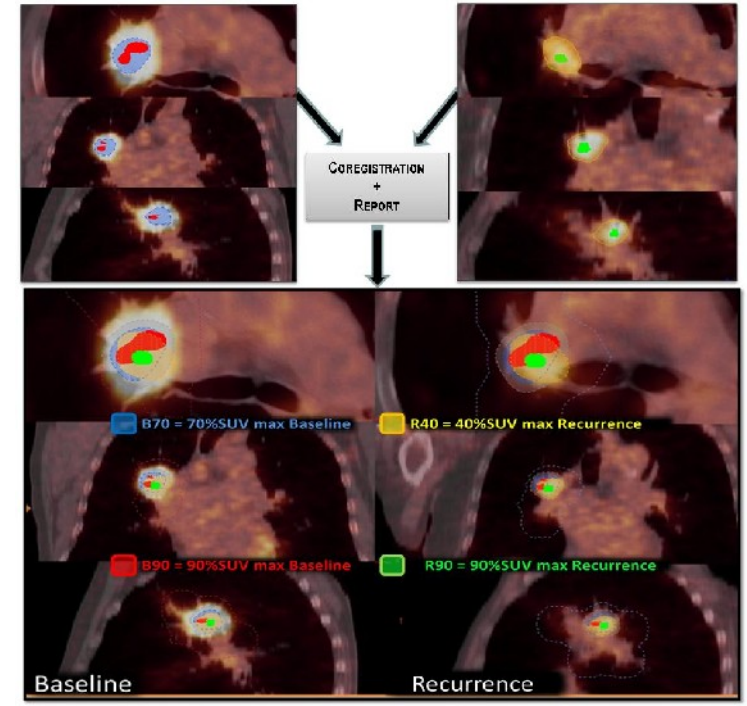




- 39 patients
- 156 PET/CT
- 117 registrations
- 507 VOI
- 1330 overlap
- 6650 indexes

	~ TOXICITY							~ EFFICIENCY						
	R_{40}							R_{90}						
Dice	0,38	0,4	0,37	0,34	0,27	0,16	0,07	0,08	0,04	0,05	0,07	0,09	0,08	0,09
Jaccard	0,25	0,26	0,25	0,21	0,17	0,1	0,04	0,01	0,02	0,03	0,04	0,05	0,04	0,05
OF	0,67	0,65	0,62	0,64	0,67	0,67	0,7	0,84	0,81	0,75	0,68	0,56	0,27	0,16
A∩R / A	0,36	0,42	0,48	0,56	0,64	0,67	0,7	0,01	0,02	0,03	0,04	0,05	0,05	0,07
A∩R / R	0,62	0,53	0,44	0,33	0,21	0,11	0,05	0,84	0,81	0,75	0,68	0,56	0,27	0,16

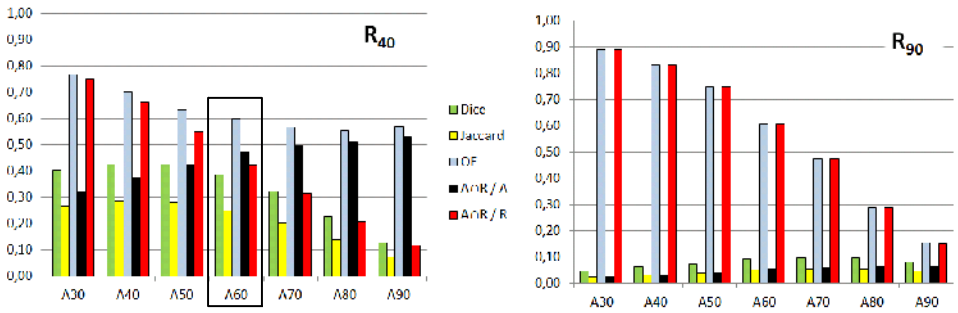


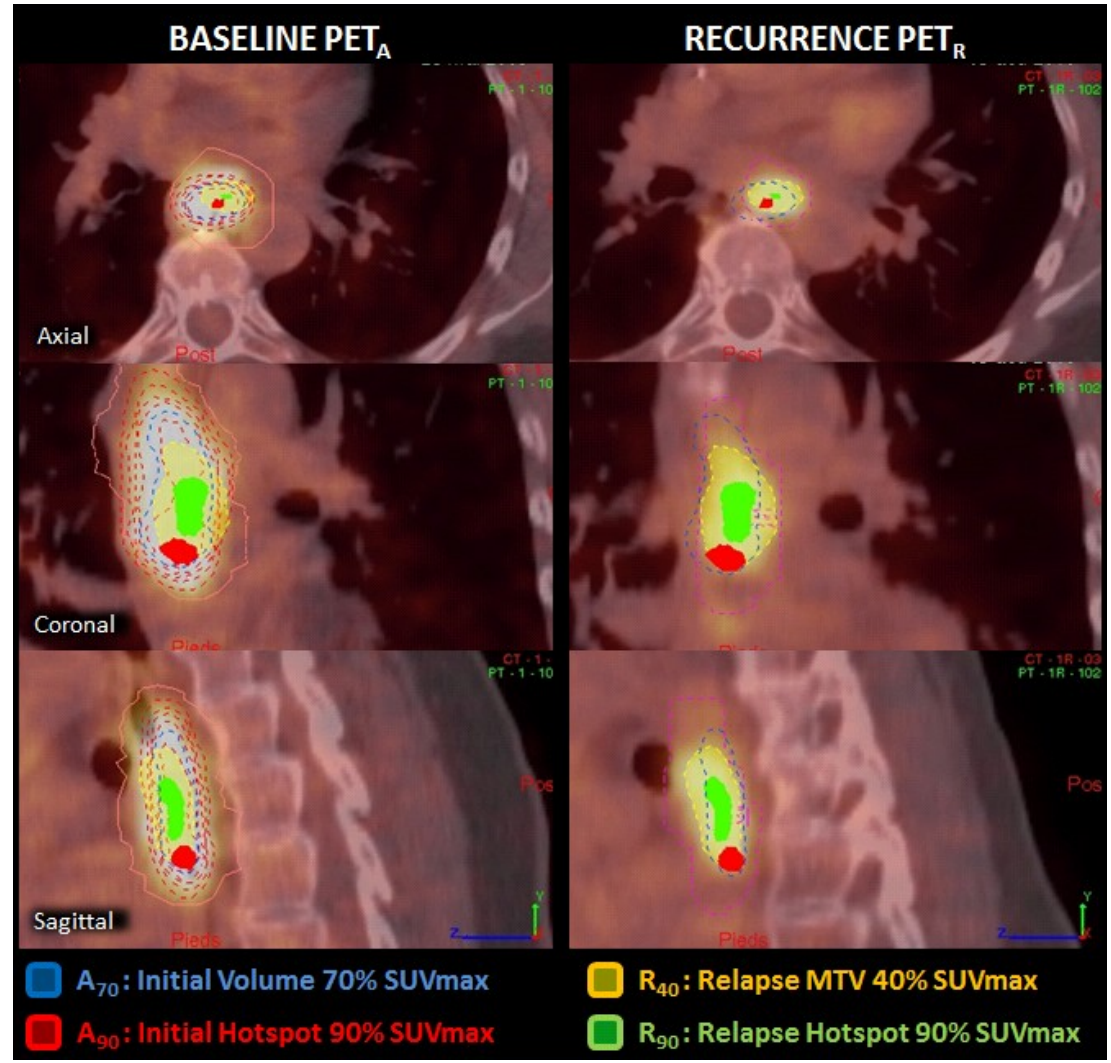


Calais JNM 2015

High uptake in pre-RT : recurrence in esophageal cancer

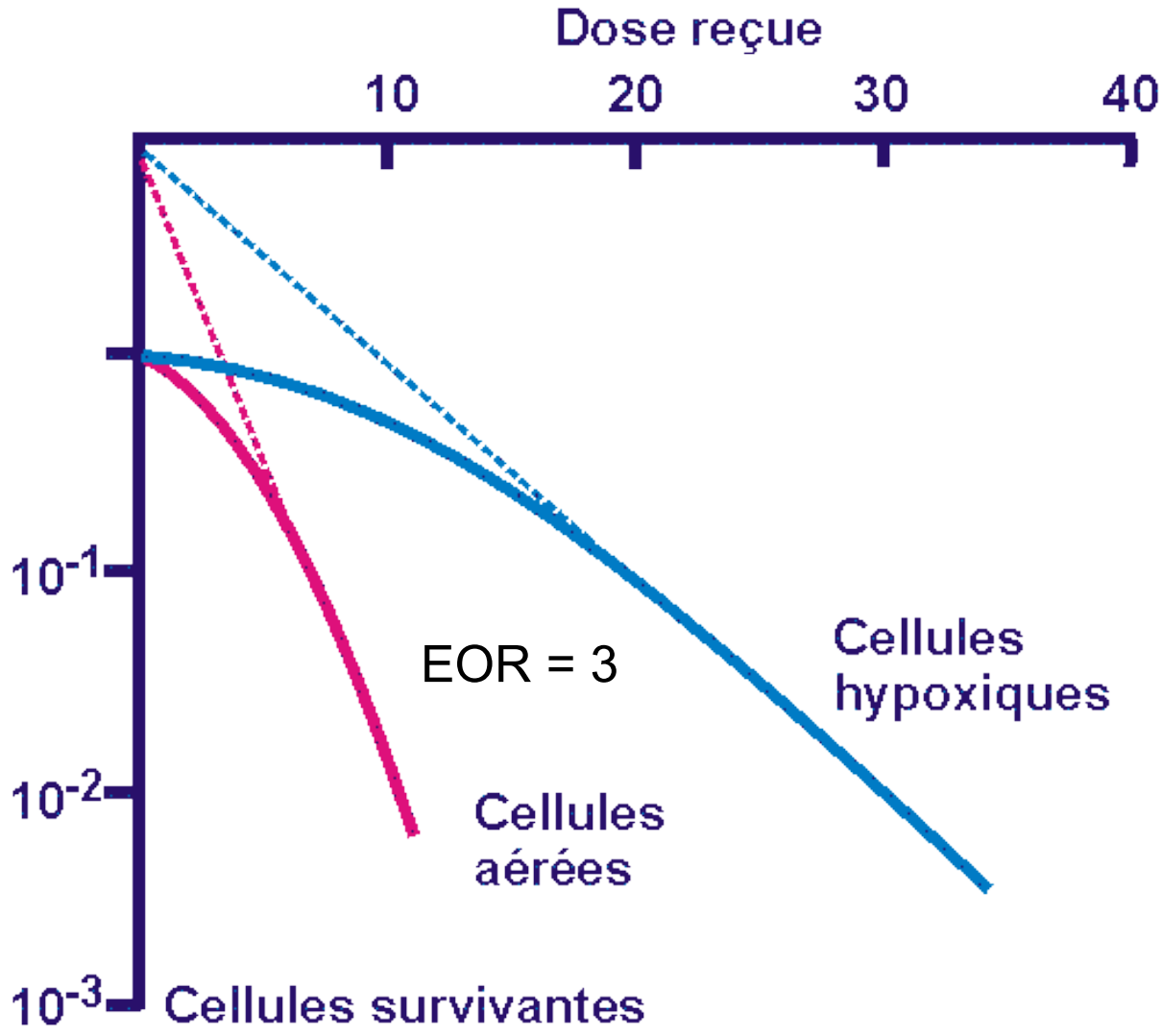
Initial Clinical and RT Characteristics	Total (n=98)	CR (n=44)	DR (n=19)	LR (n=35)
Age	63 ± 11	63 ± 12	64 ± 9	63 ± 12
Gender				
Male	81 (83%)	33 (75%)	16 (84%)	32 (91%)
Female	17 (17%)	11 (25%)	3 (16%)	3 (9%)
Histology				
SCC	76 (78%)	35 (80%)	14 (74%)	27 (77%)
ADC	22 (22%)	9 (20%)	5 (26%)	8 (23%)
Tumor Location				
Superior	20 (20%)	5 (11%)	3 (16%)	12 (34%)
Middle	43 (44%)	21 (48%)	10 (53%)	12 (34%)
Inferior	43 (44%)	20 (45%)	9 (47%)	14 (40%)
Tumor Stage				
II	25 (26%)	12 (27%)	5 (26%)	8 (23%)
III	56 (57%)	24 (55%)	10 (53%)	22 (63%)
IV	17 (17%)	8 (18%)	4 (21%)	5 (14%)
Endoscopic Tumor Length (cm)	5.1 ± 2.9	4.6 ± 1.8	4.9 ± 2.6	5.9 ± 3.9
>5 cm	33 (34%)	10 (23%)	7 (37%)	16 (46%)
Weight Lost (%)	9 ± 7	8 ± 7	8 ± 6	10 ± 8
Albumin (g/L)	39.0 ± 5.2	39.0 ± 5.2	39.3 ± 5.8	38.9 ± 5.1
RT Duration (Days)	43 ± 12	46 ± 16	41 ± 7	42 ± 9
RT Dose (Gy)	52 ± 4	51 ± 4	53 ± 4	51 ± 4





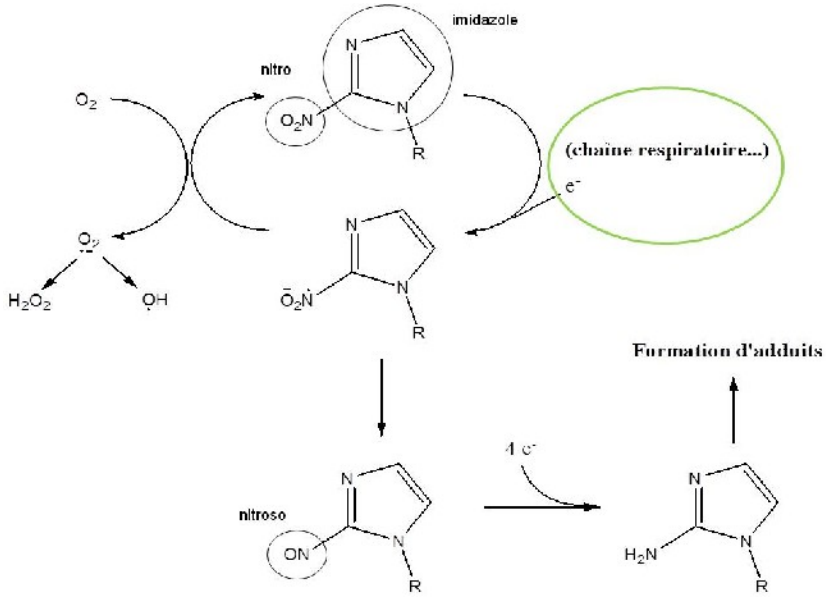
Calais, EJNMMI 2015

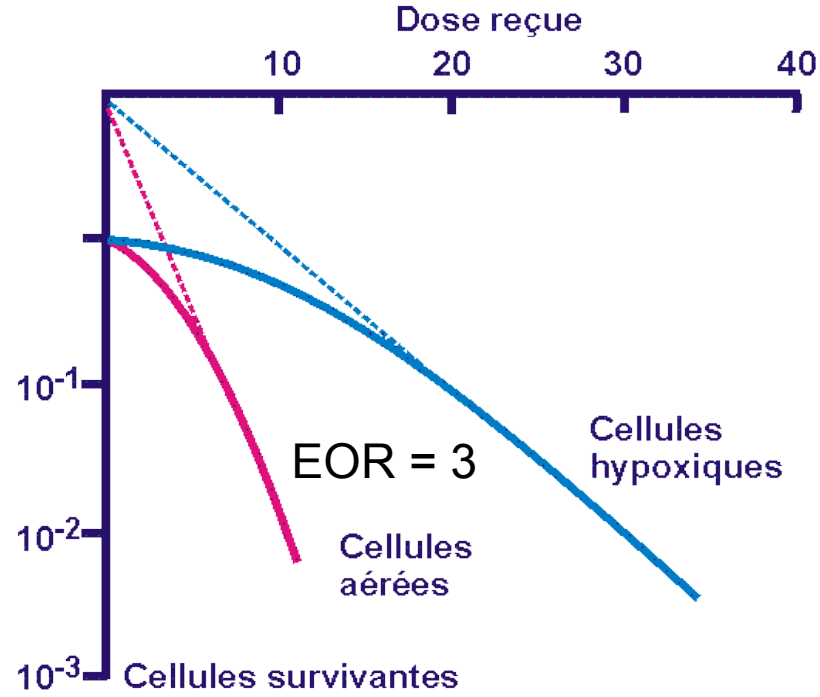
Tumoural **hypoxia** and RT



Tumoural hypoxia and RT

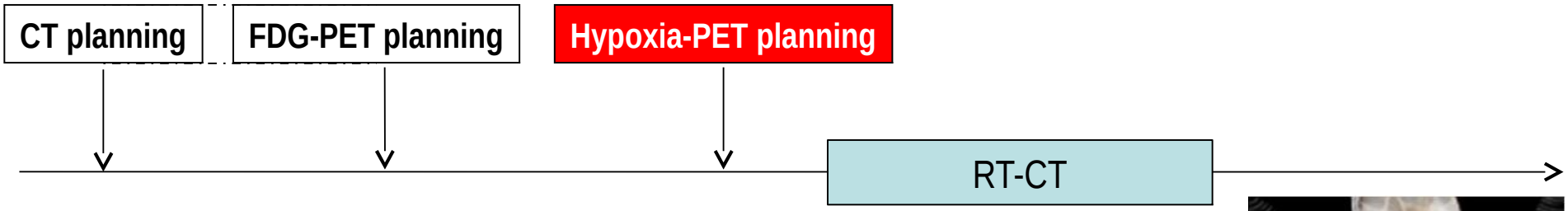
- TEP/PET-Imidazolé
  - ✓ **^{18}F-misonidazole**
  - ✓ ^{18}F-FAZA
  - ✓ ^{18}F-FETA
  - ✓ ^{18}F-FETNIM
  - ✓ ^{18}F-EF1
  - ✓ ^{18}F-EF3
  - ✓ ^{18}F-EF5
  - ✓ ^{124}I-IAZA
  - ✓ ^{124}I-IAZG
  - ✓ ^{124}I-IAZGP
  - ✓ ^{18}F-FRP10
  - ✓ ^{18}F-HX4
  - ✓ ^{68}Ga-NOTA-NI
  - ✓ …

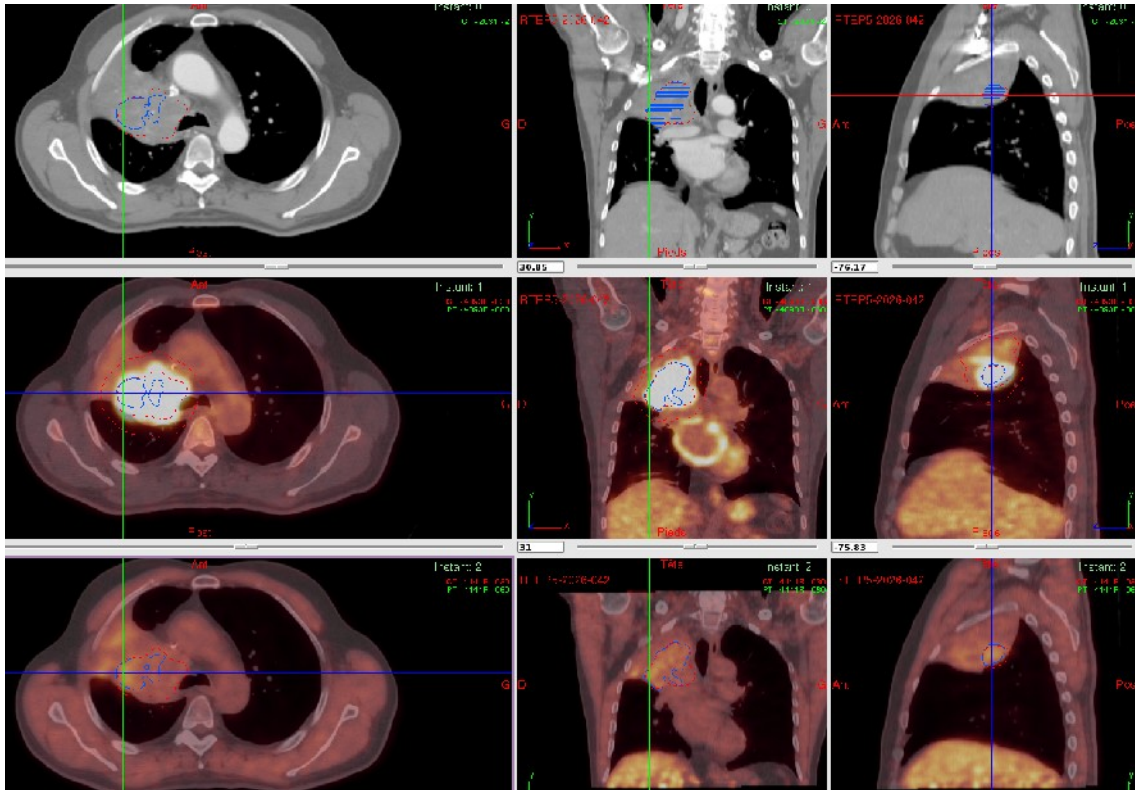




- TEP/PET-non-imidazolé
  - ✓ Cu-ATSM
  - ✓ ^{89}Zr-cG250-F(ab')$_2$, ^{124}I-cG250-F(ab')$_2$ (HIF-1α, CA-IX)

Dose painting based on pre-treatment hypoxia-PET





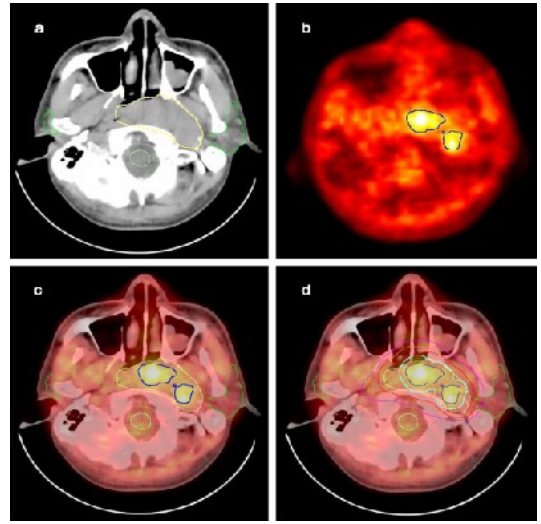
CT

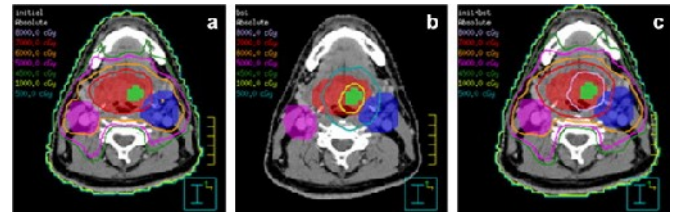
FDG-PET/CT

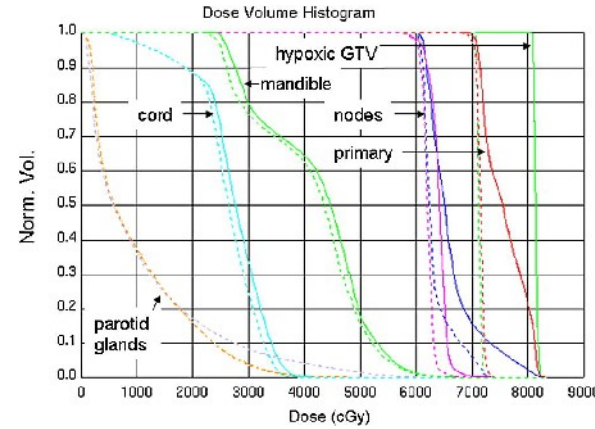
F-MISO-PET/CT

PET-F-miso & boost (H&N)

- Lee, IJROBP07
  - ✓ 10 pts H&N
  - ✓ **84 Gy** on GTVh
  - ✓ 70 Gy on GTV
  - ✓ **105 Gy** on GTVh - 2/14
- Choi, R&O 2010
  - ✓ 8 pts H&N
  - ✓ **84 Gy** (4) on GTVh,
  - ✓ 78 Gy (2), 72 Gy (2)
- Hendrickson, R&O 2011
  - ✓ 10 pts H&N
  - ✓ 70 Gy on PTV
  - ✓ **80 Gy** on GTVh
  - ✓ 60 Gy on nodes





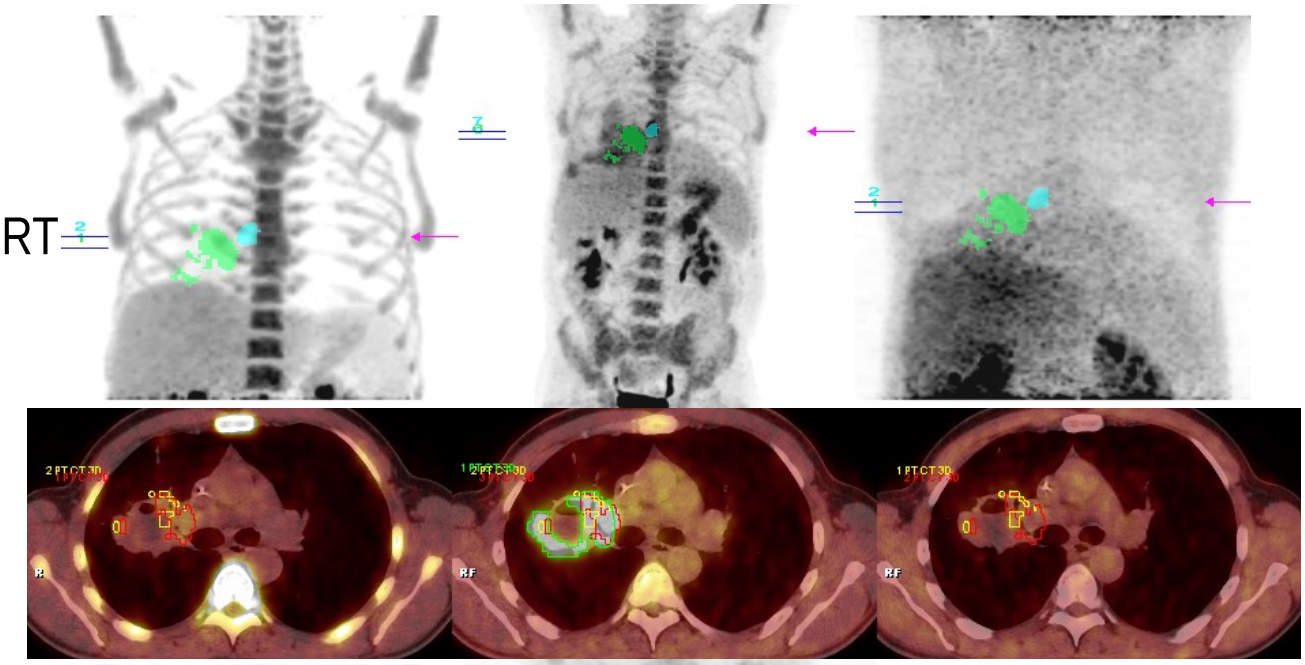


Proliferation

Metabolism

Hypoxia

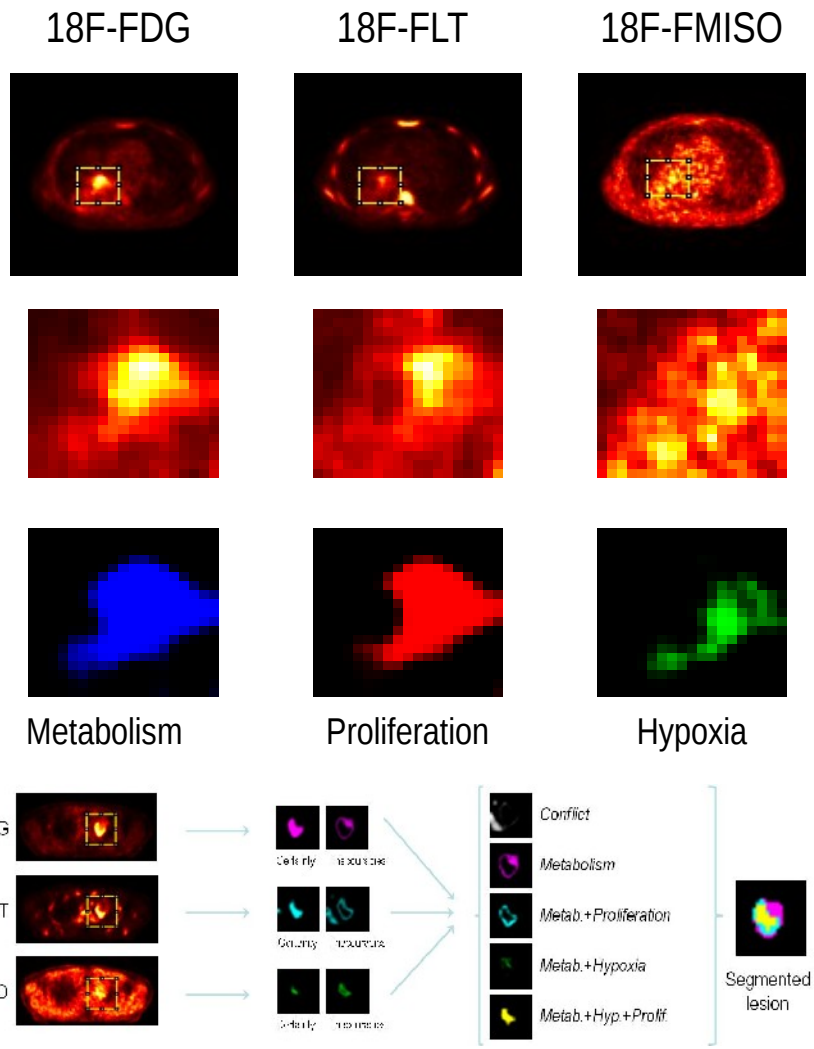
Before RT

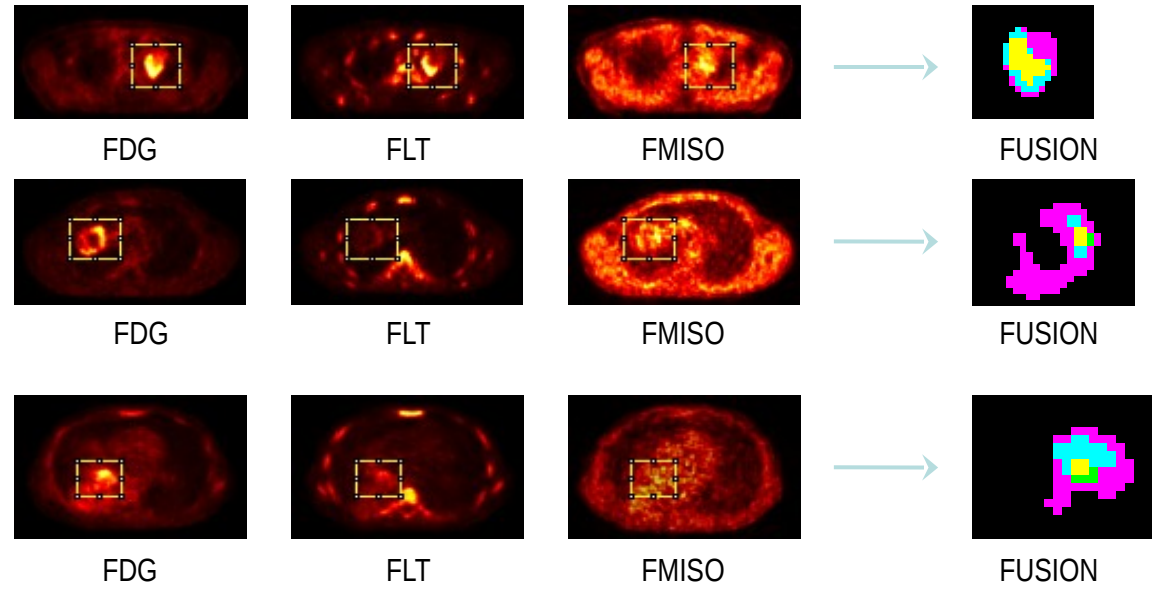


42 Gy

Vera, R&O 2012

Belief Function : multitracer images segmentation





Lelandais, PMB2012, MICCAI2012, IJAR2014, MIA 2014

Multitracers imaging using Belief function

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Fusion of multi-tracer PET images for dose painting

Benoît Lelandais [a,*], Su Ruan [a], Thierry Denœux [b], Pierre Vera [c], Isabelle Gardin [c]

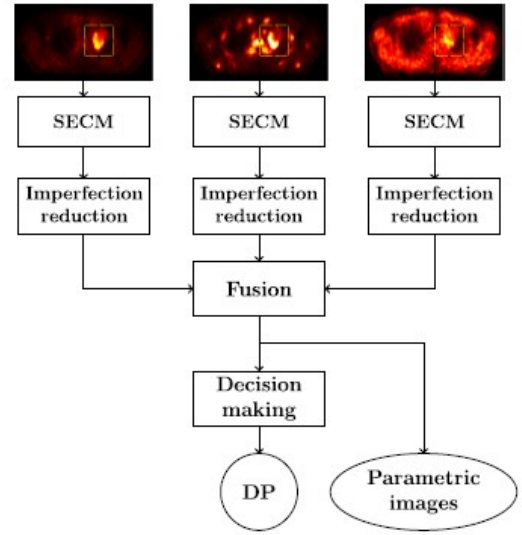
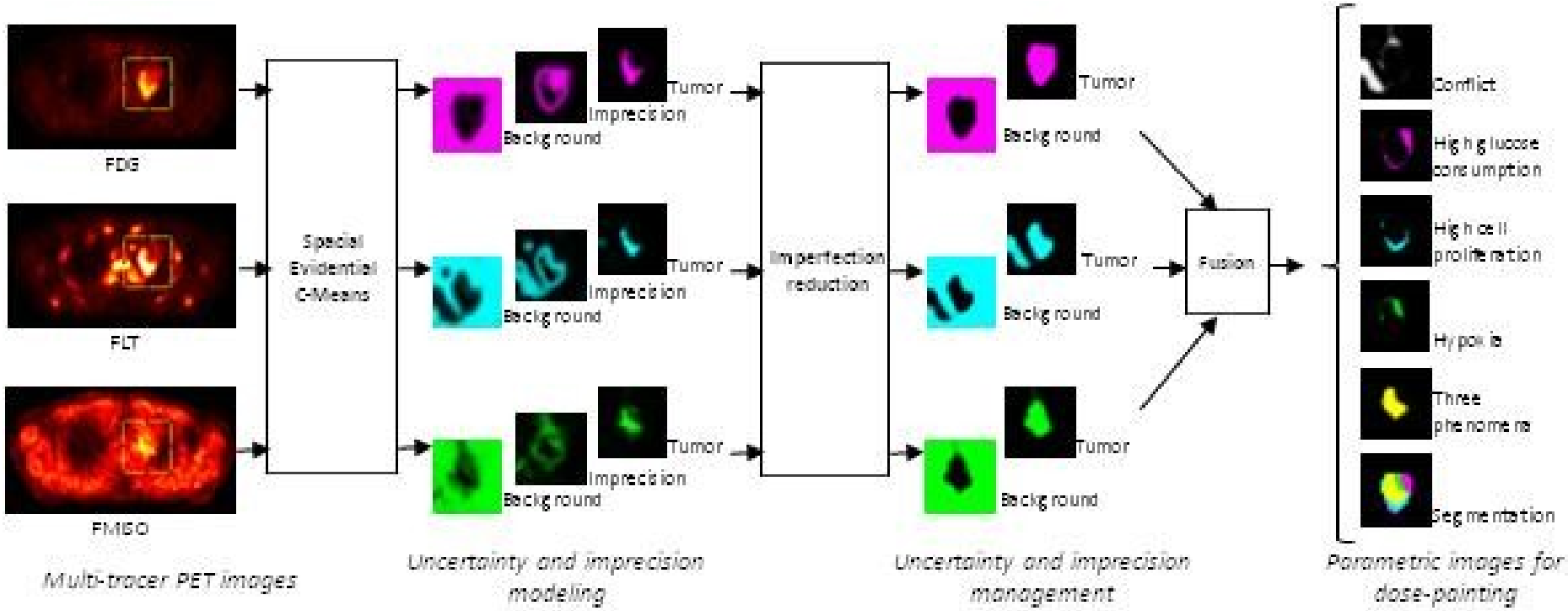
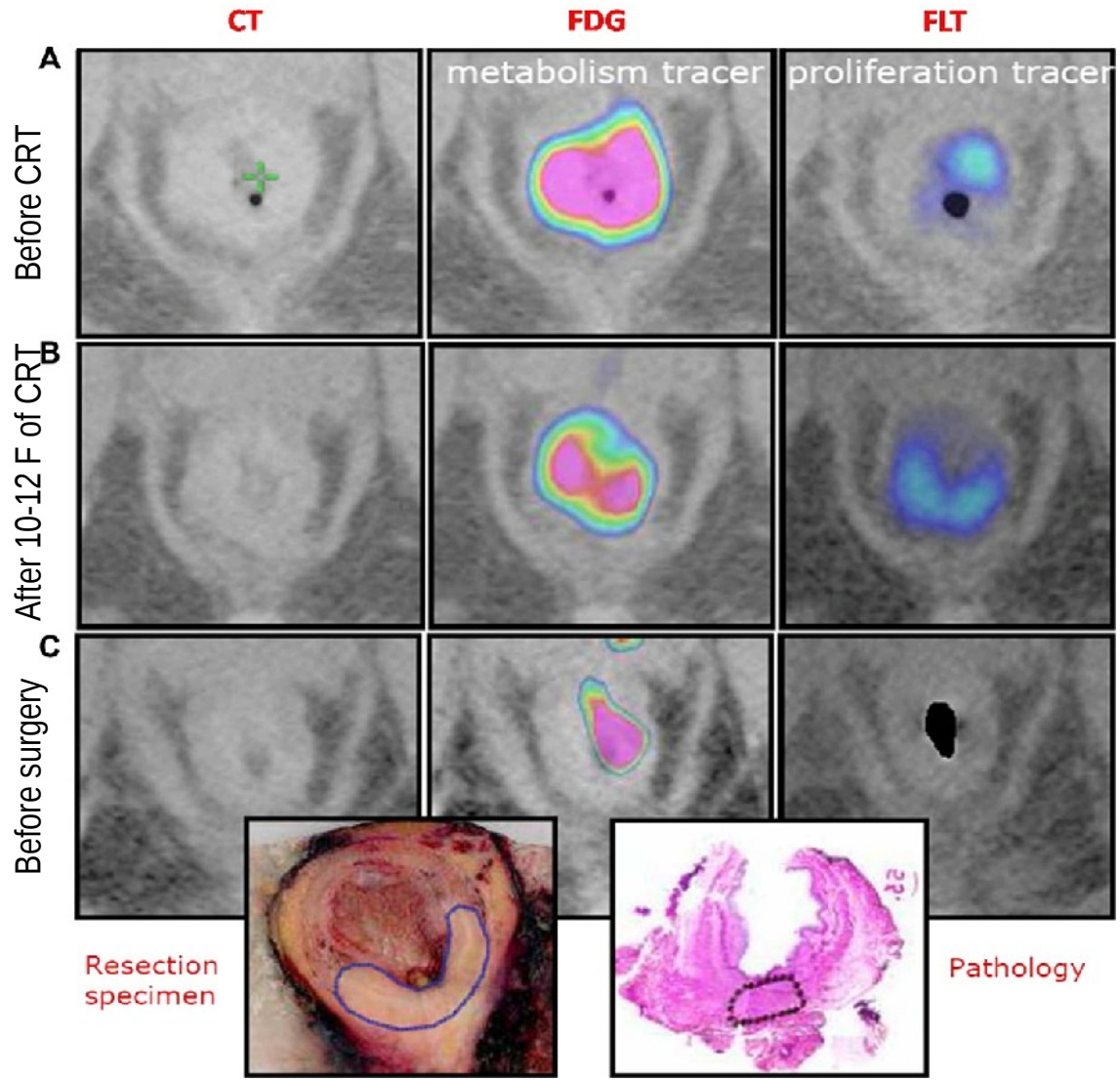
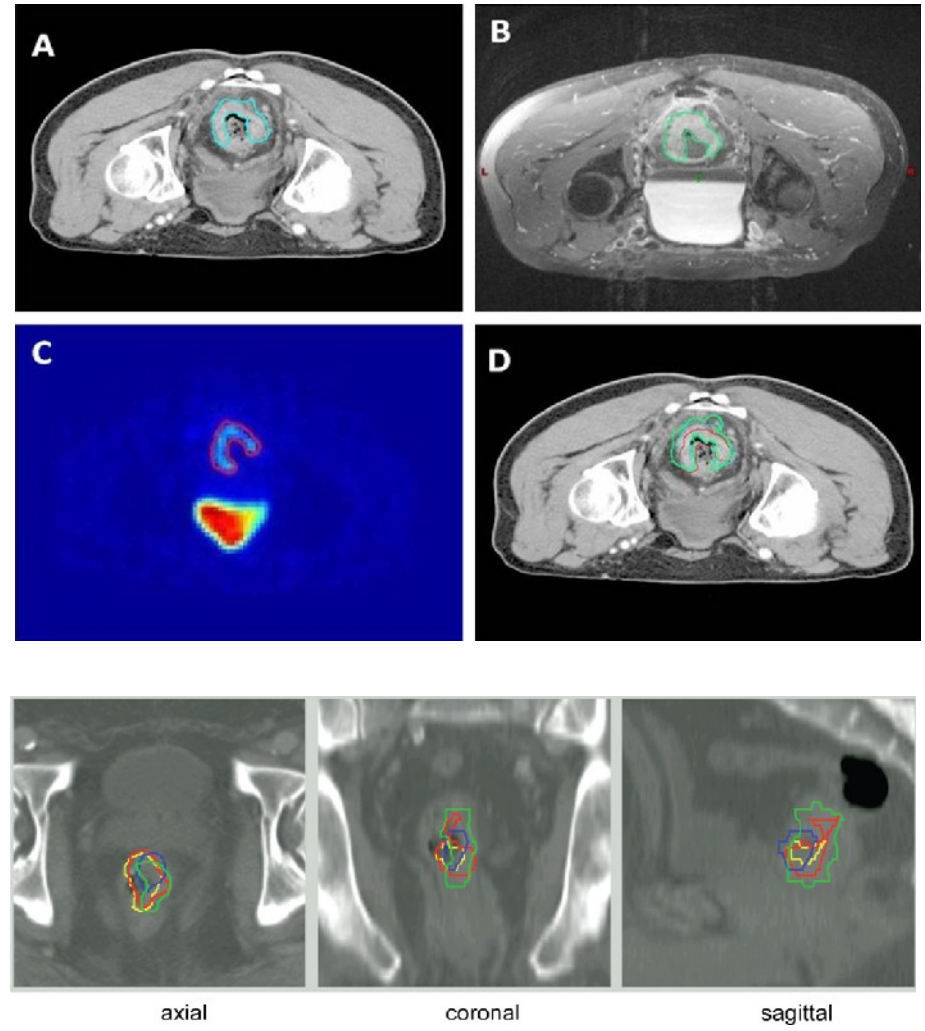


Fig. 2. Proposed fusion sheme from multi-tracer PET images.



FDG, FLT, F-miso in rectal cancer (n=15)

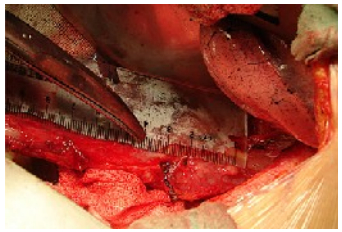


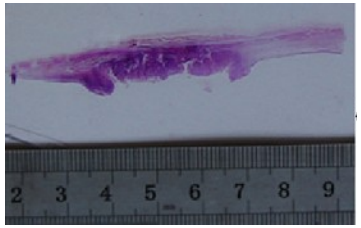


FDG (green), FMISO, (red), FLT (red)

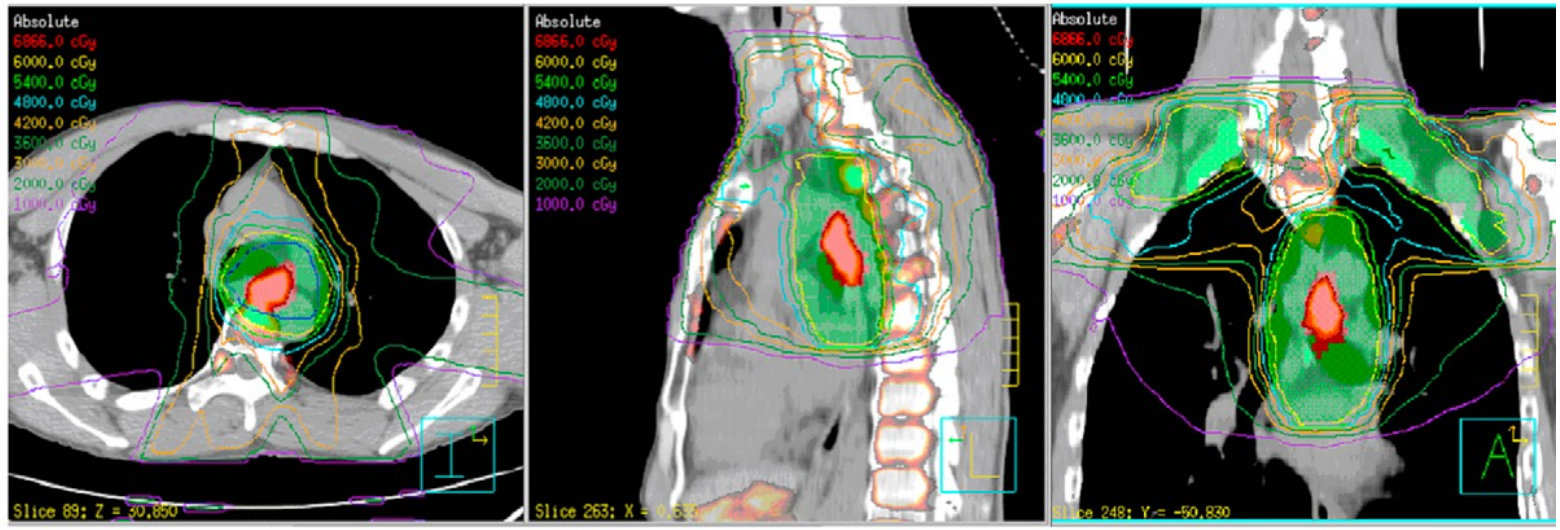
Lambrecht and Haustermans, R&O 2010; Roels, Acta Oncol 2008

FDG, FLT in SCC esophagus cancer (n=22)

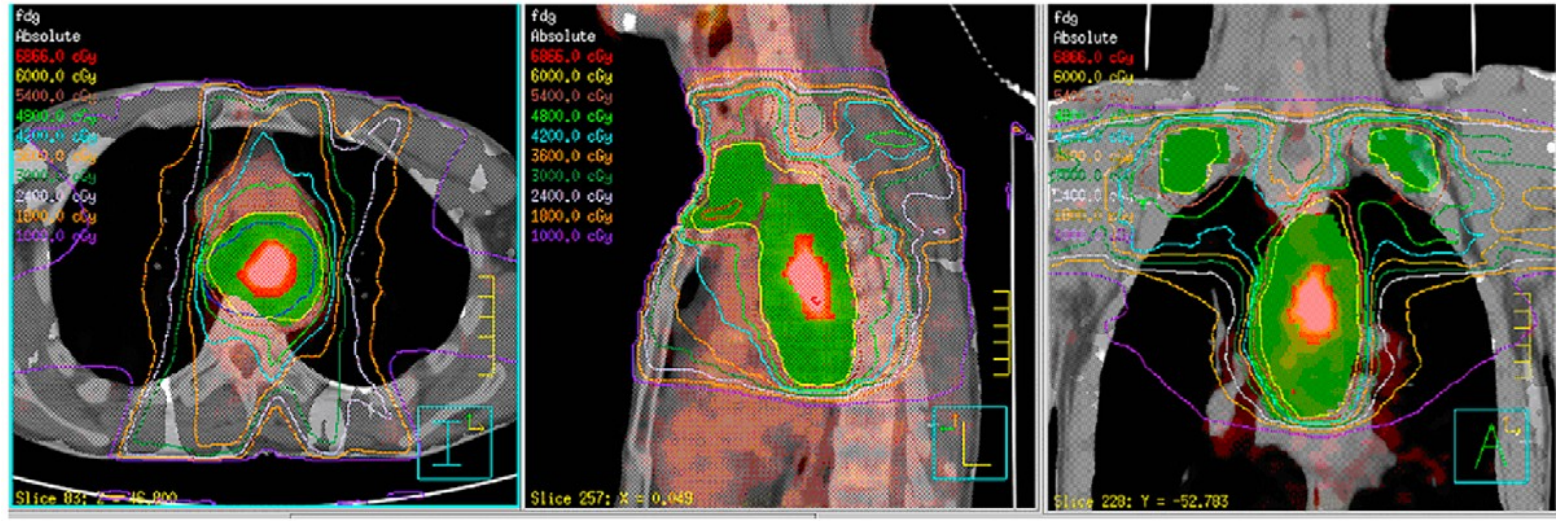




(a)



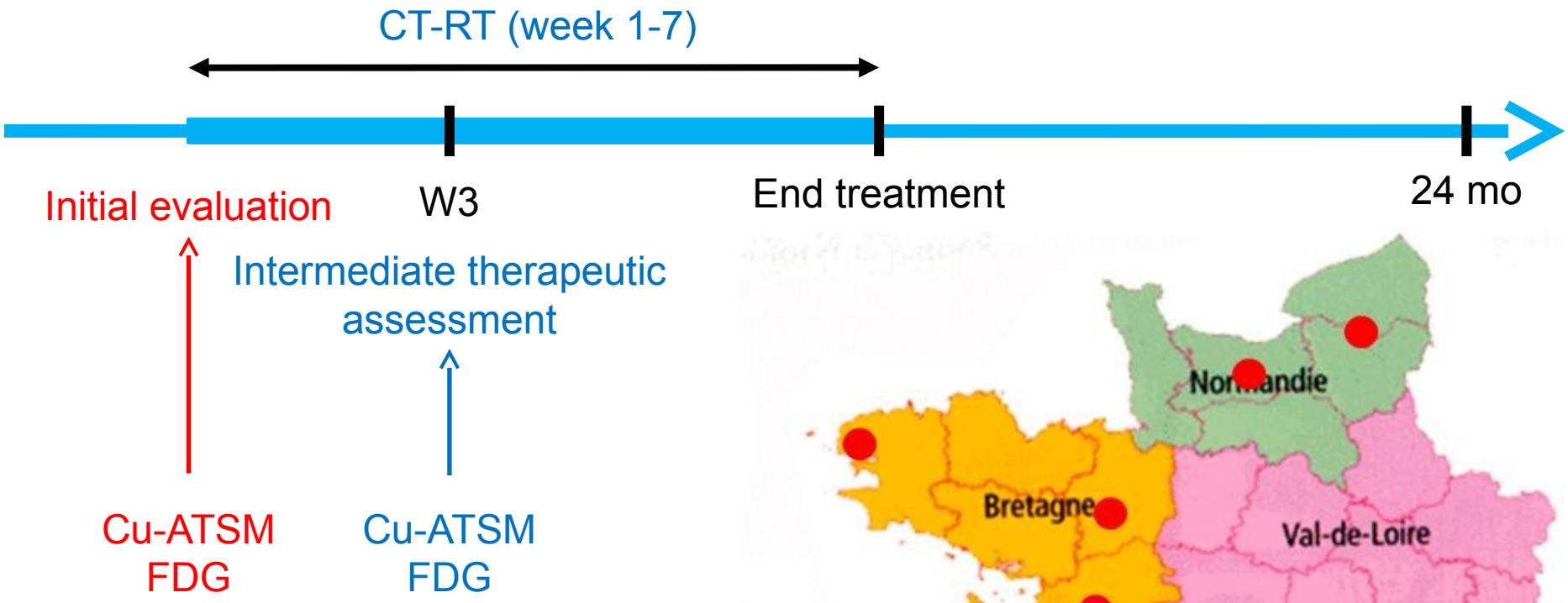
(b)



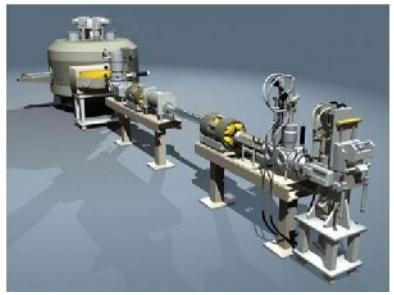
"FLT PET/CT-based treatment planning provided potential benefits to the lungs and heart"

Han, IJROBP 2010

HYPOXIC : **Prognostic interest of tumor hypoxia imaging by 64Cu-ATSM PET in patients with locally advanced stage III/IV HNSCC treated by concurrent chemo-radiotherapy** (Lettre intention PHRC2015)



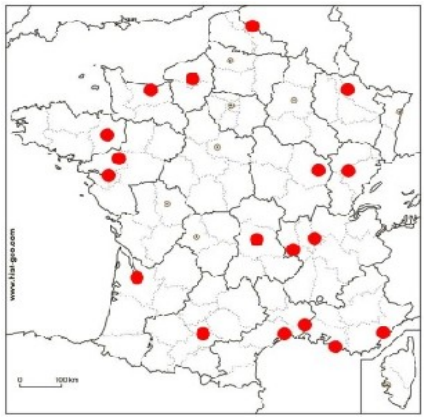
ARRONAX



RTEP5 - Phase II RT-boost in lung cancer

PHRC 2011

Date du bilan à 3M du dernier pt inclus **14/3/15**



6 sorties

F-miso1
n=**61**

F-miso2
n=**31**

FDG1 +
n=**61**

FDG2 +
n=**32**

3 months
n=**34**/25

1 year
n=?

Hypoxia
n=**40**/30

CT induction

RT-CT
Boost *(max dose)*

RT-CT
66 Gy
n=**21**/30

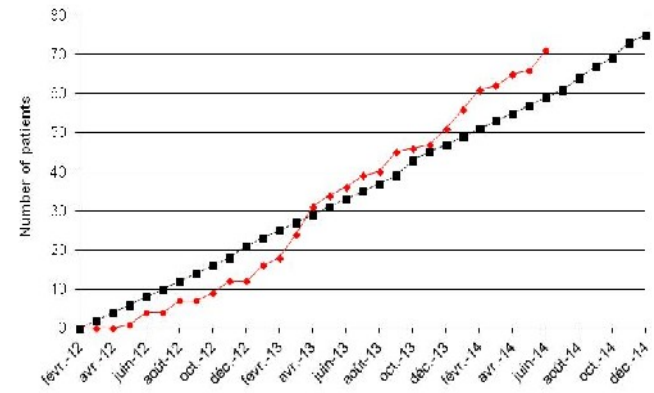
Pre-inclusion
n=**79**/75

Inclusion
n=**61**/60

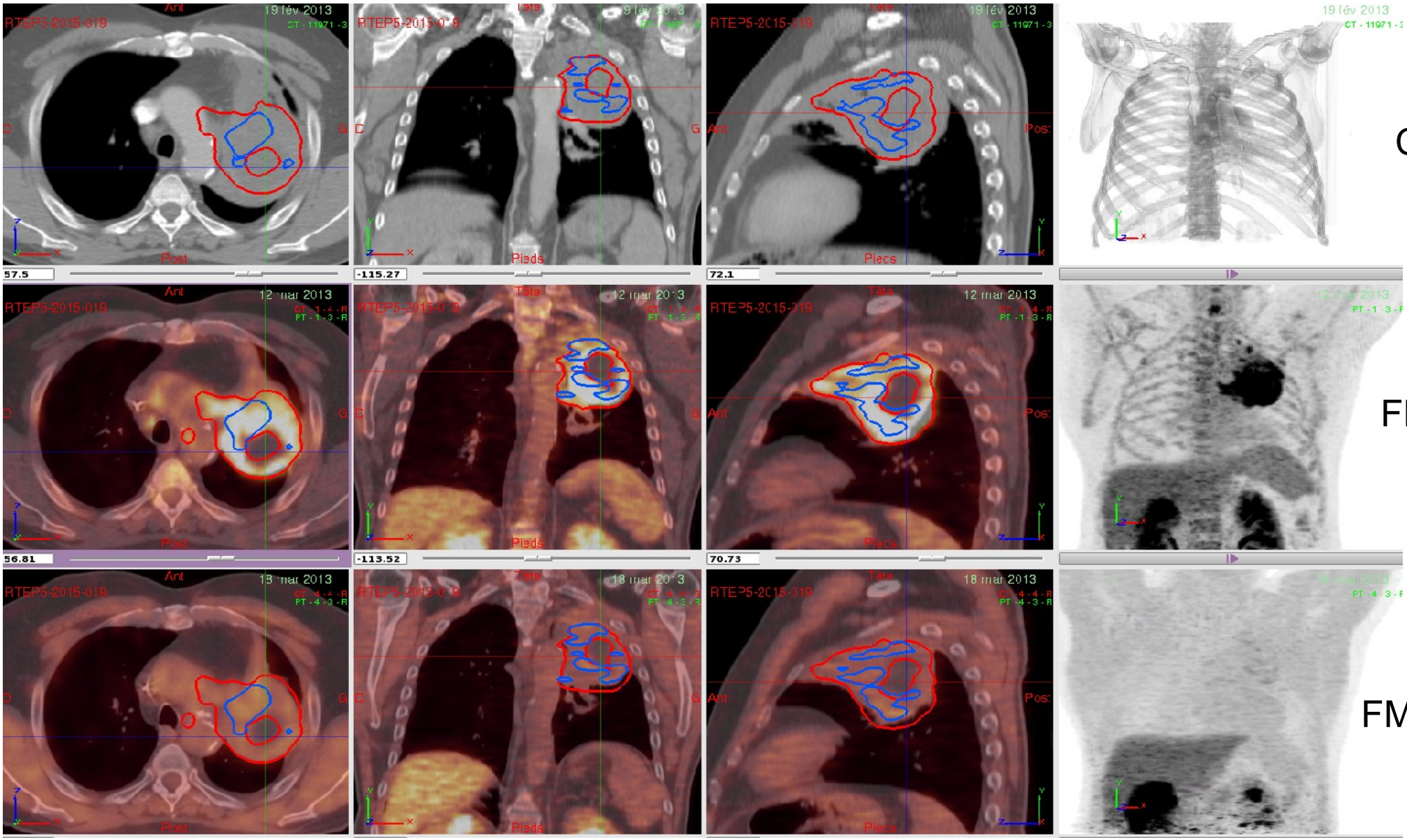
No hypoxia
n=**21**/30

18 sorties (dont 7 M+ sur FDG1)

1 sortie



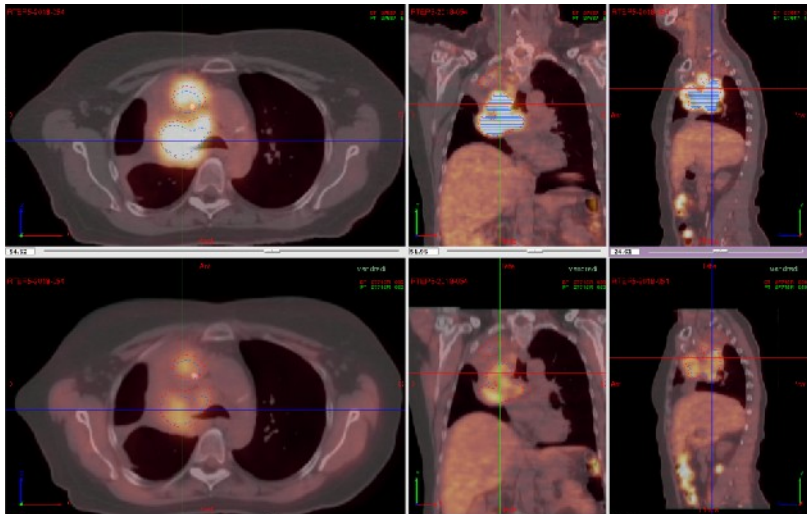
RTEP 5 : GTVm et GTVh

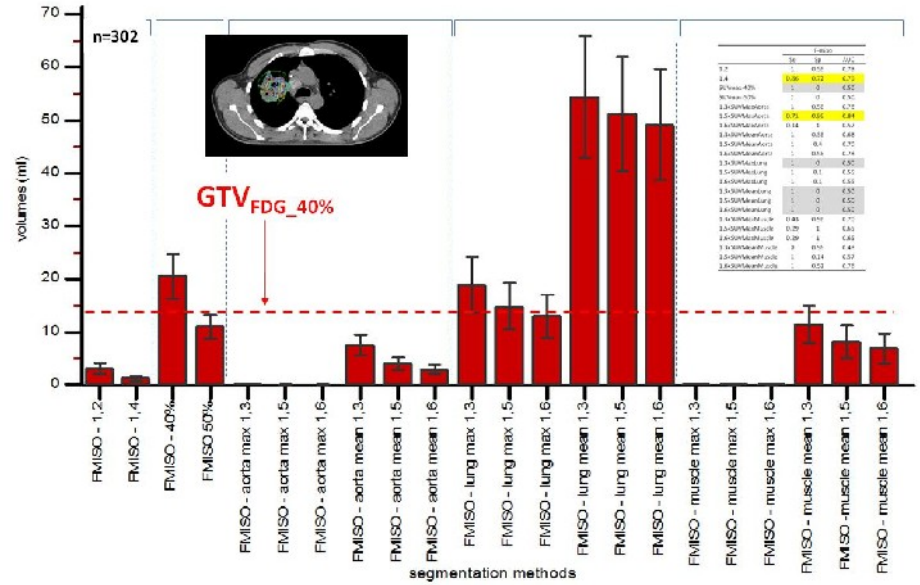


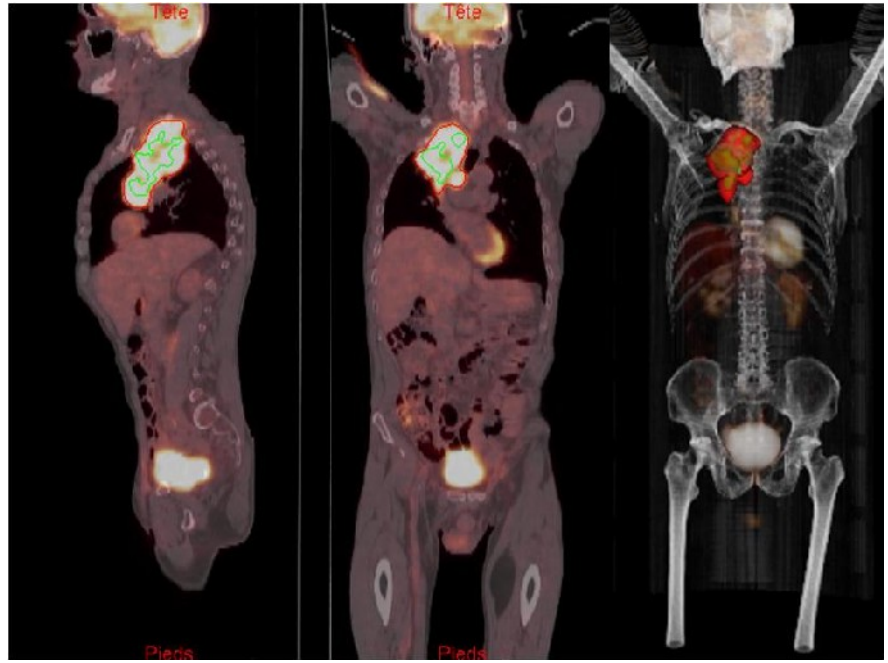
RTEP5 - BTVh

kappa	FDG	F-miso
5 classes	0.59	0.44
2 classes	0.81	0.77

GTVh = 1.4 SUVfmiso (à l'intérieur du GTVm)

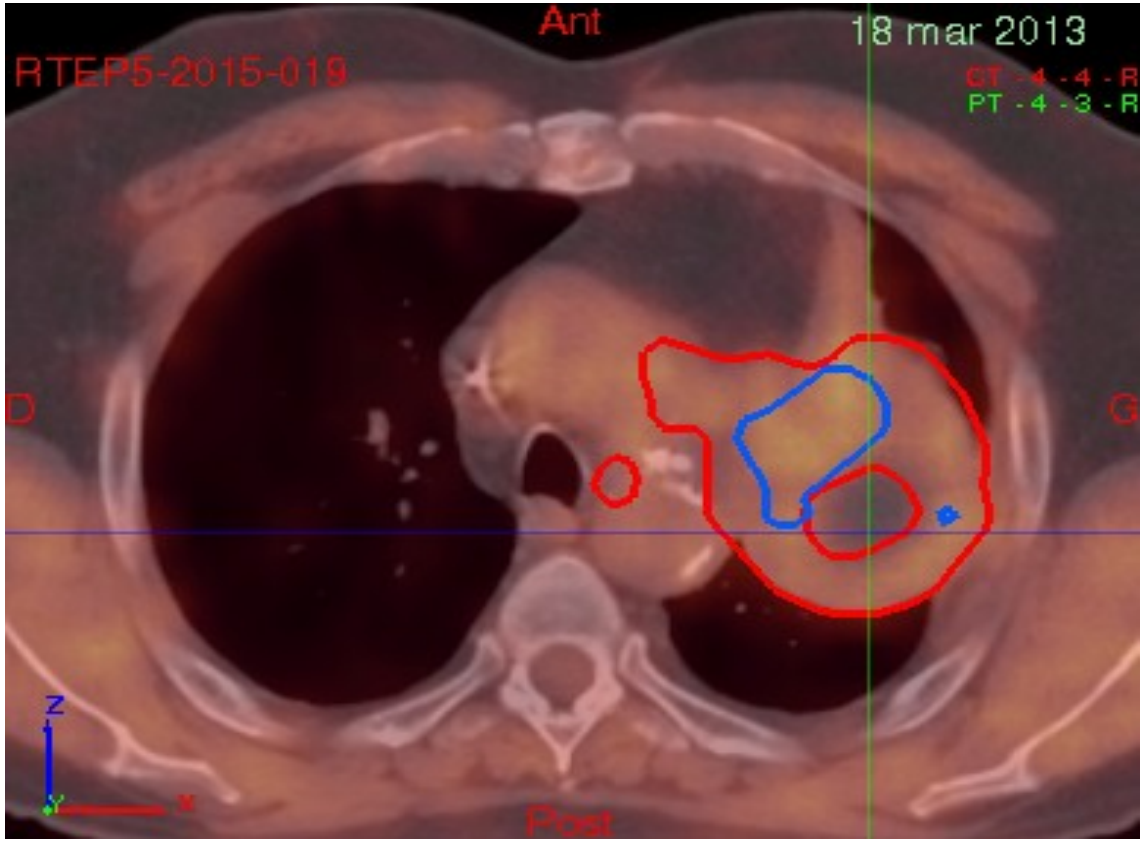


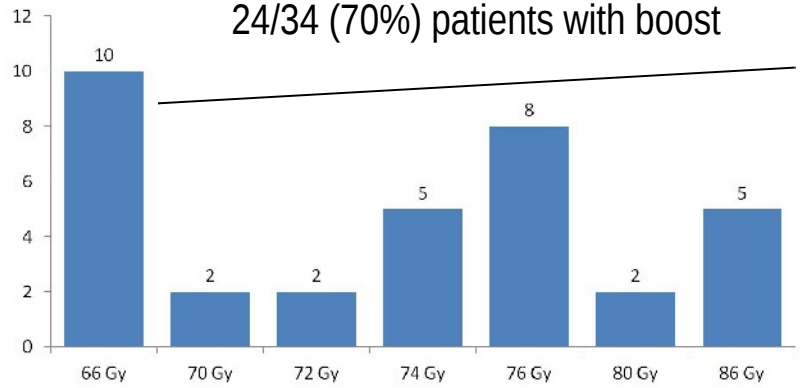




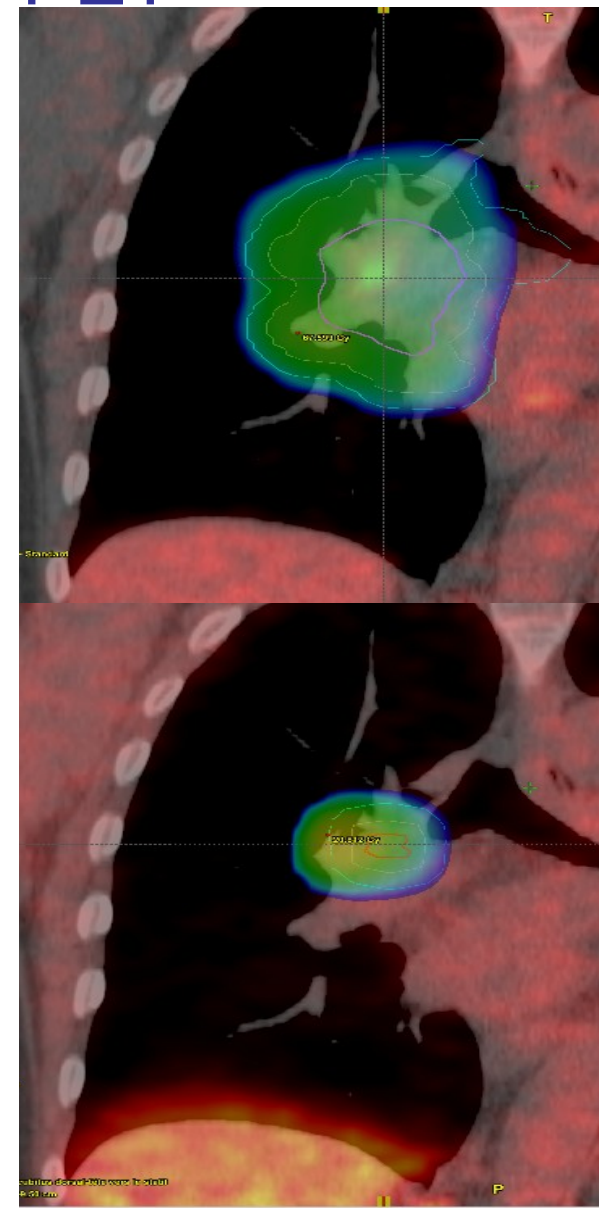
Thureau, JNM 2013

RTEP5 : Boost on pre-treatment F-miso PET



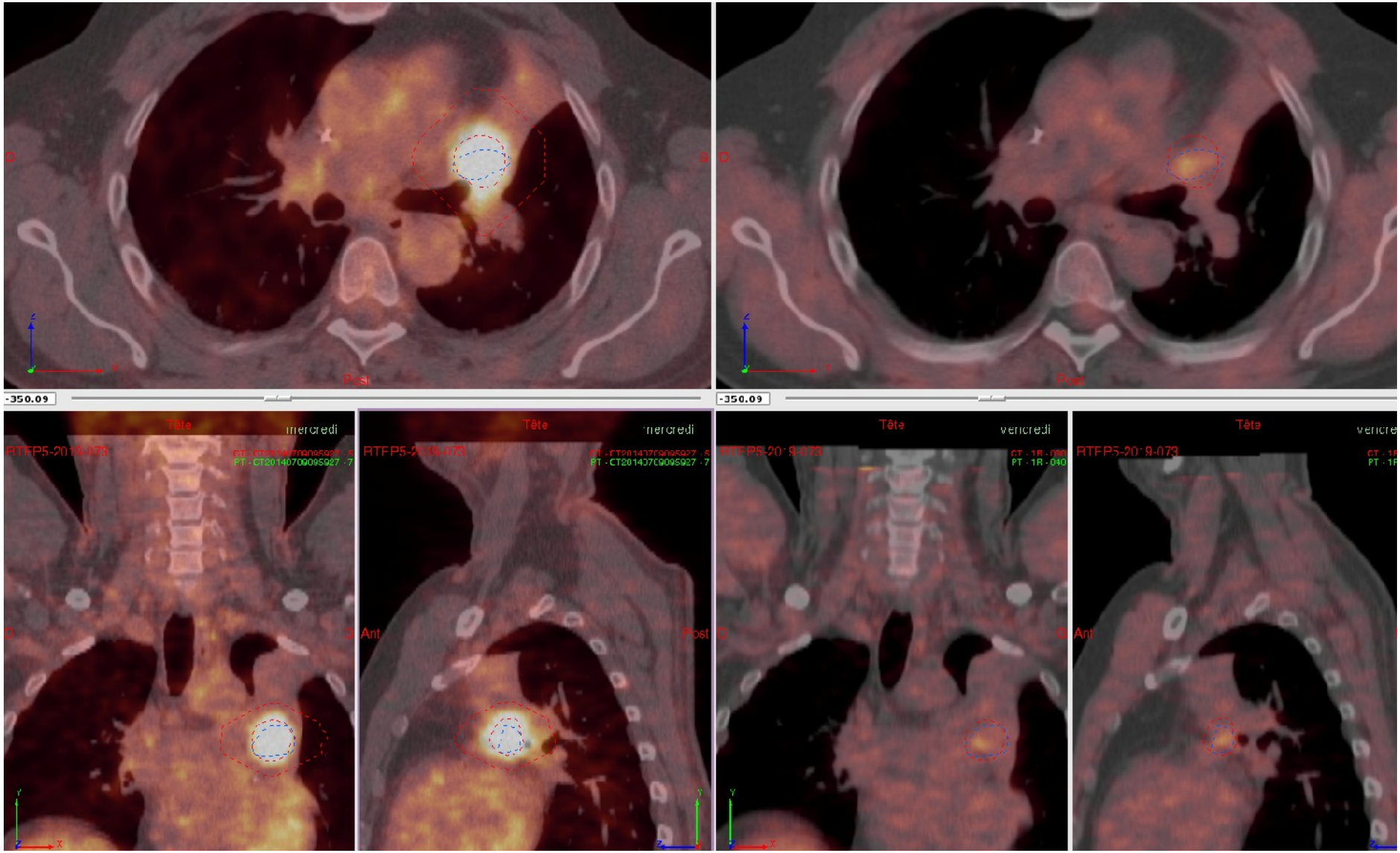


Toxicity
0 grade 4
2 grade 3
(86 & 66 Gy)



66 Gy + boost 20 Gy

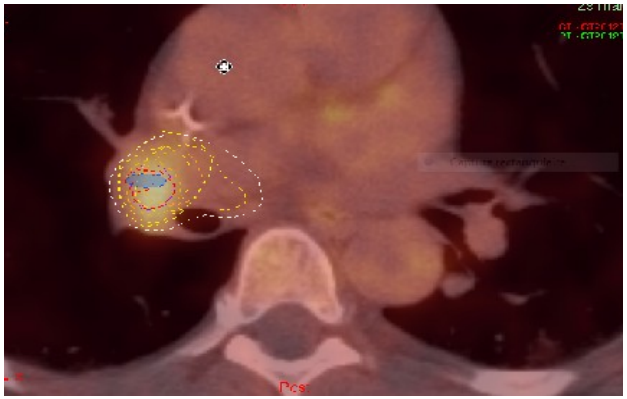
RTEP 5 : BTVm et BTVh

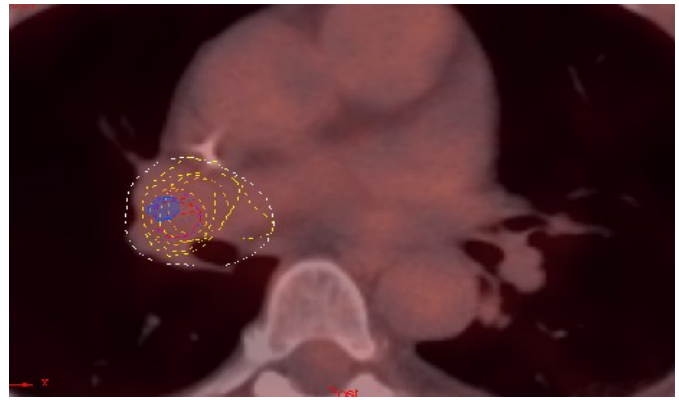


Résultats préliminaires (n=33 pts hypoxiques)

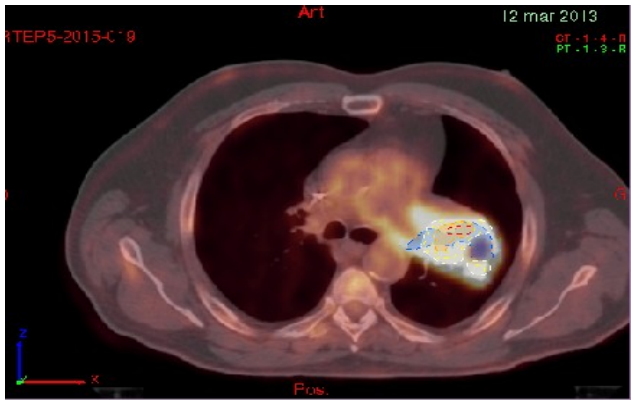
FDG | FMISO

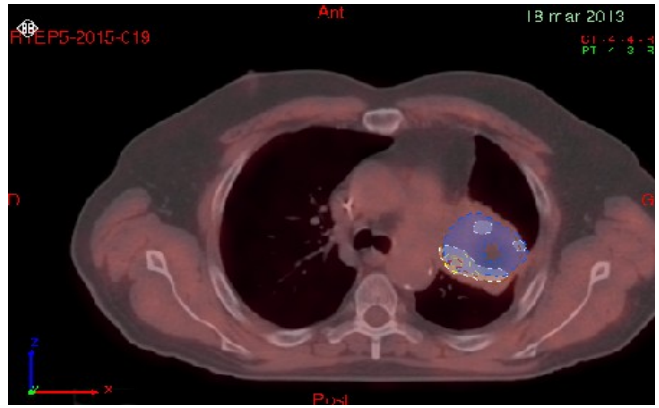
#1



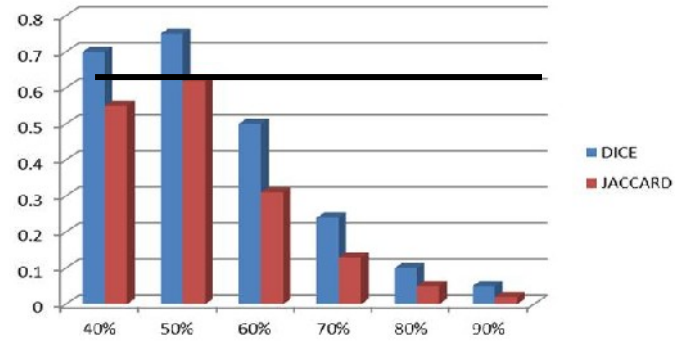


#2

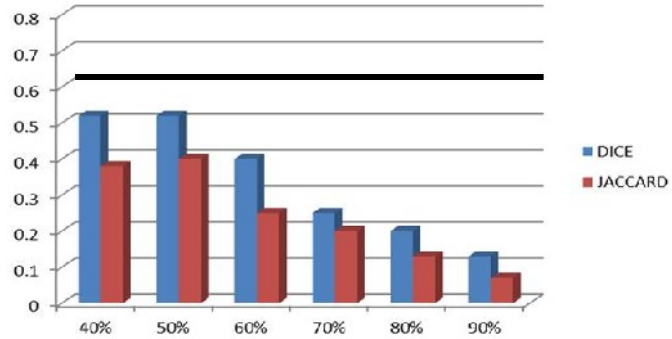




Ensemble des volumes (n=70)



Volumes avec fixation Fmiso ≥ 2 (n=35)



Thureau, RTEP5, La Rochelle 2015

RTEP6. Etude comparative de l'hypoxie mesurée en TEP/TDM au F-miso et au FAZA chez les patients atteints d'un cancer broncho-pulmonaire non à petites cellules au moment du diagnostic : Corrélation avec l'immunohistochimie

< 21 j

24h

24h

TEP/TDM FDG

TEP/TDM F-miso

TEP/TDM FAZA

Diagnostic
Bilan pré-thérapeutique
Preuve histologique
n=20

J5/J6

-J2

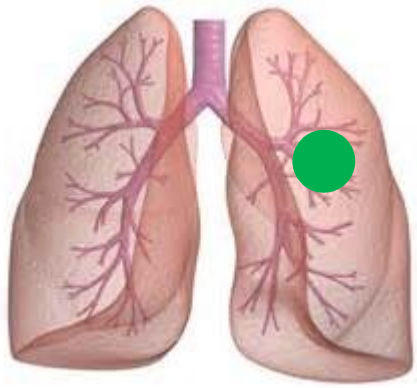
-J1

J0

Chirurgie

3 mois

1 an



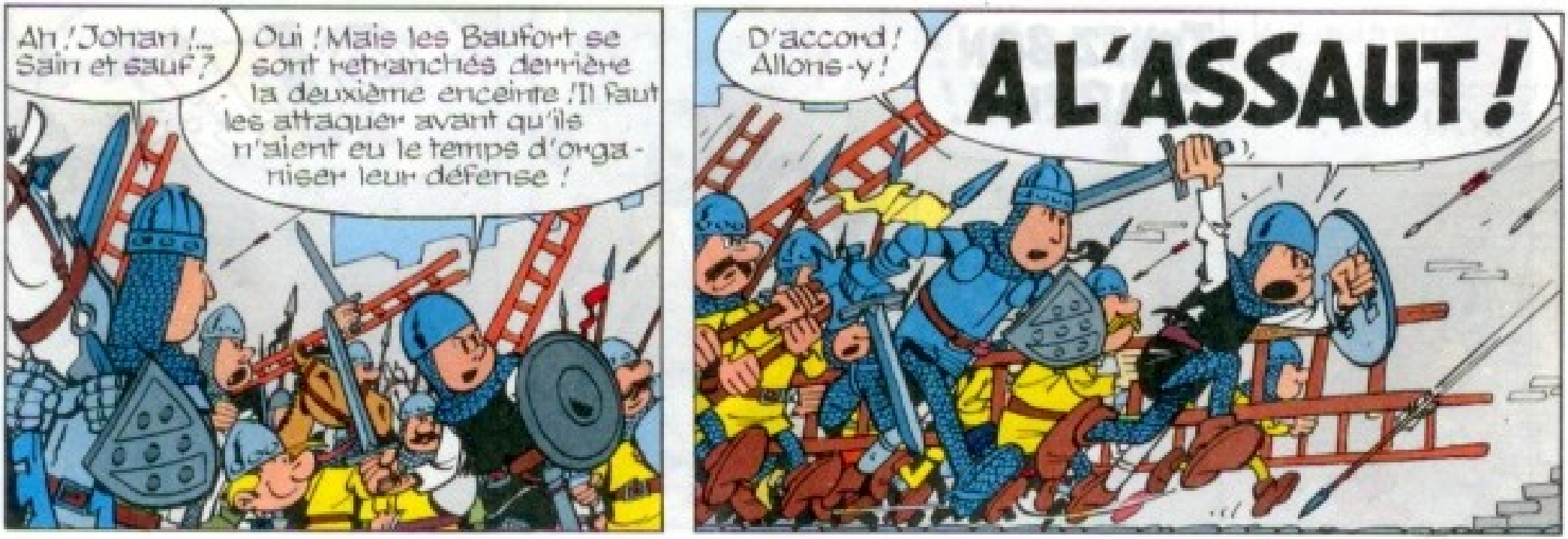
Inclusion
n=20

Anapath - IHC

Etude

Suivi

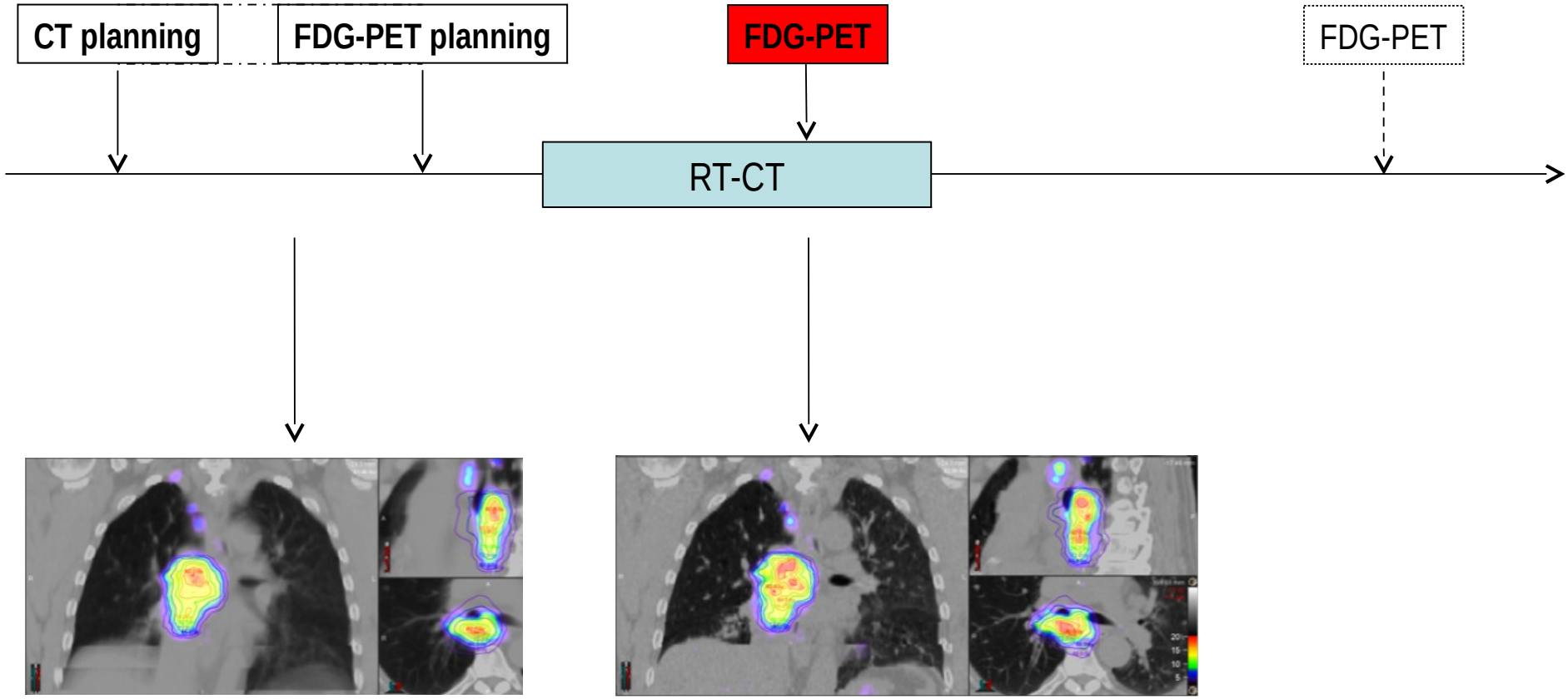
When target?


Ah ! Johan !... Sain et sauf ?
Oui ! Mais les Baufort se sont retranchés derrière la deuxième enceinte ! Il faut les attaquer avant qu'ils n'aient eu le temps d'organiser leur défense !
D'accord ! Allons-y !
A L'ASSAUT !

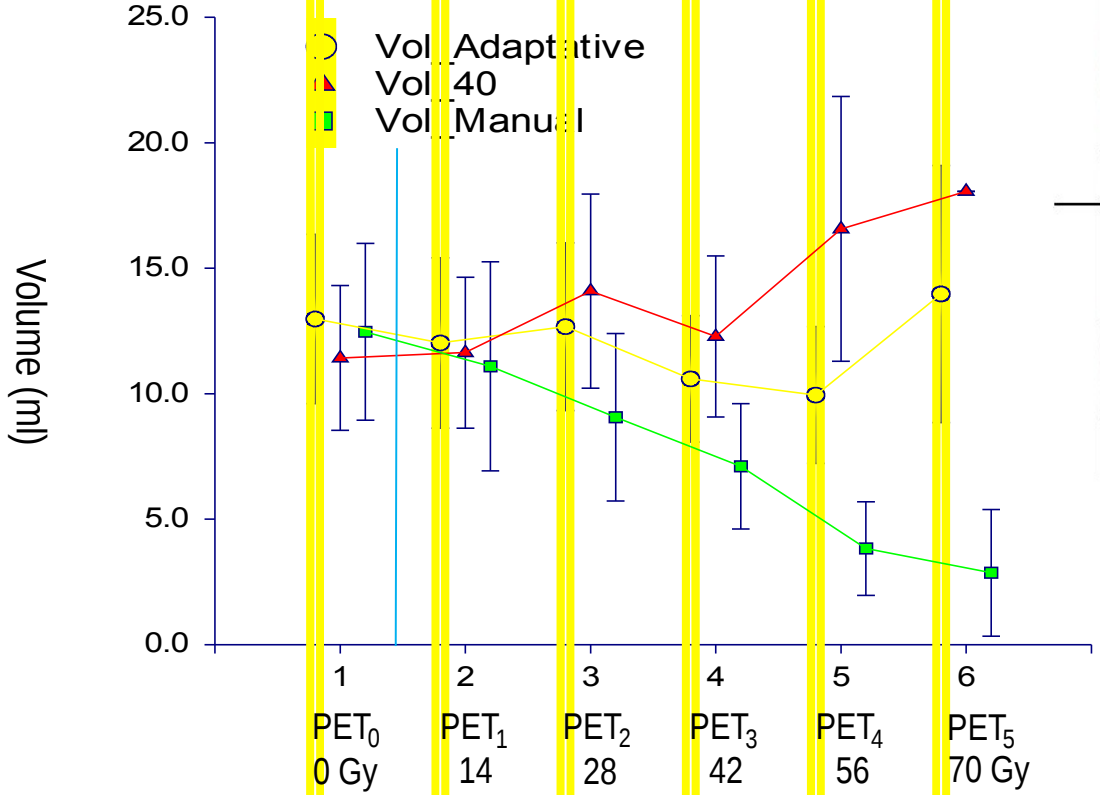
PET/CT for RT during-treatment

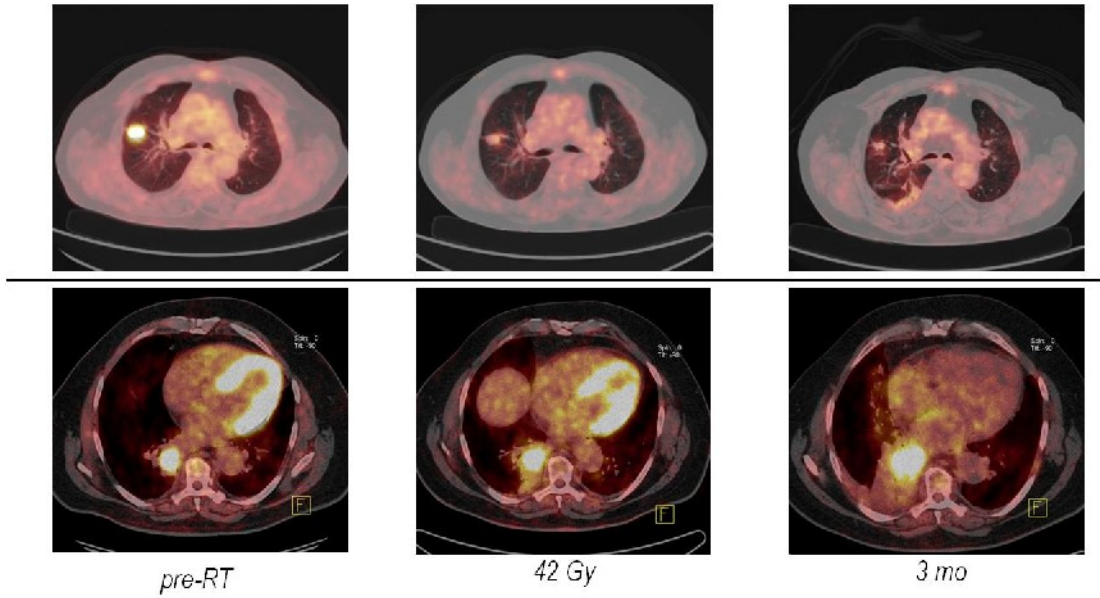
1. FDG
2. Hypoxia

Dose redistribution based on per-treatment FDG-PET



PET-FDG during RT (RTEP1)

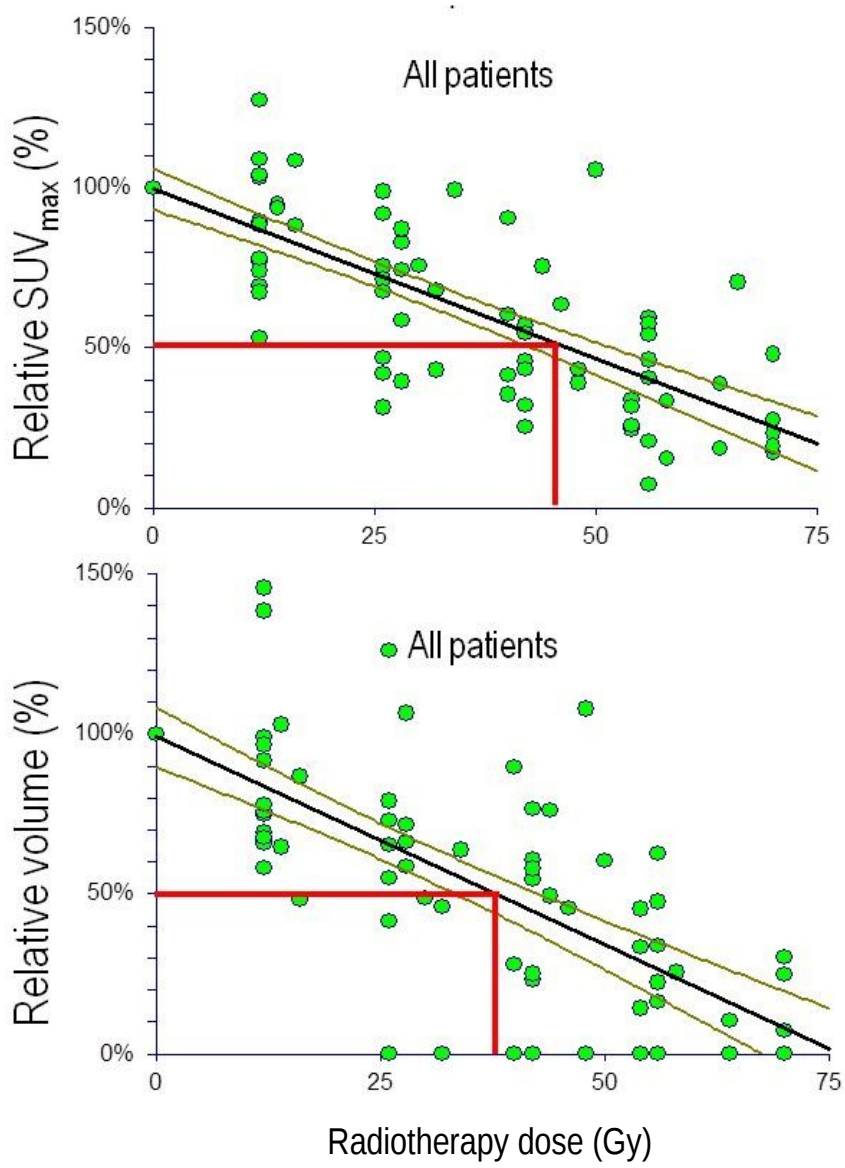




No artefact during RT

Edet-Sanson, R&O 2012

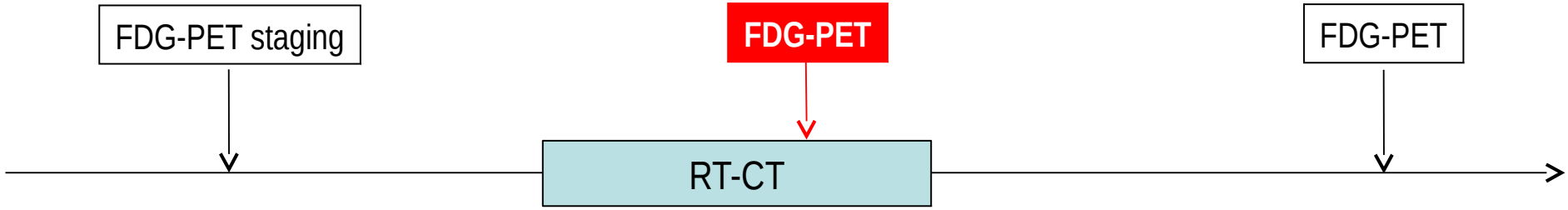
PET-FDG during RT (RTEP1)



Arround 42 Gy (5 we)

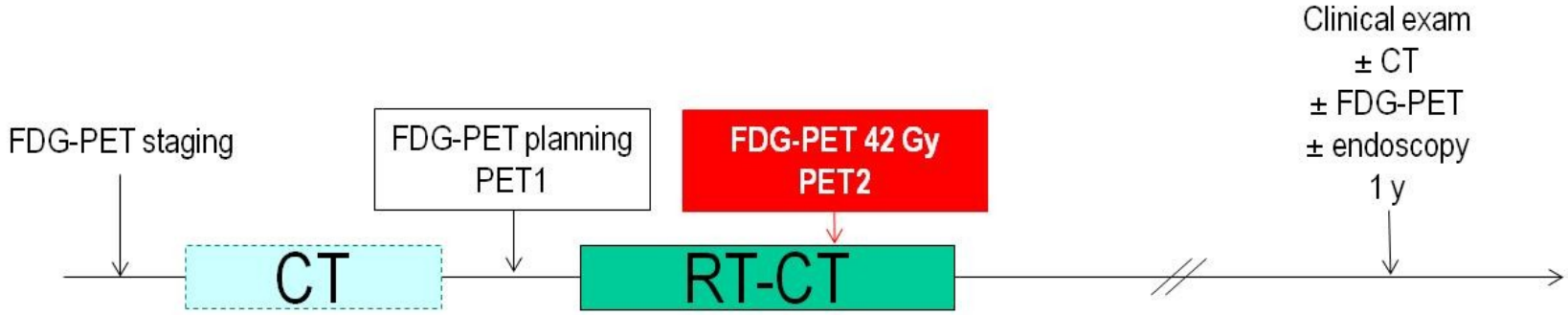
Edet-Sanson, R&O 2012

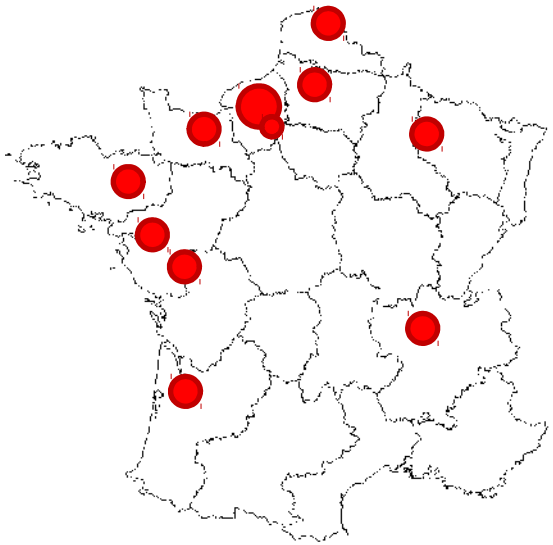
PET-FDG **during** treatment for **prognosis**



Study	n	Type	Stage	Delay	Treatment	Cut-off	Predictive value
Hoestra 2005	47	Retrosp.	IIIA	1 à 3 cycles	Chir ou RT	Residual MRglu = 0.13	OS: yes
Pottgen 2006	50	Retrosp	III	3 cycles	RT-CT±surg	na	Histological response: yes
Kong 2007	15	Retrosp	I-III	45 Gy	(CT-)RT	Metabolic response	MR 3 mo after tt: yes
Van Baarwijk 2007	23	Retrosp	III	D7-D14	(CT-)RT	Follow-up	SUVNR > SUVR at D7: yes
Decoster 2008	31	Retrosp	III	3 cycles	RT	Metabolic response	PFS: yes ; OS: tendancy
Hellwig 2009	47	Retrosp	IIB-III	After induction	Surg	SUVmax = 4	OS: yes
Zhang 2011	46	Retrosp	III	40-50 Gy	CT-RT	Decrease 50% SUVmax	OS: yes
Huang 2011	37	Retrosp	III-IV	40 Gy	CT-RT	SUVmax ,SUVmean, MTV	RECIST 1 mo: yes
Van Elmpt 2012	34	Prospect. Mono	II-IV	D14	(CT-)RT	Decrease 15% SUVmax	OS 2y : yes (MTV no)
RTEP2 2014	*77*	*Prospect. Multi*	*III*	*42 Gy*	*(CT-)RT*	*SUV2 (> SUV1 > MTV)*	*OS 1y*

Prognostic value of FDG SUVmax during RCT (PTEP2)





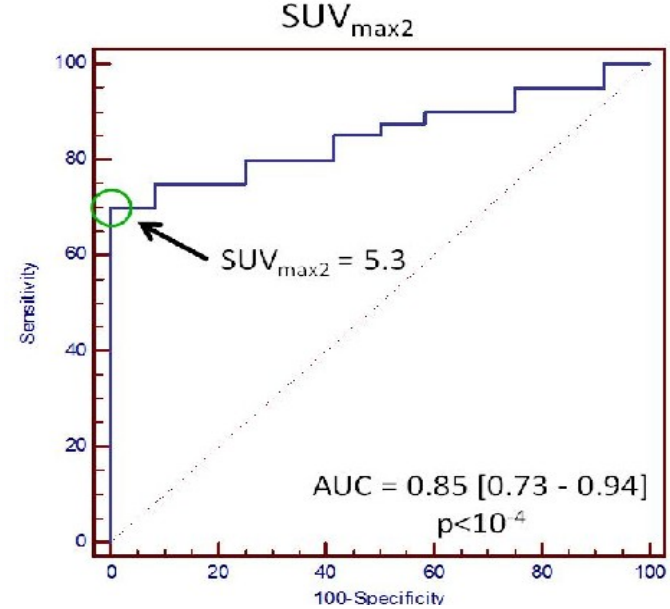
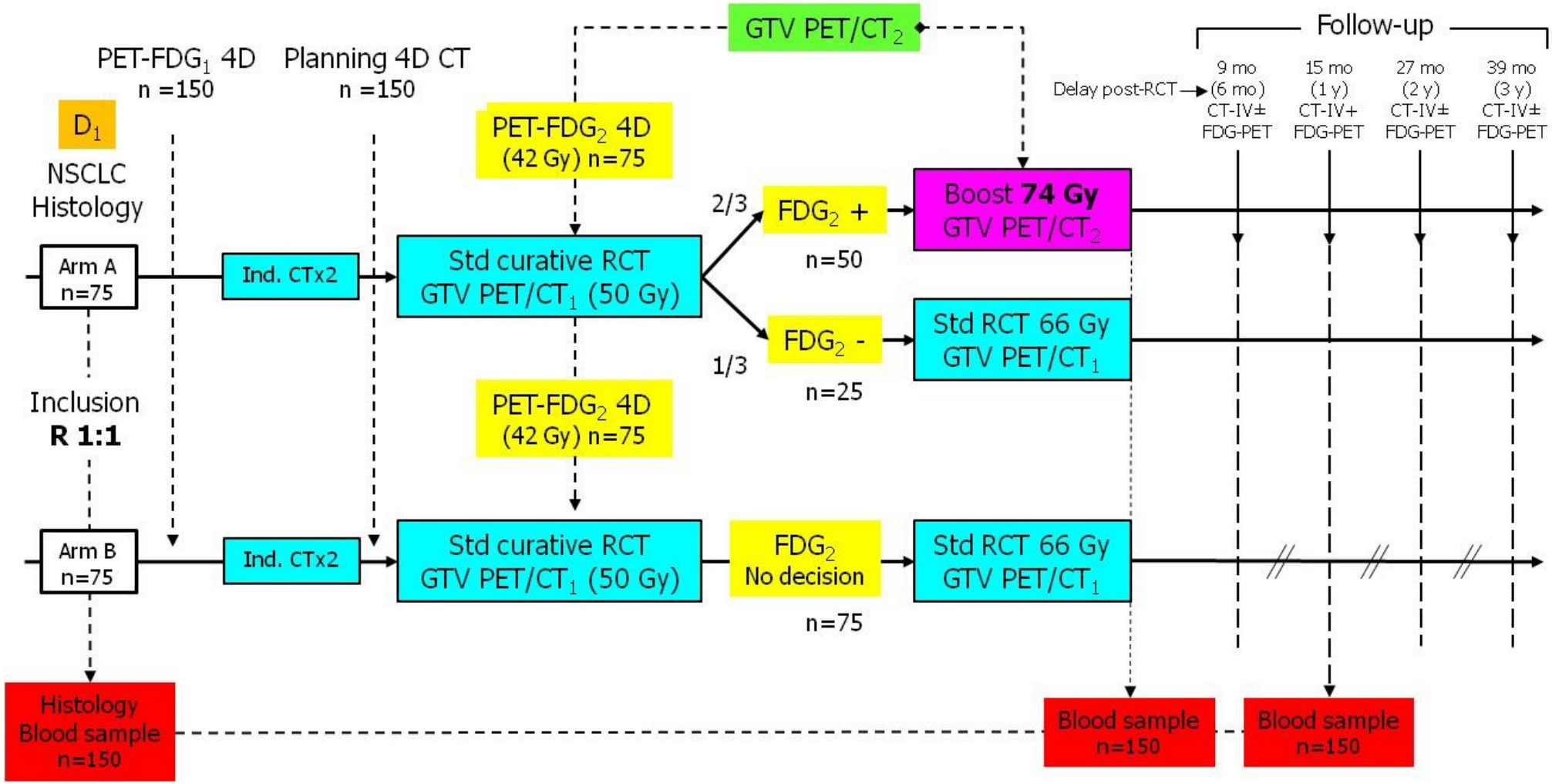


Table 4 Multivariate analysis of outcome at 1 year (logistic regression). The tested variables were age, sex, stage (IIIB vs. other), histology (squamous cell carcinoma vs. other, induction chemotherapy (yes vs. no), treatment regimen (RT or RCT), SUV_{max} and metabolic volumes from PET_1 and PET_2

Endpoint	Variable	Odds ratio	*p* value	Correctly classified	Area under ROC curve
Disease-free survival at 1 year (40 events)	SUV_{max2}	1.97 (95 % CI 1.25 – 3.09)	0.003	75 %	0.85 (95 % CI 0.71 – 0.92)

Vera, EJNMMI 2014

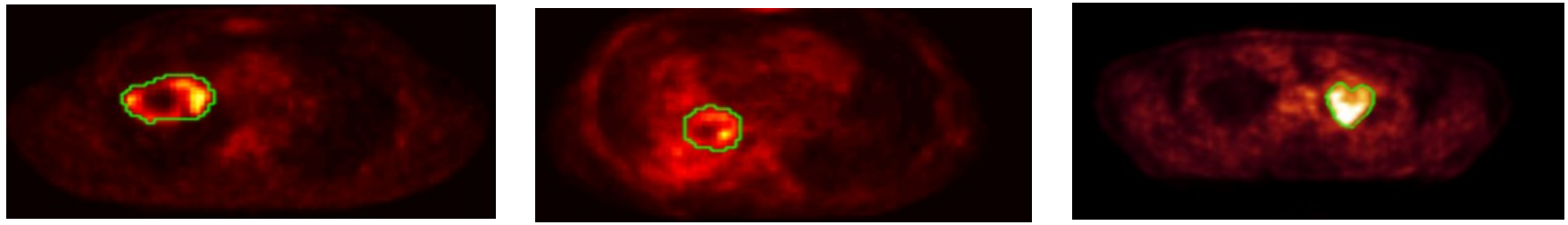
RTEP7/IFCT1401 – Randomized phase II-III study of personalized radiotherapy dose redistribution in patients with inoperable stage III non-small cell lung cancer and a persistent FDG uptake at 42 Gy during concomitant radio-chemotherapy



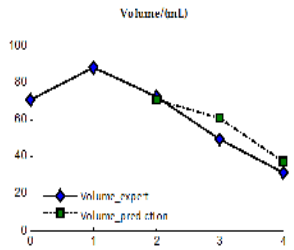
34 centres in France, 1 centre belge, 1 centre allemand

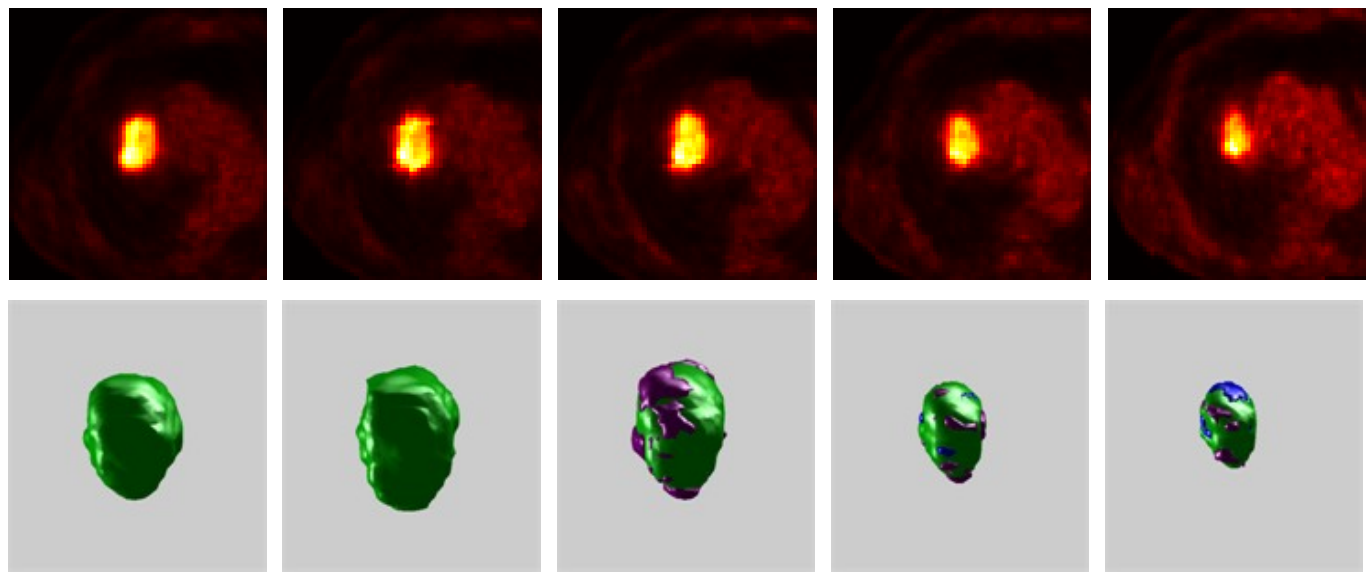
Segmentation et modèles d'évolutivité tumorale

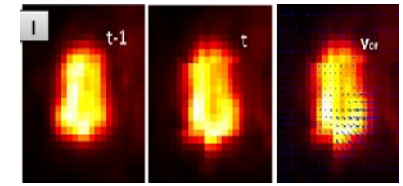
Segmentation des tumeurs hétérogènes (RW)



Segmentation dynamique (3D+t) en intégrant du modèle spatio-temporel



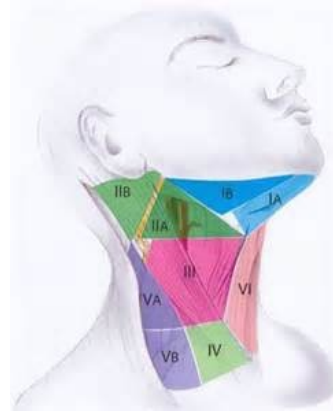


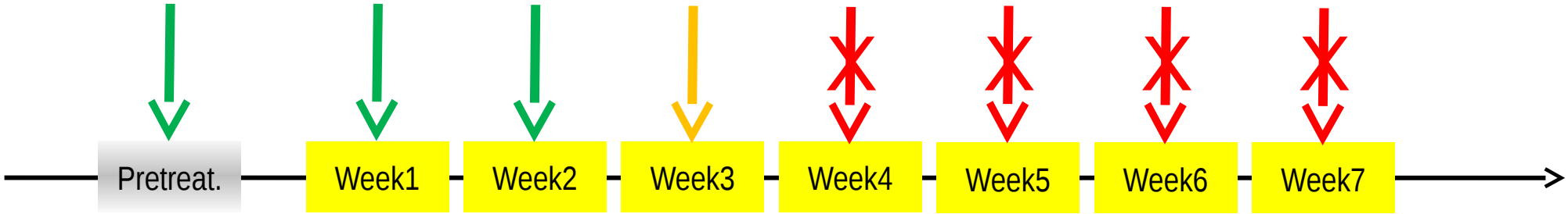


$$\frac{\partial u(x,t)}{\partial t} = -k\,\underbrace{\nabla \cdot (\boldsymbol{v}_{\mathrm{of}} u)}_{\text{Advection}} + \underbrace{S(u)}_{\text{Proliferation}} - \underbrace{T(u)}_{\text{Treatment}}$$

Onoma , IEEE ISBI2012; Mi, IEEE TMI2014 , Mi, MIA 2015

FDG-PET for H&N

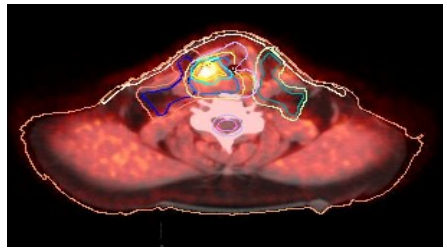




Pretreat. → Week1 → Week2 → Week3 → Week4 → 70 Gy (35f x 2)

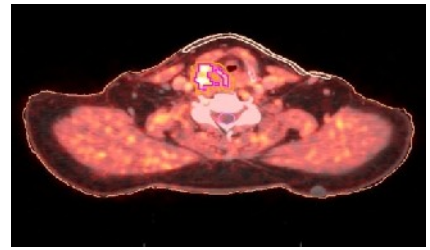
PET H0f | PET H7f | PET H17f

PET



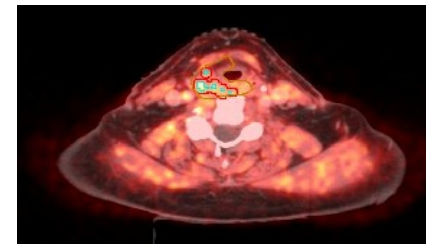
GTV H0f

PTV H0f: 86Gy 2.46Gy/f
(86 Gy planned)



GTV H7f= GTV H7f - GTV H0f

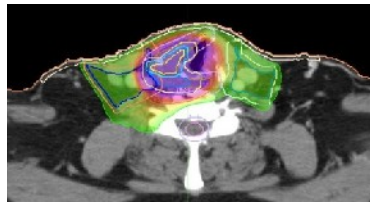
PTV H7f: 86Gy 2.57Gy/f
(89.95 Gy planned)



GTV H17f= GTV H17f - GTV H7f - GTV H0f

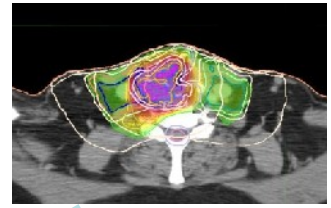
PTV H17f: 86Gy 2.89Gy/f
(101.15 Gy planned)

Dose planned



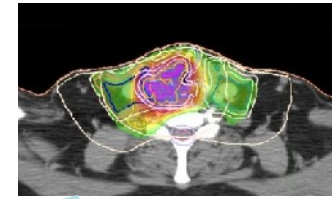
Plan 1
Fractions 1 – 7

7f



Plan 2
Fractions 8 - 17

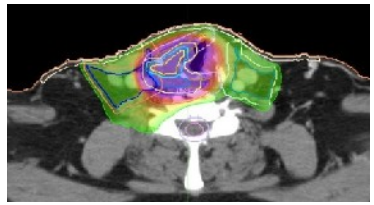
10f

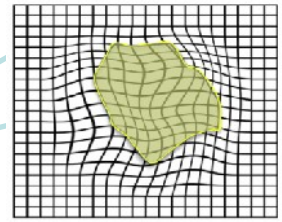


Plan 3
Fractions 18 - 35

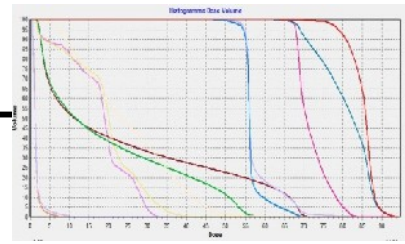
18f

Accumulated dose





All ROI 3



MIM VistaR

Anti-chronological reporting

Servagi-Vernat, Acta Oncol 2014 & EJNMMI 2014

UCL Université catholique de Louvain

miro molecular imaging, radiotherapy & oncology

PET/CT–MR : dose redistribution

- **Personalized dose redistribution**
  - ✓ **In space** (pre-treatment FDG PET)
  - ✓ **In time** (during treatment)
  - ✓ **In dose** (boost)

	Pre-RT	During TT	Potential tracers	Device
Lung	FDG	FDG ?	Hypoxia ?	PET/CT
H&N	FDG	Tracer ?	Hypoxia ?	**PET/MR, DW-MR ?**
Esophagus	FDG		Proliferation ? Hypoxia ?	PET/CT
Brain	FET		Methionine ?	**PET/MR ?**
Prostate	Choline			**PET/MR ?**
Cervix	FDG		Hypoxia ?	**PET/MR ?**
Rectum	FDG		Hypoxia ?	**PET/MR ?**

Conclusion : PET/CT for **therapy planning** in **lung cancer**

- **Pre-treatment**
  - ✓ **FDG for GTV/BTV delineation**
  - ✓ GTV = primary tumour + nodes [**before induction chemotherapy**]
  - ✓ Pre-treatment boost : Contradictory results (RTOG 0617)
  - ✓ On going phase II-III trials
  - ✓ FDG dose painting : not validated
  - ✓ Hypoxia : Ongoing phase II-III trials
- **During treatment**
  - ✓ **FDG No artefact during RT**
  - ✓ PET-FDG during RT : ~42 Gy
  - ✓ **Major prognosis value** during RT-CT (but not a standard in 2014)
  - ✓ Interest for dose redistribution and boost ? On going clinical trial II-III

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