Hospices Civils de Lyon

Lyon 1

Les Radiothérapies.

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Centre Hospitalier Lyon Sud, LYON, France, EMR 3738.

20 Septembre 2016, LYON

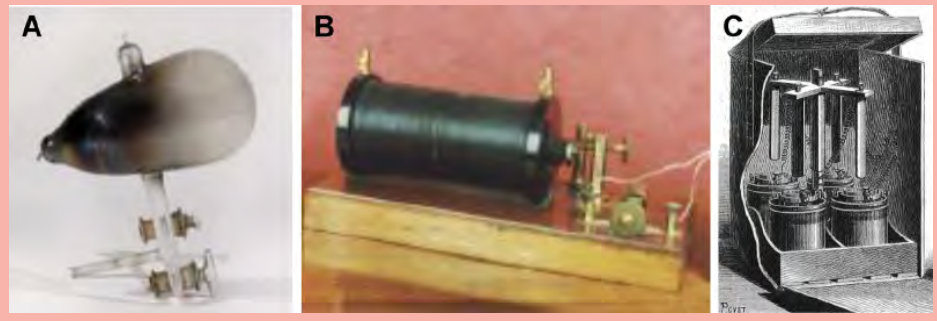
W. C. RÖNTGEN découvre les rayons X

(8 Novembre 1895)

Victor Despeignes (1866-1937)

médecin hygiéniste lyonnais, pasteurien convaincu

Dispositif d'irradiation de Despeignes

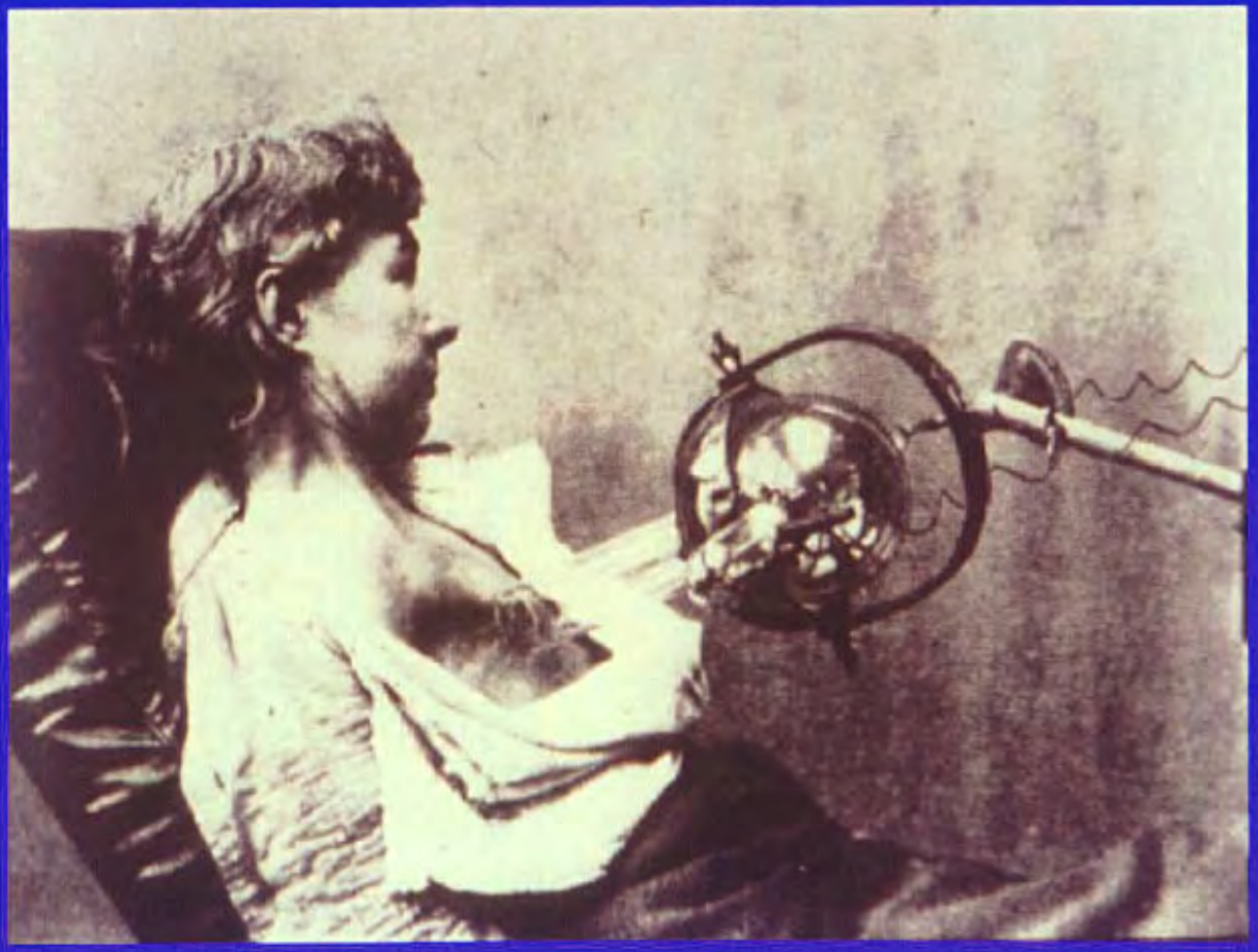


A. Tube de Crookes en forme de poire
B. Bobine d'induction (matériel conservé par les hospices civils de Lyon
C. La pile de Radiguet, pile-batterie au bichromate de potasse composée de plusieurs éléments cylindrique

1er patient traité

- patient de 52 ans traité pour un néoplasme de toute la région épigastrique
- Radiothérapie : **du 4 juillet au 23 juillet 1896**
- 2 séances d'une demi-heure par jour tous les jours
- 8 jours après: la tumeur a sensiblement diminué de volume

Irradiation d'un cancer du sein en 1903



Régression complète d'un sarcome de la face en 1905

Dr HARET (1874-1932)

« Premiers essais du traitement du cancer par les rayons X »
Georges CHICOTOT 1907

RADIOTHERAPIE

2 Gy/jour (fraction, Fx). 1,8 Gy USA

2 Gy/jr, 5 Fx/sem, 30 Fx =6 Sem, 60 Gy

> 1 Fx/jr = hyperfractionnement

>2 Gy/jr : hypofractionnement, Accéléré

Stop pendant RT: Split course (tolérance)
Utilisé pour RT >2 Gy, accélérée, peu Fx.

RTOG 0617

A Randomized Phase III Comparison of Standard-Dose (60 Gy) Versus High-Dose (74 Gy) Conformal Radiotherapy with Concurrent and Consolidation Carboplatin/Paclitaxel +/- Cetuximab In Patients with Stage IIIA/IIIB Non-Small Cell Lung Cancer (NSCLC)

Presenting Author: Jeffrey D. Bradley, MD

NCI Sponsored Cooperative Groups:
RTOG, NCCTG, CALGB

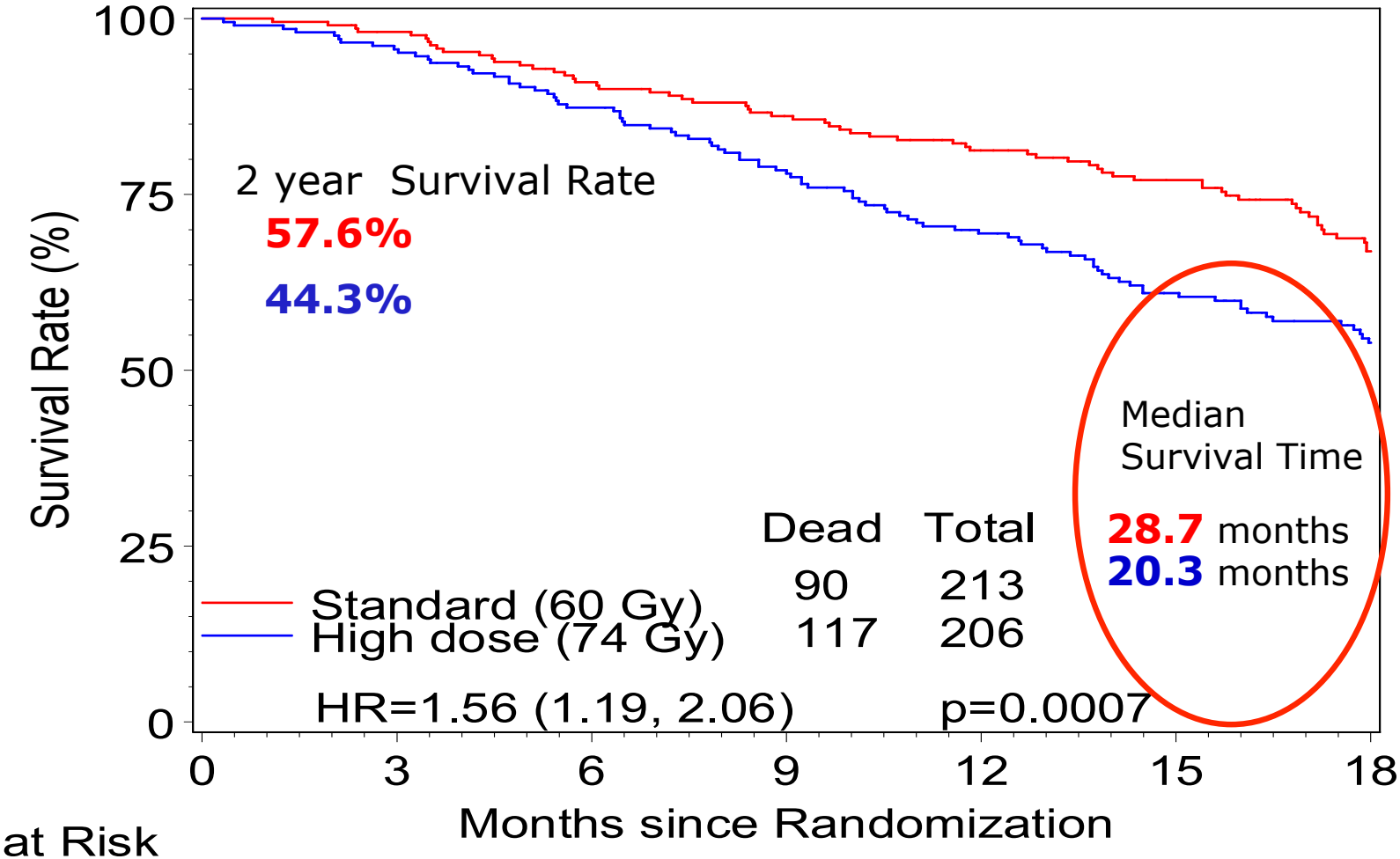
Jeffrey D Bradley, Rebecca Paulus, Ritsuko Komaki, Gregory A. Masters, Kenneth Forster, Steven E. Schild, Jeffrey Bogart, Yolanda I. Garces, Samir Narayan, Vivek Kavadi, Lucien A Nedzi, Jeff M. Michalski, Douglas Johnson, Robert M MacRae, Walter J Curran, and Hak Choy

Schema

STRATIFY	RANDOMIZE	Concurrent Treatment	Consolidation Treatment
RT Technique 1.3D-CRT 2.IMRT **Zubrod** 1.0 2.1 **PET Staging** 1.No 2.Yes **Histology** 1.Squamous 2.Non-Squamous		**Arm A** Concurrent chemotherapy* RT to **60 Gy**, 5 x per wk for 6 wks	Arm A Consolidation chemotherapy*
		Arm B Concurrent chemotherapy* RT to **74 Gy**, 5 x per wk for 7.5 wks	Arm B Consolidation chemotherapy*
		Arm C Concurrent chemotherapy* and **Cetuximab** RT to **60 Gy**, 5 x per wk for 6 wks	Arm C Consolidation chemotherapy* and Cetuximab
		Arm D Concurrent chemotherapy* and **Cetuximab** RT to **74 Gy**, 5 x per wk for 7.5 wks	Arm D Consolidation chemotherapy* and Cetuximab

*Carboplatin and paclitaxel

RTOG 0617 Overall Survival



420 pts

Patients at Risk

Standard	213	207	190	177	161	141	108
High dose	206	197	178	159	135	112	87

RTOG undertook a careful re-analysis of all heart contours and doses received by the heart.

Radiation dose	**60Gy v 74 Gy**	**1.55 (1.07, 2.23)**	**0.020**
Histology	**Non-squam v Squam**	**1.37 (0.94, 1.98)**	**0.097**
Gross Tumor Volume	**Continuous**	**1.002 (1.000, 1.003)**	**0.034**
Heart V5	**Continuous**	**1.010 (1.004, 1.017)**	**0.002**

Exit criteria = p>0.10; radiation dose and histology forced to remain
Covariates dropped from the model were: gender, age, lung V5.

RTOG 0617 : Multivariate Cox Model Backwards Selection

Heart radiation dose = important prognostic factor

Pretreatment Characteristics

	60 Gy (n=213)	74 Gy (n=206)
Age (median)	64	64
Gender		
Male	125 (58.7%)	120 (58.3%)
Female	88 (41.3%)	86 (41.7%)
Race		
Other	26 (12.2%)	29 (14.1%)
White	187 (87.8%)	177 (85.9%)
RT Technique		
3DCRT	**115 (53.9%)**	**109 (52.9%)**
IMRT	**98 (46.1%)**	**97 (47.1%)**
PET Staging	**91.1%**	**88.8%**
Histology		
Adenocarcinoma	**84 (39.4%)**	**71 (34.5%)**
Squamous	**89 (41.8%)**	**97 (47.1%)**
NSCLC NOS	**40 (18.7%)**	**38 (18.4%)**
AJCC Stage		
Stage IIIA	**143 (67.1%)**	**131 (63.6%)**
Stage IIIB	**70 (32.9%)**	**75 (36.4%)**

Heart Dose in RTOG 0617: IMRT vs. 3D RT

- 53% of patients in RTOG 0617 received 3D RT and 47%, IMRT
- The IMRT group had more Stage IIIB patients; larger PTVs (486 mL vs. 427 mL) and larger PTV: lung ratio than the 3D RT group
- In spite of the above, IMRT was associated with:

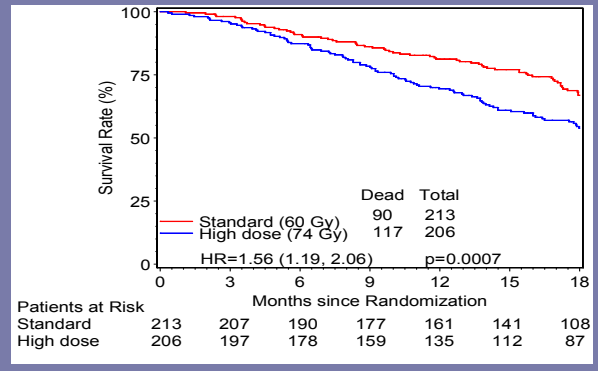
Outcome	3D-CRT	IMRT	P-value
Grade 3+ pneumonitis	8%	3.5%	0.0462
Heart V40	11.4%	6.8%	0.0026

- **"IMRT is able to lower heart dose as compared to 3D RT"** (no difference in OS/PFS between IMRT and 3D RT)

Chun S et al, Oral #20, IASLC 2015

IASLC

Les patients irradiés en IMRT ont eu une dose cardiaque plus faible Et moins de toxicité cardiaque, expliquant au moins en partie les résultats observés



Qu’est ce que l’IMRT (modulation d’intensité) ?

A quoi sert-elle?

Radiothérapie de conformation 3D

Radiothérapie de conformation: RT3D

- Technique « de base » qui remplace le 2D des années 60-95
- Utilisée dans 100% des centres en France
- Champs carrés ou rectangulaires, avec lames qui sculptent le faisceau
- 2 à 8 champs, 4 champs en moyenne

forme du faisceau définie

par les lames du Collimateur

Lames fixes

RADIOTHERAPIE :

LES TECHNIQUES

3D : conformation

IMRT: RCMI

SBRT/SABR: stéréotaxie

C’est une façon complexe de délivrer une dose hétérogène, dans le volume à traiter, ou pour protéger des tissus sains environnants

On découpe les volumes (Tissus tumoraux ou organes) en sous-volumes, qui peuvent chacun recevoir une dose différente

forme du
faisceau définie

par les
lames du
Collimateur,

qui sont **mobiles**

Modulation d'intensité: IMRT/ RCMI

On dispose en 2016 de 3 techniques

Modulation d'intensité : IMRT=RCMI

Technique sophistiquée qui permet de

protéger les tissus sains

- **Elle irradie la tumeur aux mêmes doses qu'en 3D**
- **Consomme du temps médecin-physicien**
- **La RCMI dynamique: VMAT, RapidArc,Tomotherapy… est une évolution de la RCMI: la tête de l'accélérateur tourne pendant l'irradiation.**

IMRT/RCMI

Plusieurs types de machines:
Tête fixe ou
Arcthérapie, tomothérapie

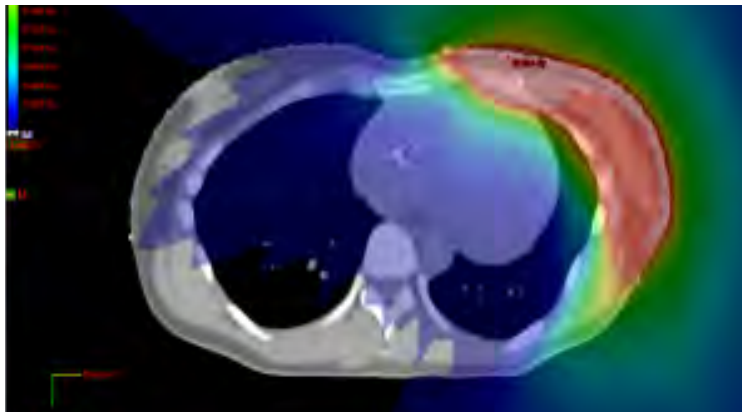
Accélérateur linéaire permettant la technique d'IMRT

- **Vitesse de bras variable**
- **Débit de dose variable**
- **Dose par degré variable**
- **Vitesse MLC variable**

Champs | Prescription de dose | Alignement des champs | Objectifs du plan | Objectifs d'optimisation | Statistiques de doses | Modèles de calcul | Somme de plans

Afficher le HDV	Structure	État d'approbation	Plan	Dossier de traitement	Volume [cm³]	Recouv. Dose[%]	Recouv. Échantillonnag...	Dose min. [cGy]	Dose max. [cGy]	Dose moyenne [cGy]
☑	PTV3	Approuvée	T1+T2+T3	C1_poumon	73.7	100.0	100.0	6747.2	7471.1	7073.5
☑	PTV2	Approuvée	T1+T2+T3	C1_poumon	135.5	100.0	100.0	6238.2	7571.2	7048.1
☑	PTV1	Approuvée	T1+T2+T3	C1_poumon	211.7	100.0	100.0	4802.6	7571.2	6857.3
☐	z_Poumons-PTV1	Approuvée	T1+T2+T3	C1_poumon	3306.8	100.0	100.0	13.8	6471.1	870.5
☐	Poumons	Approuvée	T1+T2+T3	C1_poumon						
☐	z_Poumons-PTV2	Approuvée	T1+T2+T3	C1_poumon						
☑	z_Poumons-PTV3	Approuvée	T1+T2+T3	C1_poumon	3390.3	100.0	100.0	13.8	7454.2	1000.0
☐	z_Coeur-PTV1	Approuvée	T1+T2+T3	C1_poumon						

Tomothérapie (Tomotherapy)



Questions concernant l'IMRT

- Incertitudes physiques :
  - Mouvements respiratoires (pénombre?)
  - Changements anatomiques (ART)
  - Hétérogénéité de dose dans le PTV

- **Augmentation de la dose totale dans le poumon sain, notamment faibles doses (V5)**

- **Risque cancérigène à long terme ? Enfant**

INDICATIONS THEORIQUES

Pour « hétérogénéiser » volontairement la dose

1) Epargne organes à risque Avantage dosimétrique
(choix de la technique selon la localisation):

Tumeur de l'apex,
tumeur paracardiaque,
tumeur paravertébrale

2) Pour augmenter la dose totale si dosi suboptimale

Int. J. Radiation Oncology Biol. Phys., Vol. 58, No. 4, pp. 1258–1267, 2004

0360-3016/04/$–see front matter

doi:10.1016/j.ijrobp.2003.09.086

PHYSICS CONTRIBUTION

DOSE AND VOLUME REDUCTION FOR NORMAL LUNG USING INTENSITY-MODULATED RADIOTHERAPY FOR ADVANCED-STAGE NON–SMALL-CELL LUNG CANCER

Hasan Murshed, M.D.,* H. Helen Liu, Ph.D.,* Zhongxing Liao, M.D.,* Jerry L. Barker, M.D.,* Xiaochun Wang, Ph.D.,* Susan L. Tucker, Ph.D.,† Anurag Chandra, M.D.,* Thomas Guerrero, M.D., Ph.D.,* Craig Stevens, M.D., Ph.D.,* Joe Y. Chang, M.D., Ph.D.,* Melinda Jeter, M.D.,* James D. Cox, M.D.,* Ritsuko Komaki, M.D.,* and Radhe Mohan, Ph.D.*

*Division of Radiation Oncology and †Department of Biomathematics, University of Texas M. D. Anderson Cancer Center, Houston, TX

Bénéfice dosimétrique « prouvé »

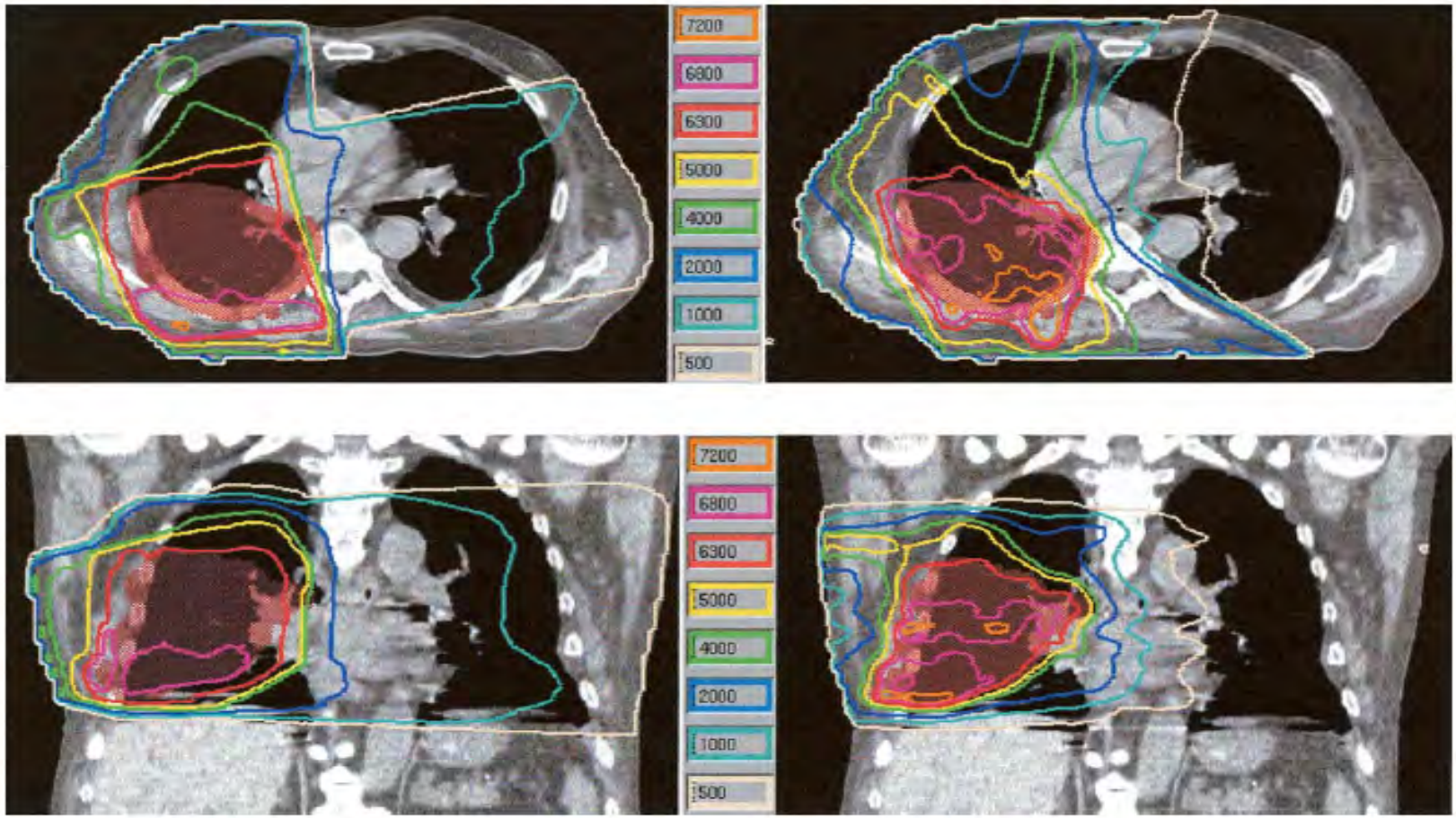
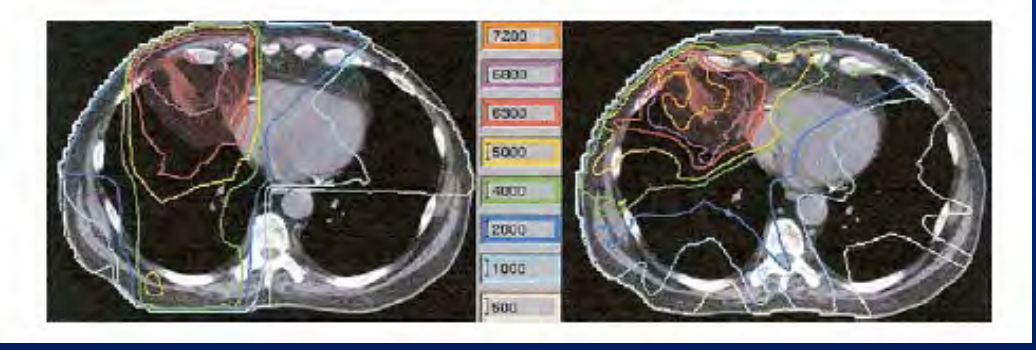
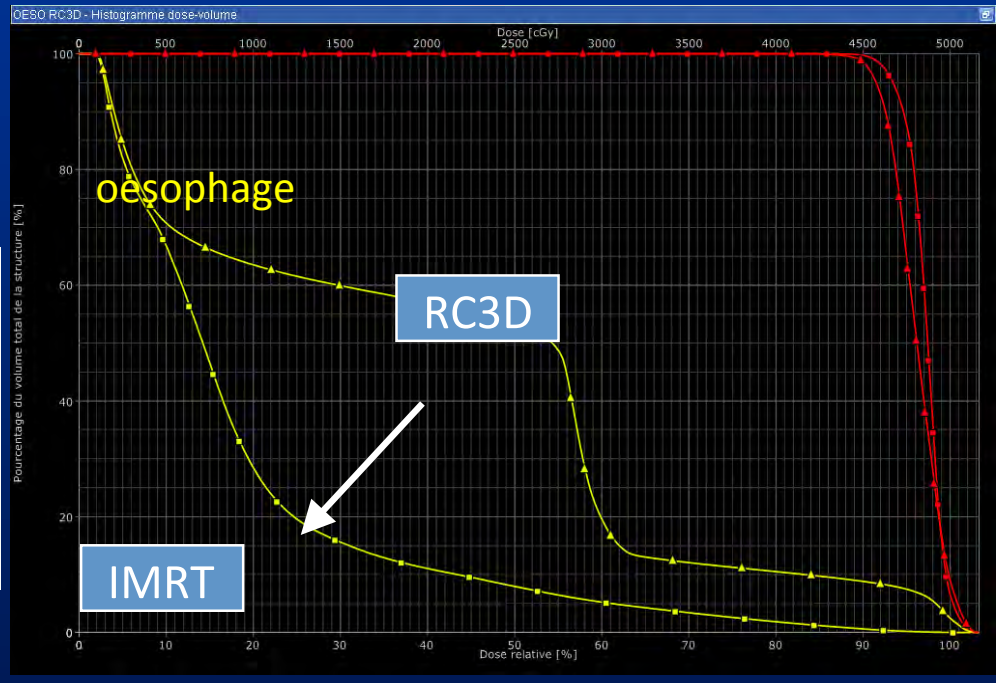


Fig. 1. Comparison of isodose distribution with (Left) 3D-CRT and (Right) IMRT in a single case. (a) Axial view. (b) Coronal view.

Avantages de l'IMRT

- **Epargne des OAR**

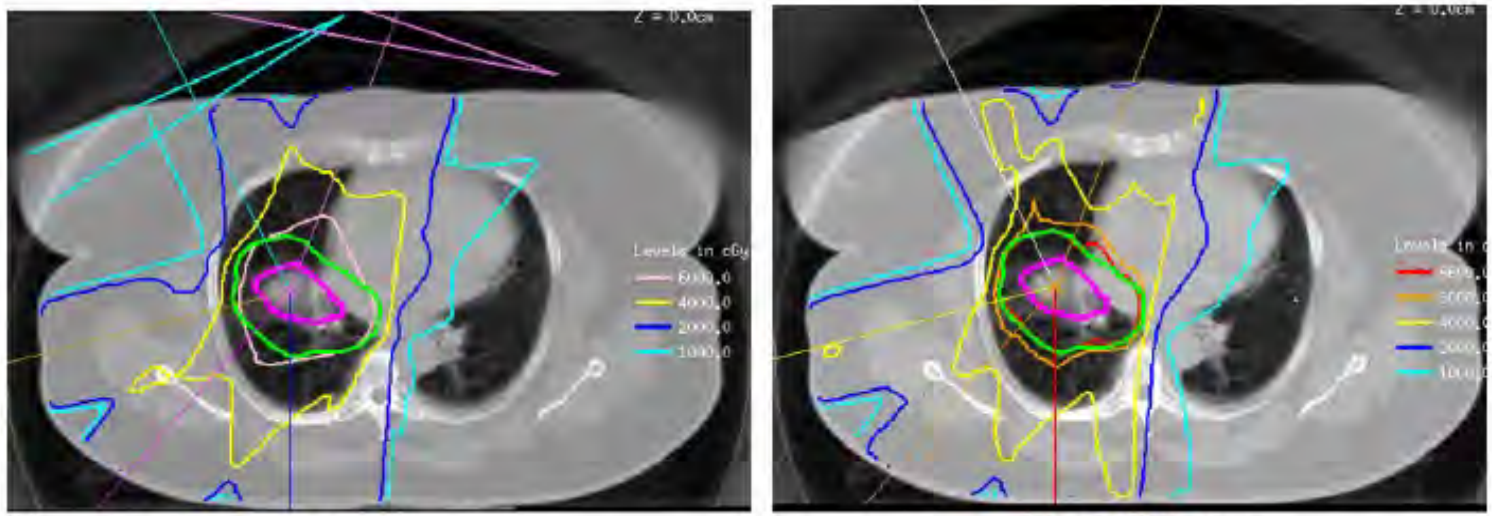




RT 3D	IMRT
Dose 70 Gy	78 Gy

Liu et al., IJROBP, 2004; 58(4): 1268-1279

Augmentation de dose totale possible grâce à IMRT

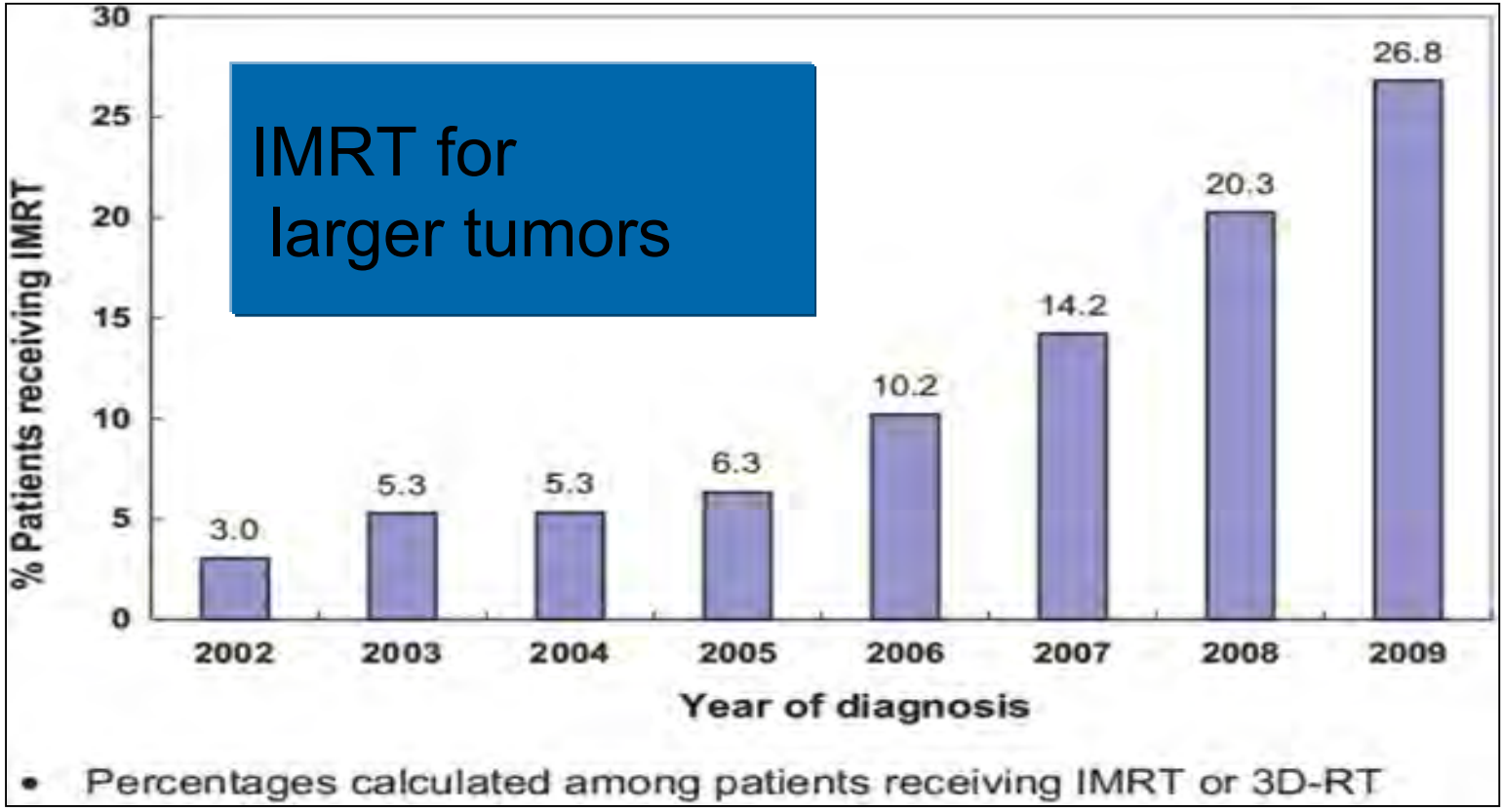


(A) 3D-CRT plan (B) IMRT plan

Fig. 1. This is a comparison of a three-dimensional conformal radiation therapy (3D-CRT) plan (A) versus an intensity-modulated radiation therapy (IMRT) plan (B) for a 79-year-old female with a $T_2N_0M_0$ (stage I_B) non-small cell lung cancer of the right lower lobe. The tumor was 4.7 × 3.1 cm in the right middle lobe. The patient, deemed medically inoperable was referred for definitive radiation treatment. Due to her ...y. This case was ideal for IMRT due to the patient's small lung ...s. With 3D-CRT plan (A), the PTV D_{95} was approximately 58 Gy ...cription dose was 66 Gy) and NTCP was 25%. In the images, the ... patient was treated to 6600 cGy with no radiation treatment-...ase for 2 years since the completion of radiation treatment.

Escalade de dose ?
R⌈irradiation ?

Comparative Effectiveness of Intensity-Modulated Versus 3D Conformal RT Among Patients with Stage III Lung Cancer



Chen, Aileen, Ling; Cronin, Angel; Schrag, Deborah; JCO. 9(12):1788-1795, 2014

PCI: La question de la préservation de l'hippocampe

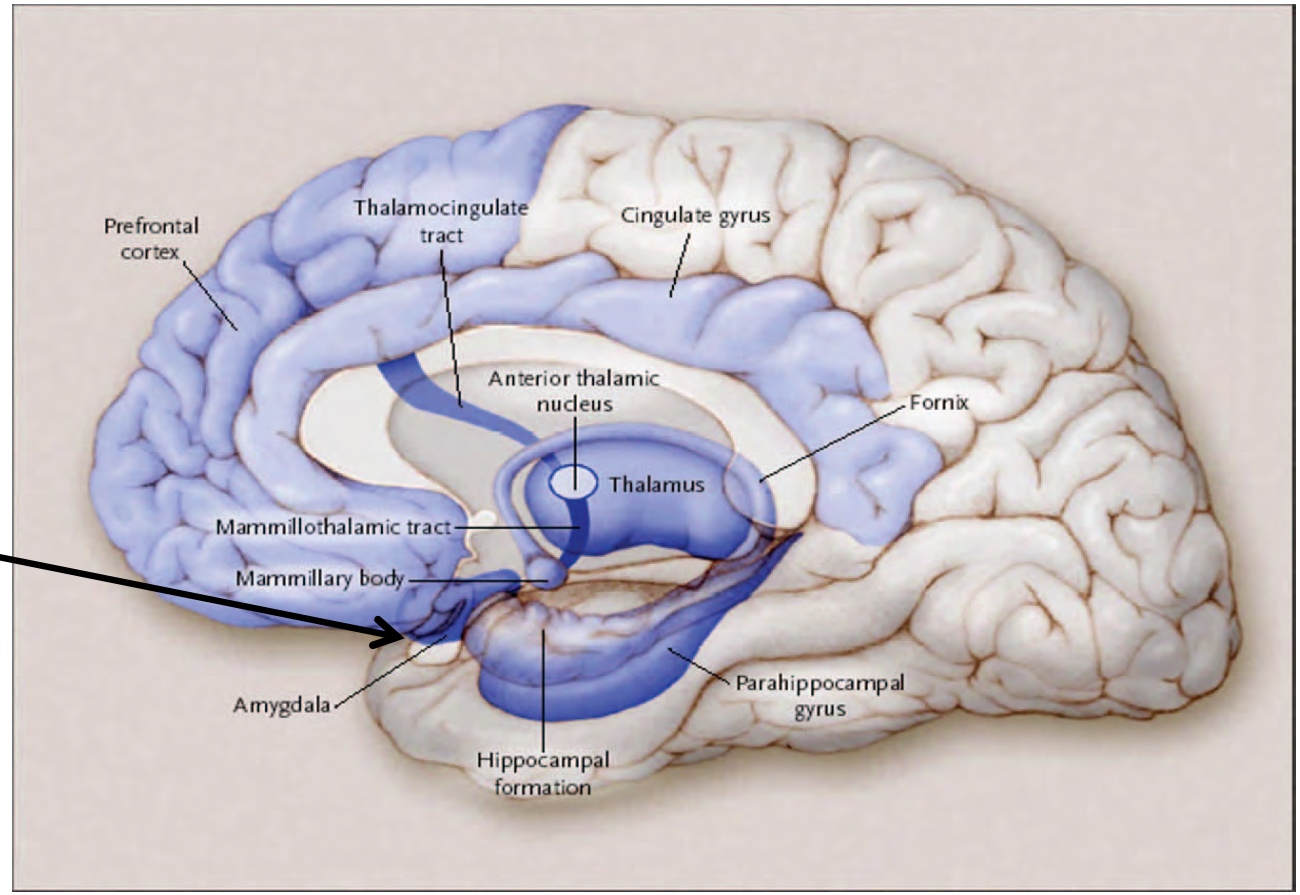
Role de l'IMRT

Le siège de la mémoire
se trouve principalement
dans l'hippocampe.

Lors d'une PCI,
la protection de cette zone/rayons
permet de respecter
la fonction de mémorisation

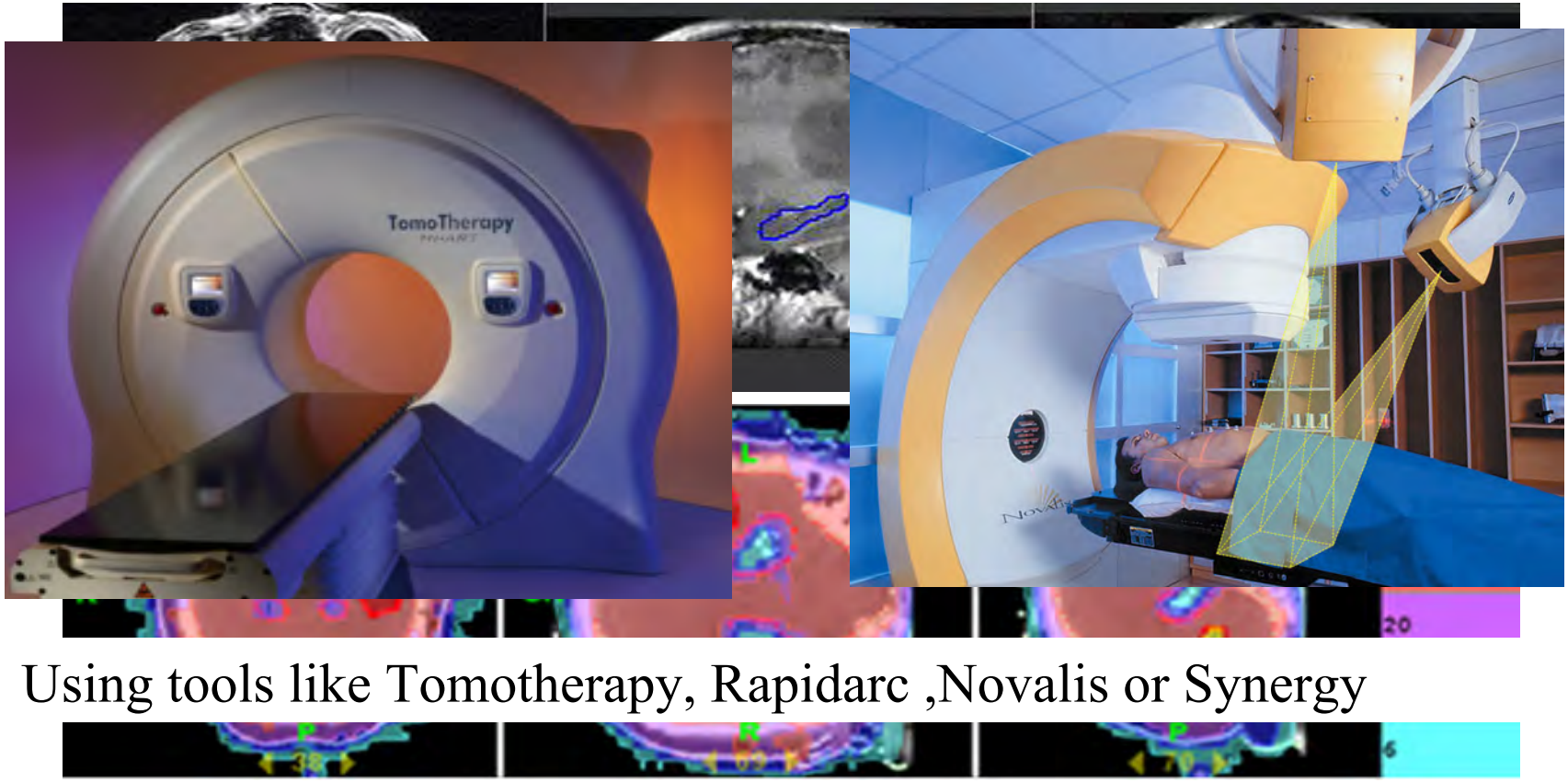
Can one decrease the risk of radiation-induced cognitive disorders?

The key-role of hippocampus



From Budson and Price, NEJM, 1989

Can one avoid technically the hippocampus?



Using tools like Tomotherapy, Rapidarc ,Novalis or Synergy

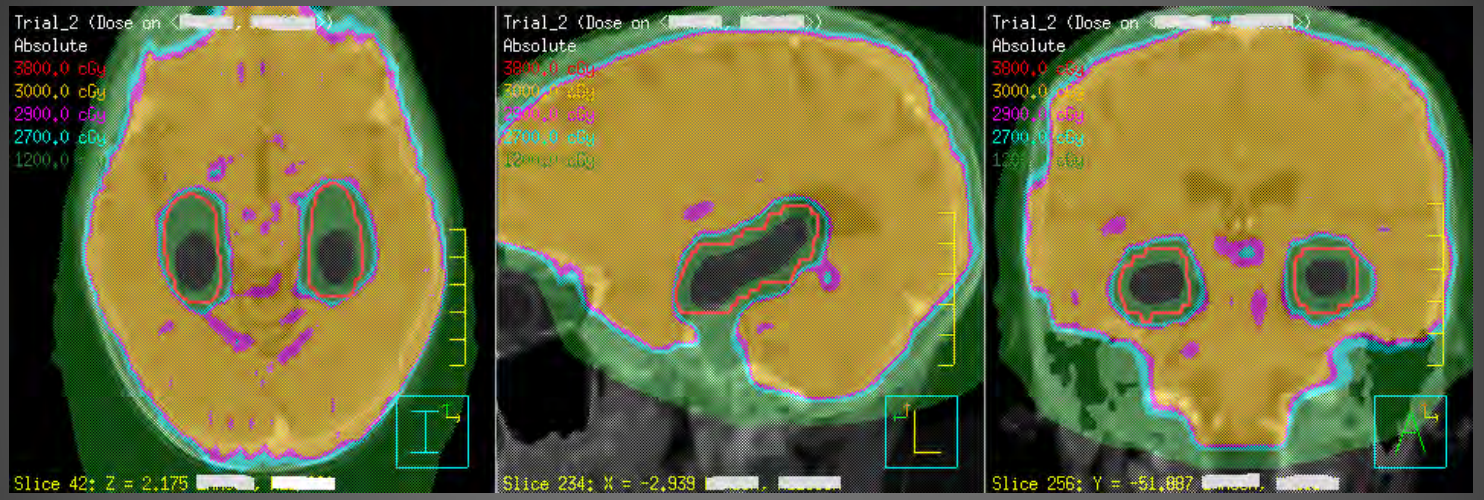
Gutierrez et al IJROBP 2007

Memory Preservation with Conformal Avoidance of the Hippocampus during Whole-Brain Radiotherapy for Patients with Brain Metastases:

Primary Endpoint Results of RTOG 0933

Inverse Planification

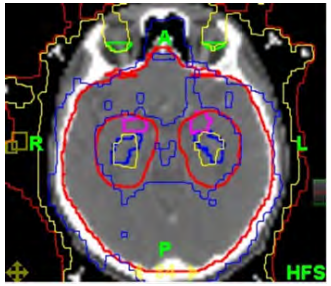
RTOG 0933



- Thin slice MRI
- Hippocampus + 5 mm to receive **≤ 9 Gy**
- IMRT
- Rapid central review of first 3 cases/institution

NRG Oncology CC003

A Randomized Phase II/III Trial of PCI with or without Hippocampal Avoidance (HA) for SCLC



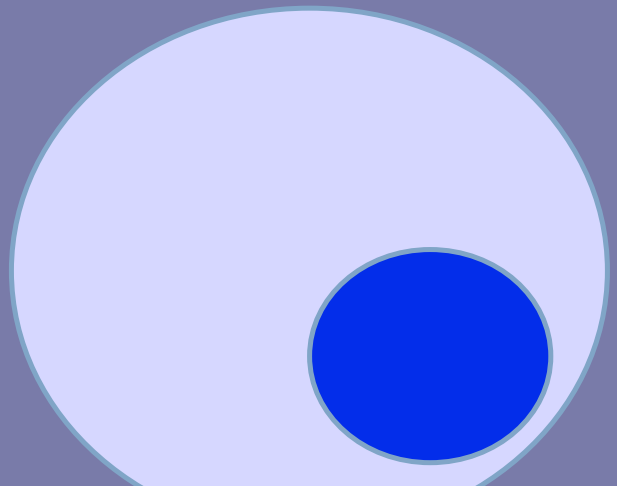
IMRT can achieve significant RT dose reduction (hippocampus), while delivering 25 Gy to the rest of the brain

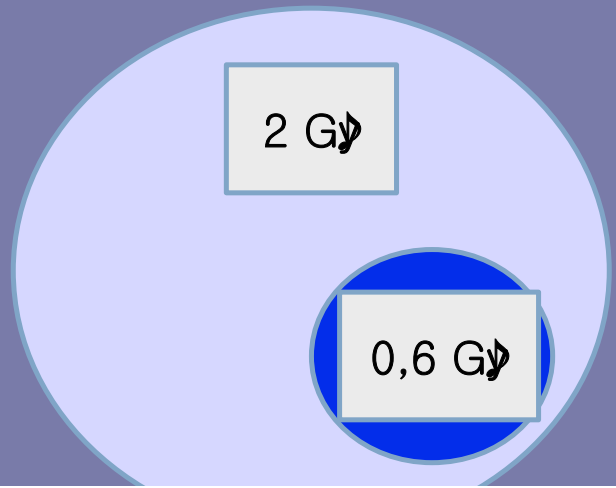
- Randomized Phase II Component (Non-Inferiority): Determine whether the 12-month intracranial relapse rate following HA-PCI is non-inferior compared to the rate following PCI for patients with SCLC
- Phase III Component (Efficacy): Determine whether HA-PCI reduces the likelihood of 6-month deterioration from baseline in HVLT-R delayed recall compared to PCI for patients with SCLC

IASLC

La radiothérapie avec boost intégré
Ou boost concomitant

Dans un sous-volume
on peut augmenter la dose par jour





KROG 0903 (Korean Radiation Oncology Group): Simultaneous Integrated Boost (SIB) Approach♪

Stratification

- Stage
  - IIIA vs. IIIB
- Histology
  - Squamous cell
    vs.
    Non-squamous

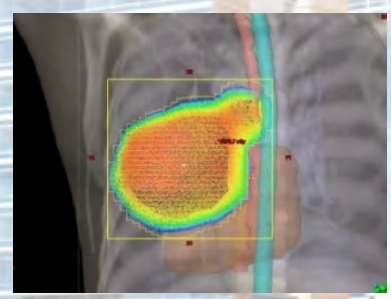
⇒ RANDOMIZE

Arm 1:
Conventionally fractionated RT
+
Concurrent Cisplatin, paclitaxel

Dose: 60 Gy to PTV; 6 weeks

Arm 2:
Accelerated RT (1.8 Gy to PTV; 2.4 Gy to GTV as SIB)
+
Concurrent Cisplatin, paclitaxel

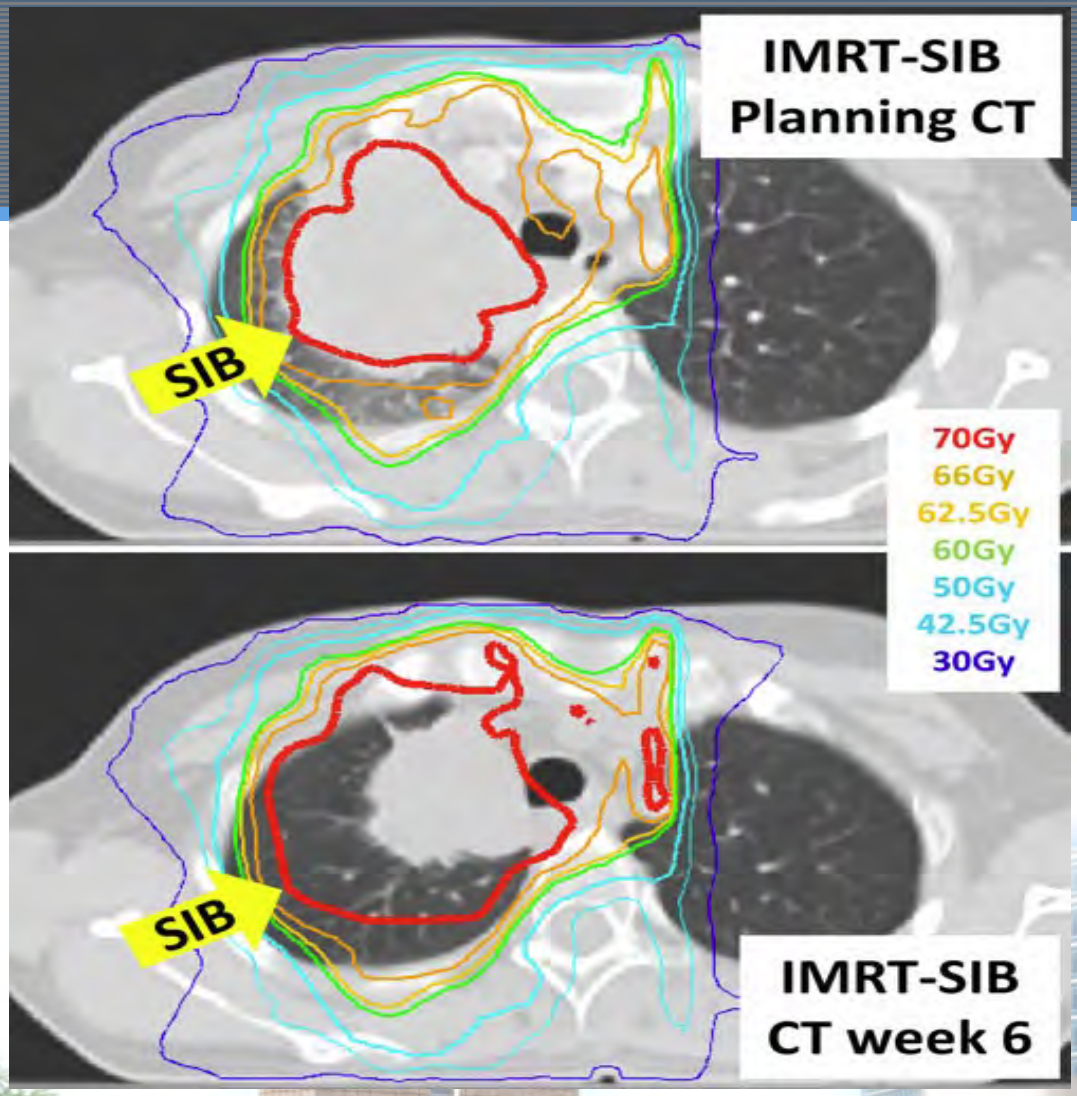
Dose: 60 Gy to GTV only; 5 weeks



Based on previous Phase II study with reported MST of 28 months.
Current study enrolled 132/ 274 (48%) patients so far.
OS rate at 2 years: approx. 60%; MST not reached; no difference between arms.

Ahn et al, ASTRO 2013

SAMSUNG 삼성서울병원



As the tumor shrinks,
not adapting the SIB volume
exposes lung to full RT doses.

Adaptive replanning of the SIB
will ensure the full dose region
is confined to the tumor.

Guckenberger M et al, 2012

SAMSUNG
삼성서울병원

NRG ONCOLOGY

Advancing Research. Improving Lives.™

NRG Oncology/RTOG 0813 Trial of Stereotactic Body Radiotherapy (SBRT) for central tumors – Adverse events

A Bezjak, R Paulus, LGaspar, R Timmerman, W Straube, W Ryan, Y Garces, AT Pu, AK Singh, GM Videtic, M Suntharalingam, P Iyengar, JR Pantarotto, EA Levine, AY Sun, ME Daly, IS Grills, PW Sperduto, DP Normolle, JD Bradley, H Choy

WCLC 2015 Denver
Sept 9 2015

Chirurgie versus Radiothérapie standard 3D

The effect of tumor size on curability of stage I NSCLC (7620 resected pts)

Survival rates @ 12 yrs

5-15 mm	69%
16-25 mm	63%
26-35 mm	58%
36-45 mm	53%
>45 mm	43%

Wisnivesky JP et al., Chest, 2005

Radiation therapy for the treatment of unresected stage I NSCLC

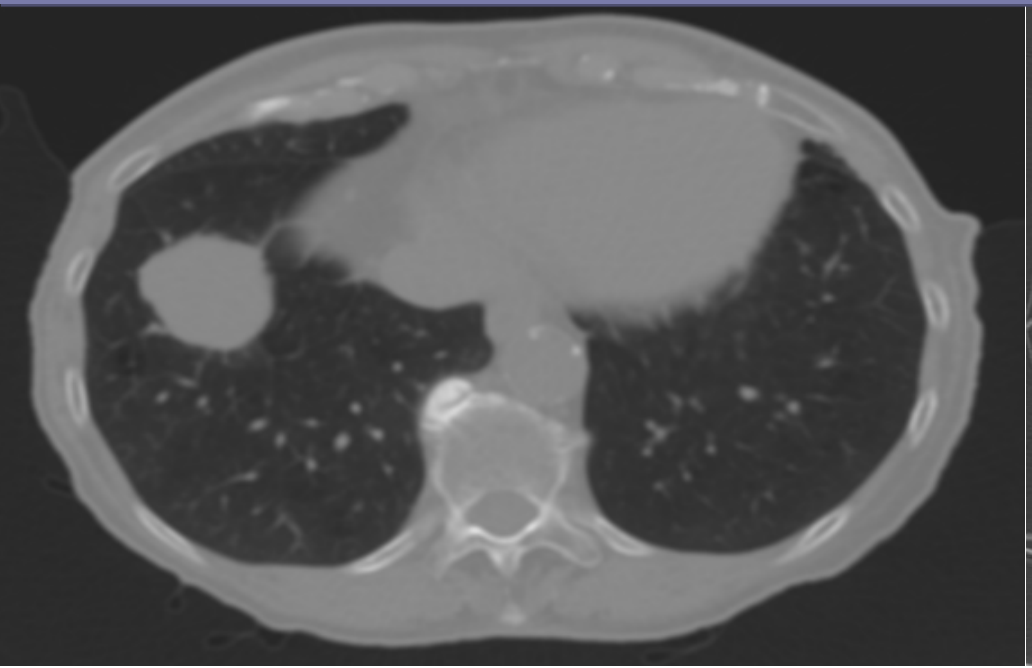
(3842 pts who did not receive surgical resection)

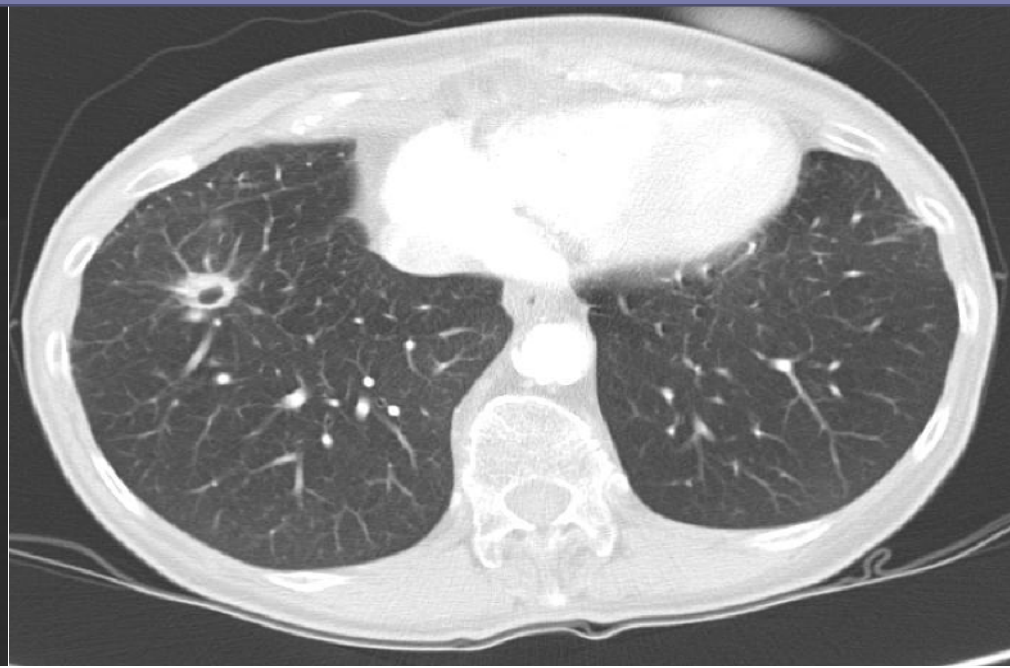
5 yrs survival rate: 15%

(local failure rates ranging from 30% to 70%)

Comment améliorer ces résultats ?

La réponse:
SBRT ou, plus récemment, SABR
(Stereotactic ABlative Radiotherapy)





Technique non invasive

Très bonne tolérance

Efficacité très élevée (cf chirurgie)

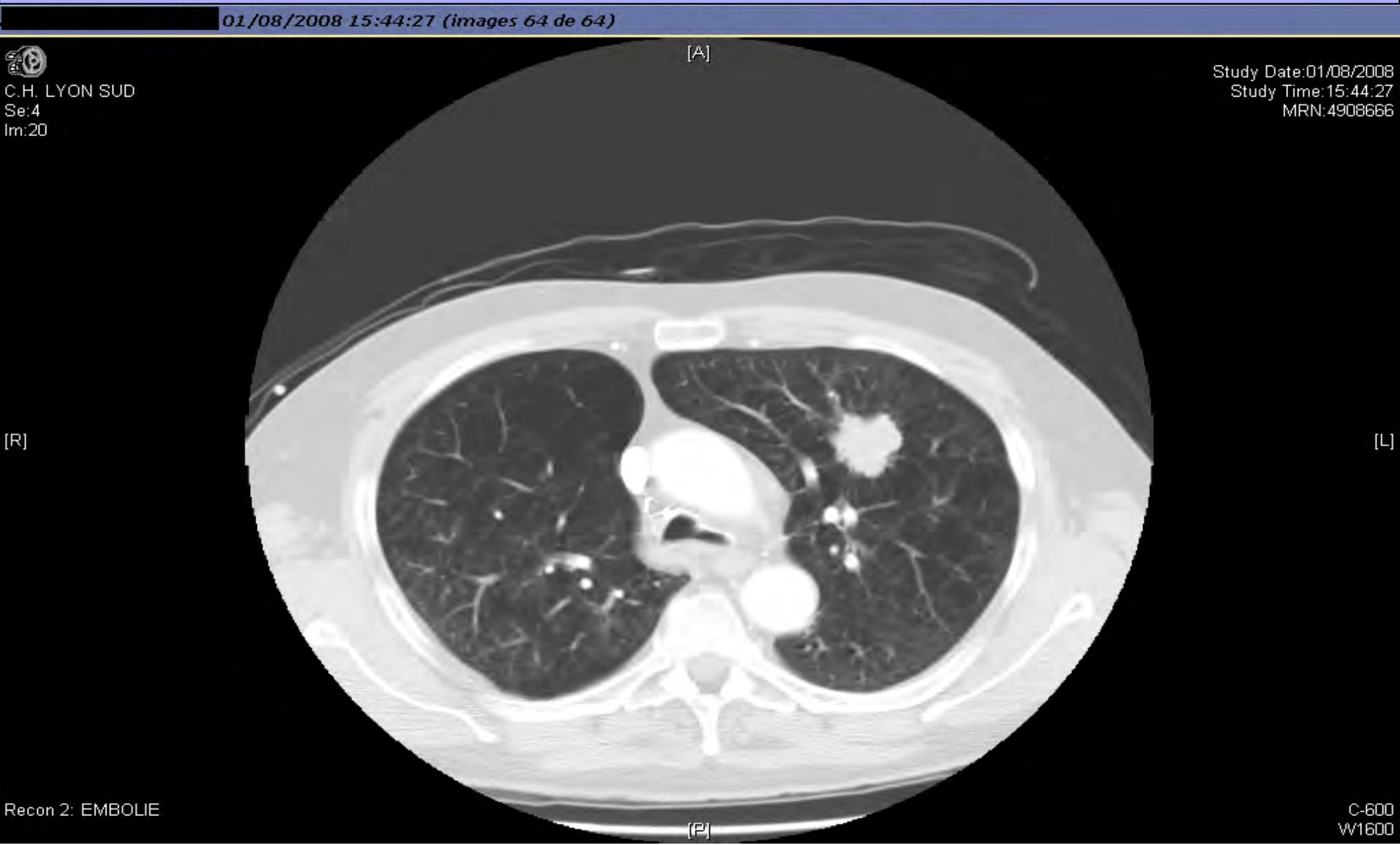
20 ans de recul

La stéréotaxie, c'est l'histoire d'un succès
C'est l'histoire d'un progrès

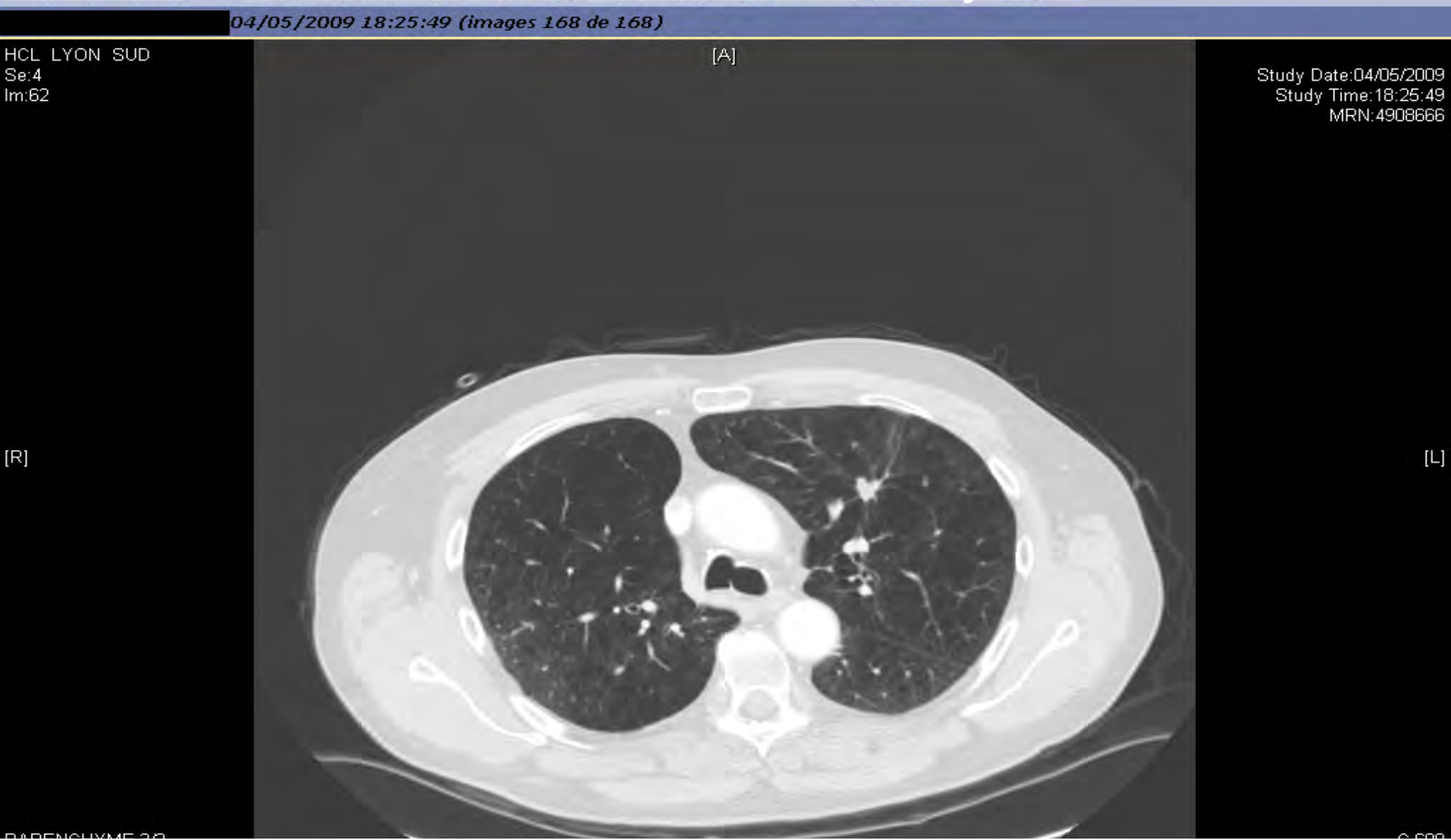
C'est une fantastique (r)évolution
de la radiothérapie

Traitement « de rupture »

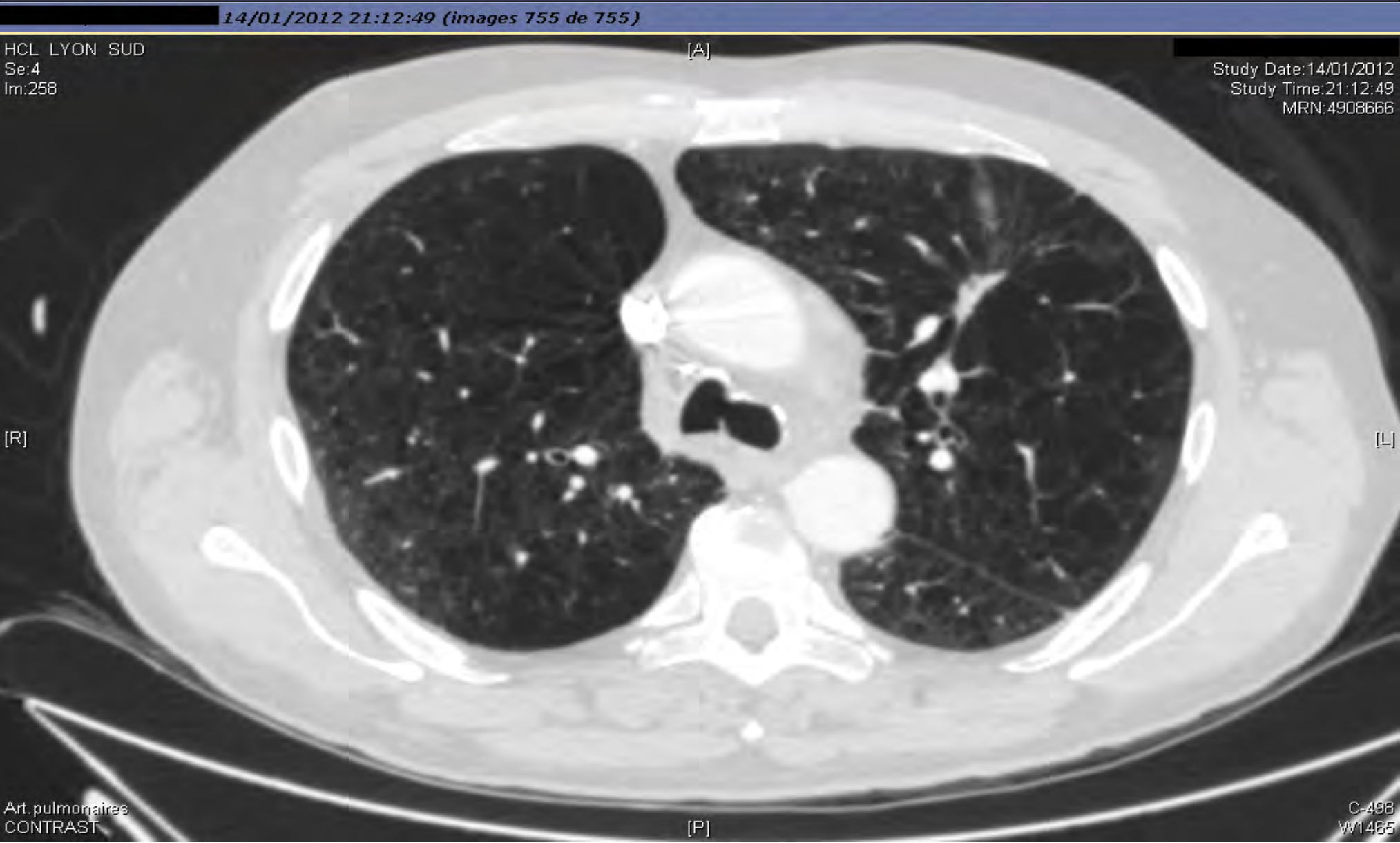
Avant traitement, IR+++, ADK LSG T1N0M0



6 semaines après fin Stéréotaxie (SBRT), 8 fractions de 7,5 Gy



3 ans après la fin de la SBRT

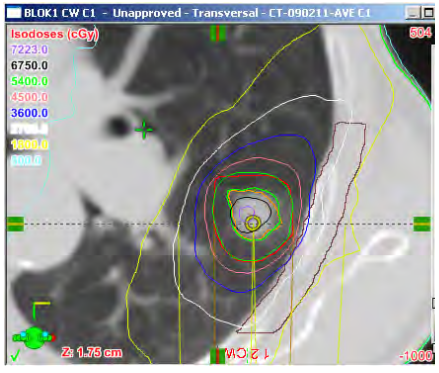


Definition of stereotactic body radiotherapy

Principles and practice for the treatment of stage I non-small cell lung cancer

M. Guckenberger[1] · N. Andratschke[2] · H. Alheit[3] · R. Holy[4] · C. Moustakis[5] · U. Nestle[6] · O. Sauer[1]

SBRT is (1) a method of external beam radiotherapy (EBRT) that
(2) accurately delivers a
(3) high dose of irradiation in
(4) one or few treatment fractions to an
(5) extracranial target



Strahlenther Onkol 2014 · 190:26–33

Radiothérapie stéréotaxique (SBRT)

- **Dose totale élevée (100-250 Gy)**
- **Délivrée dans un petit volume**
- **Large dose par fraction (4 à 12-20 Gy).**
- **Peu de séances (1 à 5, voire 10).**

- **Nombreux microfaisceaux (>10)**
- **Contrôle de qualité quotidien, + intrafraction**
- **Très haute précision, conformation, dosimétrie.**
- **Traitement en 4 D (temps, respiration).**
- **Faible dose autour de la tumeur (gradient élevé).**
- **Approche personnalisée**

preliminary report

Extracranial Stereotactic Radioablation*

Results of a Phase I Study in Medically Inoperable Stage I Non-small Cell Lung Cancer

Robert Timmerman, MD; Lech Papiez, PhD; Ronald McCarty, MD; Laura Likes, RT; Colleen DesRosiers, MS; Stephanie Frost, MS; and

(CHEST 2003; 124:1946–1955)

Phase I

8 Gy x 3

20 Gy x 3

Isodose 80%

37 pts

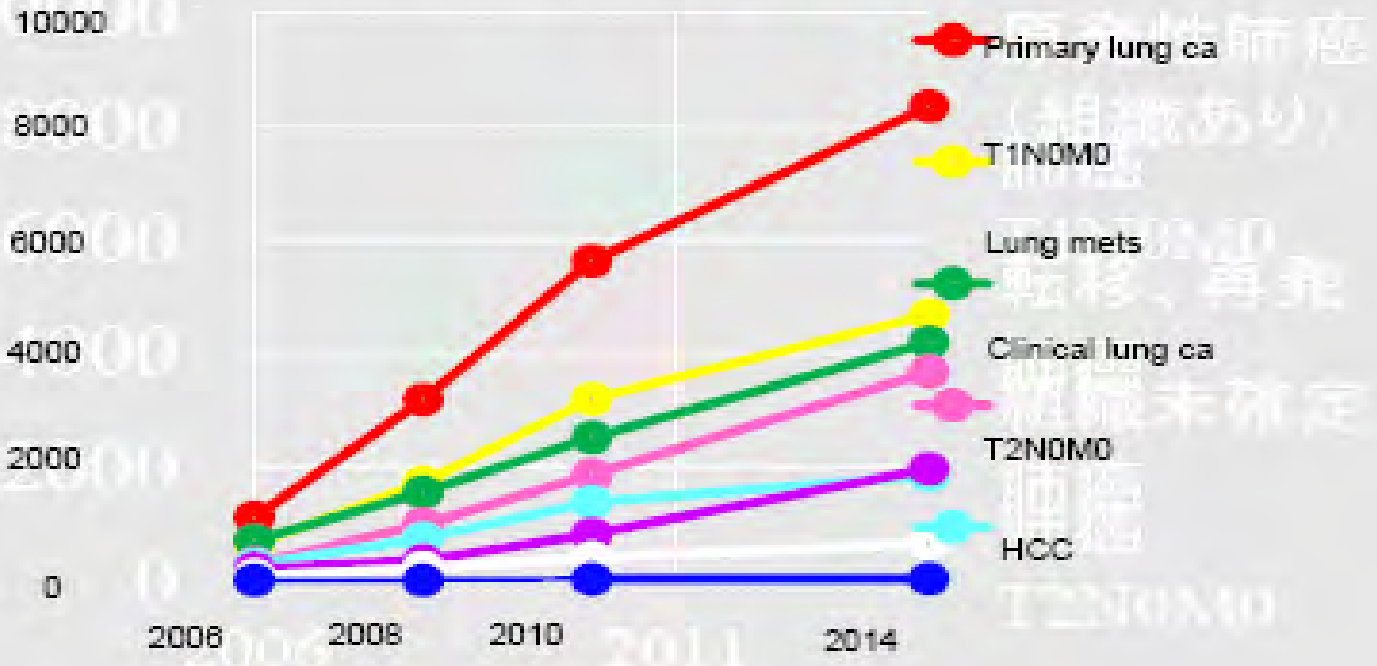
75 ans (56-91)

Pts strictement inopérables

16 Gy x 3

FIGURE 3. CXRs of a patient with a stage T2 tumor located behind the left ventricle that was treated with a dose of 1,600 cGy per fraction times three fractions before treatment (*left*) and at 6 weeks after treatment (*right*).

Cumulative No. of Pts treated with SBRT in Japan



137 institutions; 16232 cas de cancers bronchiques:
8358 1tifs, 4195 MTS, 3679 cas cliniques
0,3% G5 (53 cas)

Selected SBRT Prospective Reports

Trial	n	Dose	FU	LC %	OS %
Kyoto	45	12 Gy x 4	32 mo	**94**	83/72 (3-yr)
Stanford	20	15 -30 x 1	18 mo	**----**	-------
Scandinavian	57	15 Gy x 3	35 mo	**92 (3-yr)**	60 (3-yr)
Indiana	70	20 -22 x 3	50 mo	**88 (3y)**	43 (3-yr)
RTOG 0236	55	20 Gy x 3	34 mo	**97**	56 (3-yr)
Heidelberg	42	19 -30 x 1	15 mo	**68**	37 (3-yr)
Torino	62	15 Gy x 3	28 mo	**88**	57 (3-yr)
Tohoku	31	15 x 3, 7.5x8	32 mo	**78/40**	71 (3-yr)
VU Univ	206	20 x 3 ,12 x 5 7.5 x 8	12 mo	**97**	64 (2-yr)

”Risk-adapted” SABR protocol

- Peripheral lesions (T1a-T1b):

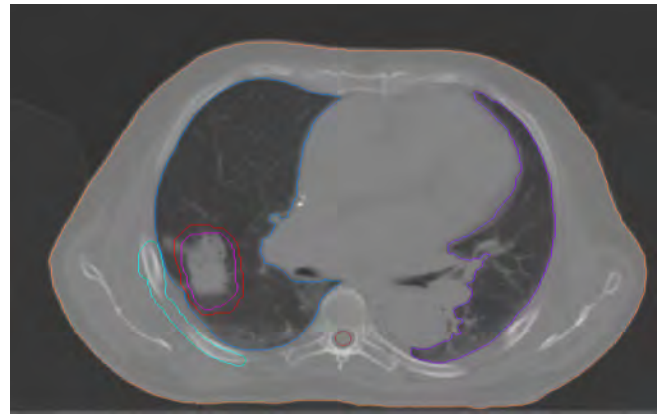
- 54 Gy/ 3 fractions 18 Gy

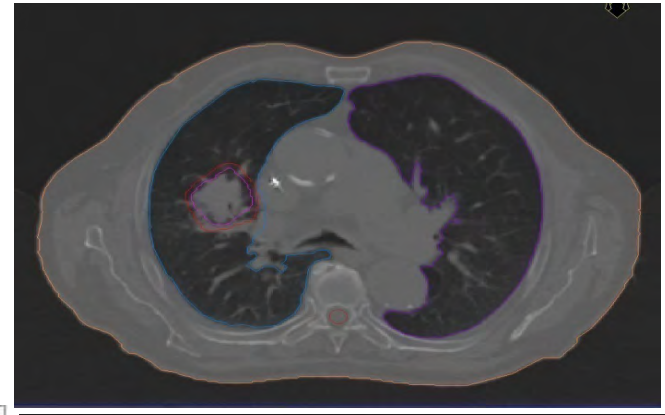
- Peripheral lesions, with extensive contact with the chest wall, or larger tumors (T2a):

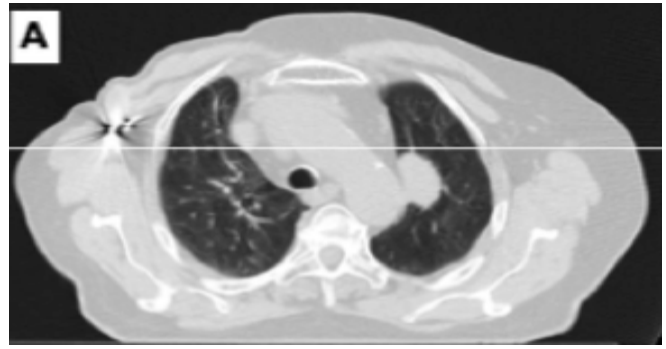
- 55 Gy/ 5 fractions

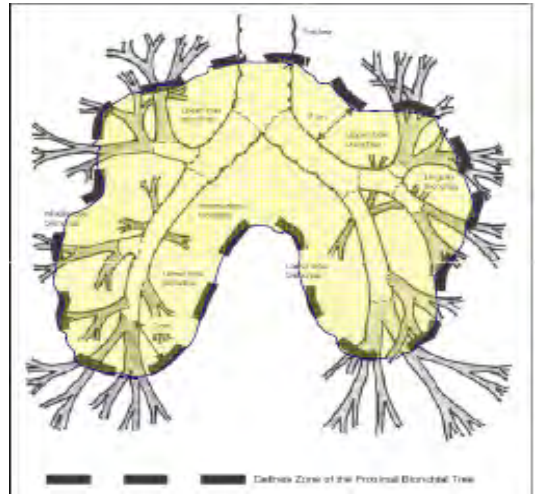
- Central lesions:

- 60 Gy/ 8 fractions









VU Amsterdam

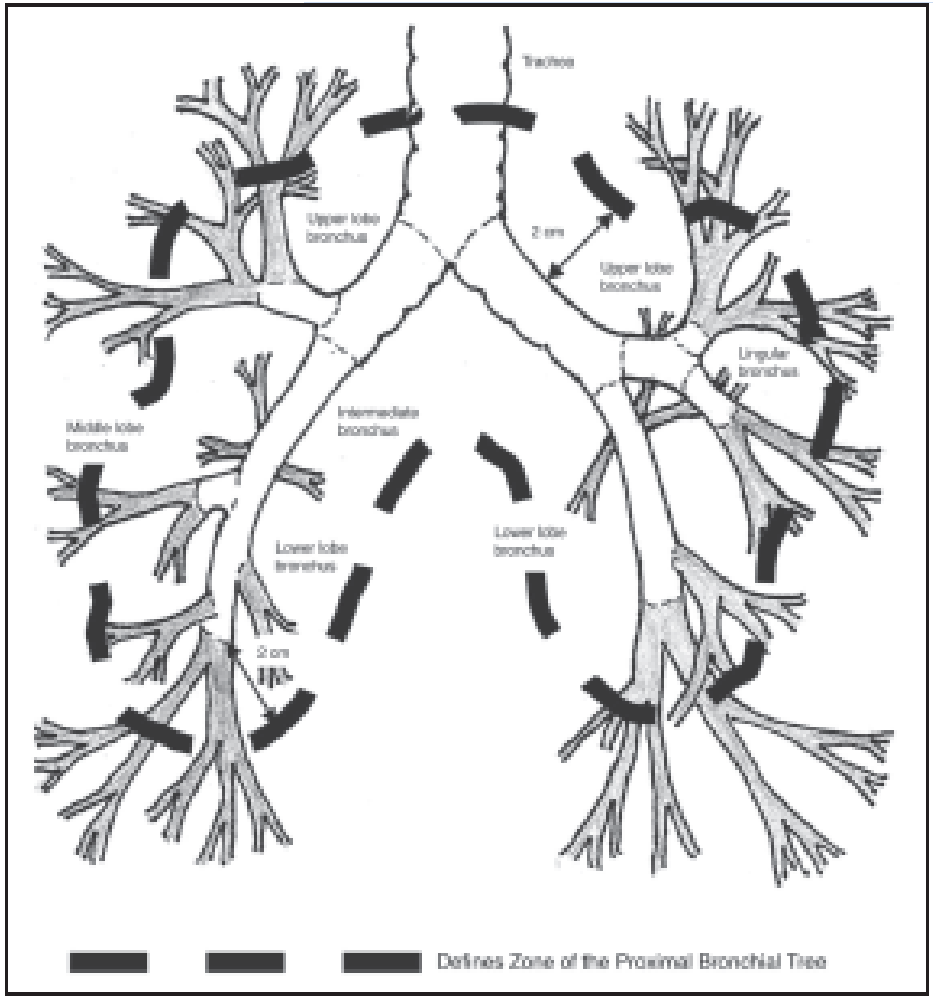
Radiation schemes (39-60 Gy in 3-8 fx)

3 x 20 Gy	**BED 180 Gy_{10}**	T_1N_0 with no or minimal contact with chest wall or mediastinum
5 x 12 Gy	**BED 132 Gy_{10}**	T_2N_0 T_1N_0 with extensive contact with chest wall or mediastinum
8 x 7.5 Gy	**BED 105 Gy_{10}**	All tumors in close proximity of the pulmonary artery or spinal cord

Notion de « no fly zone »

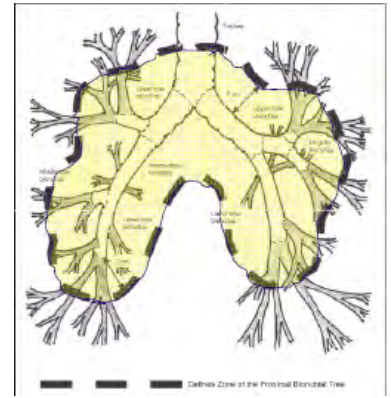
Excessive Toxicity When Treating Central Tumors in a Phase II Study of Stereotactic Body Radiation Therapy for Medically Inoperable Early-Stage Lung Cancer

Robert Timmerman, Ronald McGarry, Constantin Yiannoutsos, Lech Papiez, Kathy Tudor, Jill DeLuca, Marvene Ewing, Rasmi Abdulrahman, Colleen DesRosiers, Mark Williams, and James Fletcher



La notion de
« no fly zone »...

Timmerman JCO 2006

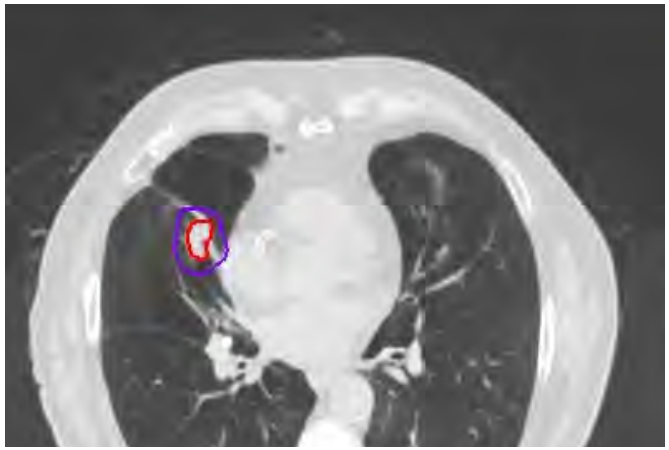


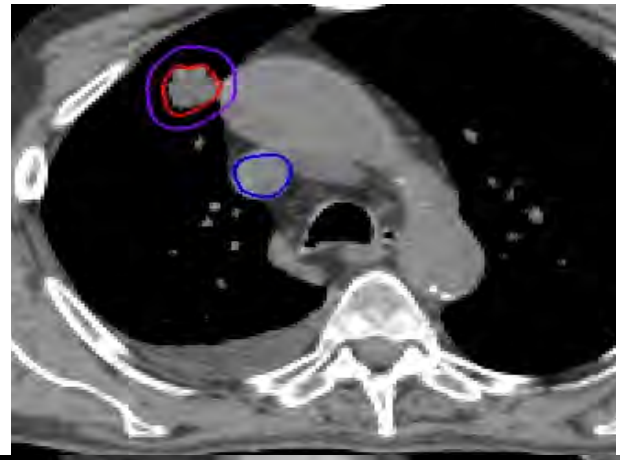
Attention à la dose totale et à la dose quotidienne

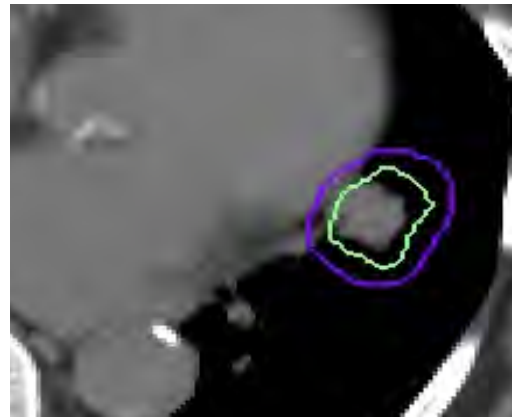
A adapter au patient!!

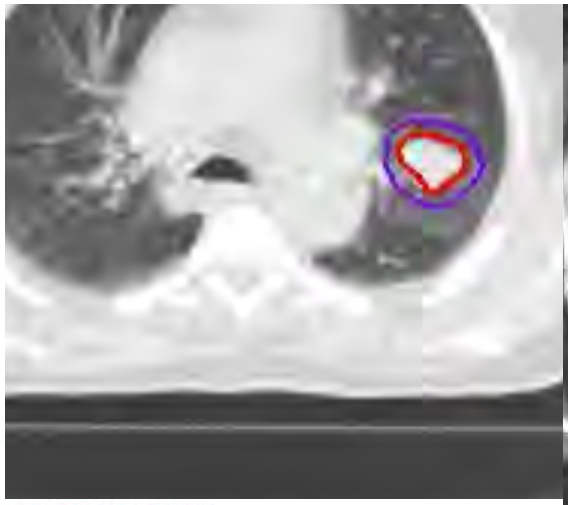
Domaine du « sur mesure »

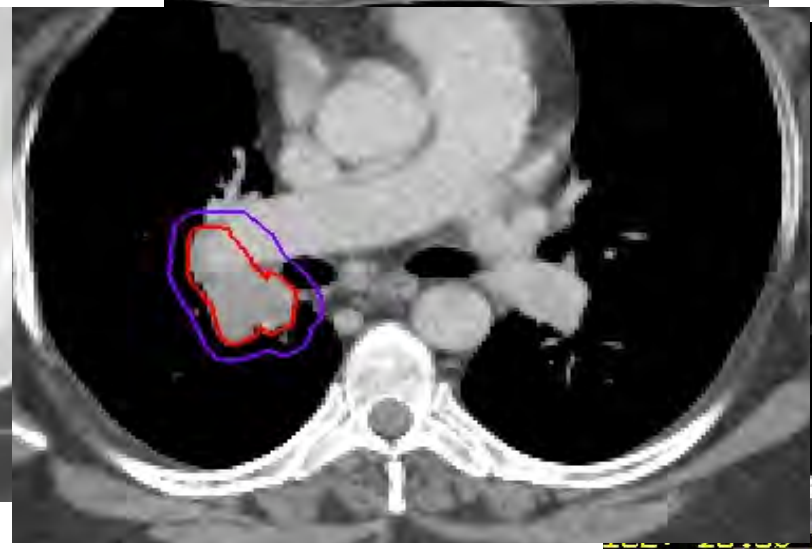
Tumors were in different locations so different OARs at risk

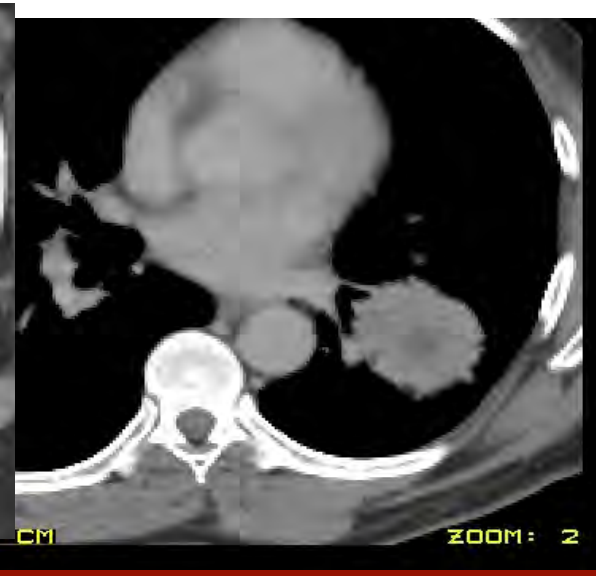












ONCOLOGY™

NRG ONCOLOGY

Advancing Research. Improving Lives.™

NRG Oncology/RTOG 0813 Trial of Stereotactic Body Radiotherapy (SBRT) for central tumors – Adverse events

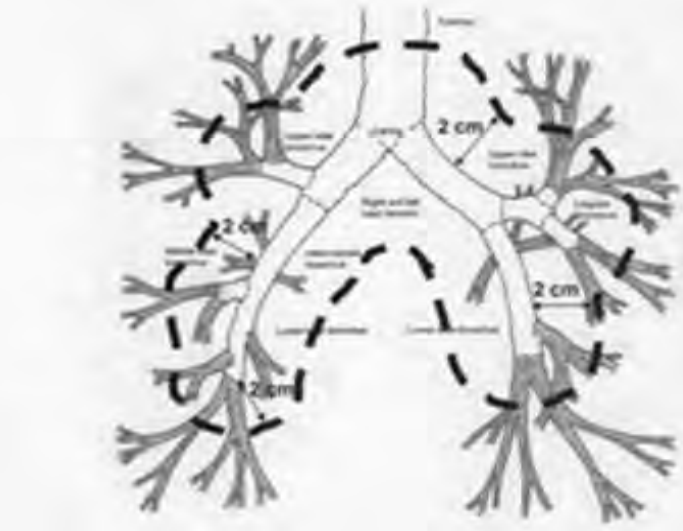
A Bezjak, R Paulus, LGaspar, R Timmerman, W Straube, W Ryan, Y Garces, AT Pu, AK Singh, GM Videtic, M Suntharalingam, P Iyengar, JR Pantarotto, EA Levine, AY Sun, ME Daly, IS Grills, PW Sperduto, DP Normolle, JD Bradley, H Choy

WCLC 2015 Denver
Sept 9 2015

Methods

Eligible patients:

- Biopsy proved NSCLC T1T2 N0 M0
- Medically inoperable
- ≤ 5 cm in size
- PS 0-2
- Not suitable for chemoRT
- Centrally located tumor



NRG ONCOLOGY™

0813 –SBRT Dose Levels/ Number of patients

Level 1	8 Gy x 5 fr	40 Gy total	
Level 2	8.5 Gy x 5	42.5 Gy	
Level 3	9 Gy x 5	45 Gy	
Level 4	9.5 Gy x 5	47.5 Gy	
Level 5	10 Gy x 5	50 Gy --------	8 pts
Level 6	10.5 Gy x 5	52.5 Gy ------	8 pts
Level 7	11 Gy x 5	55 Gy --------	18 pts
Level 8	11.5 Gy x 5	57.5 Gy ------	43 pts
Level 9	12 Gy x 5	60 Gy --------	43 pts

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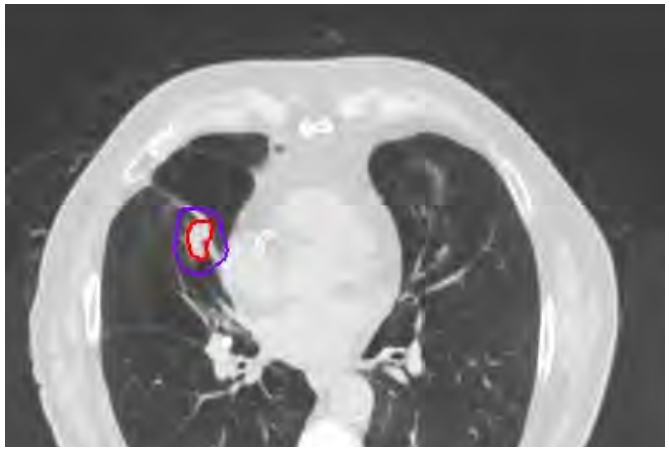
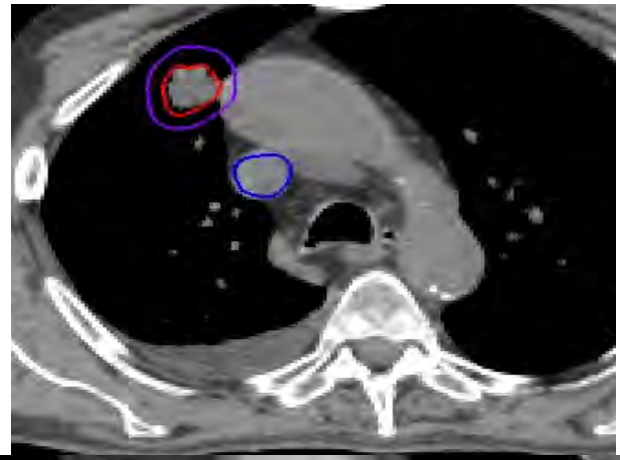
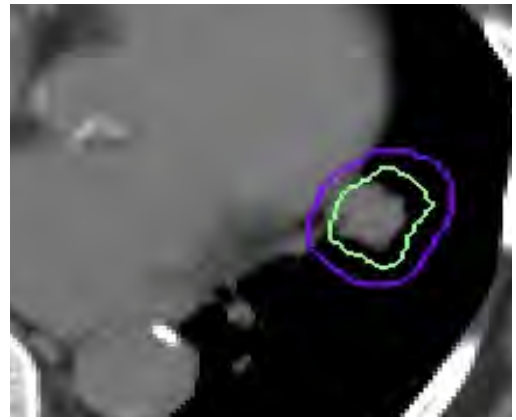
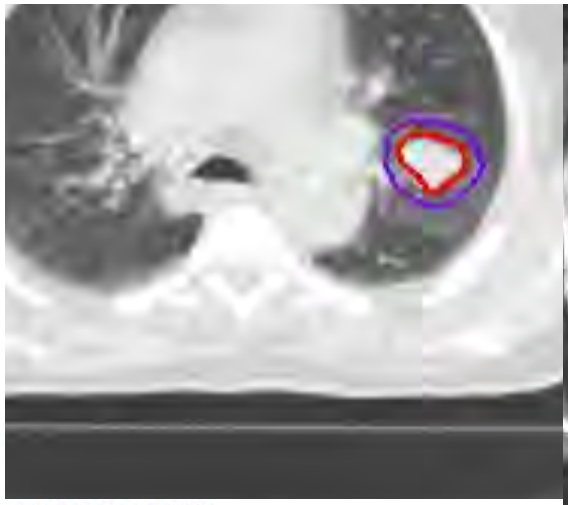
120 pts

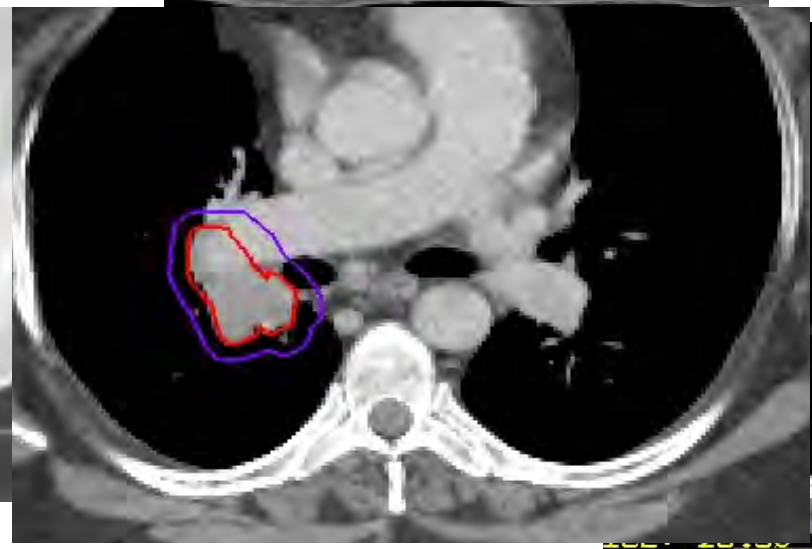
Tumors were in different locations so different OARs at risk

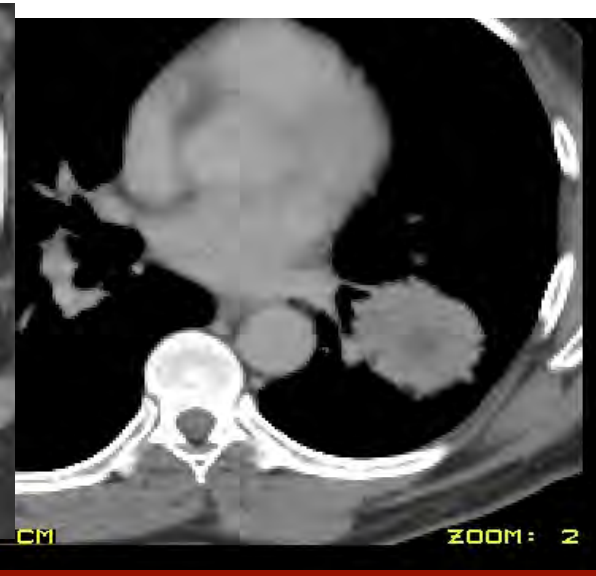












ONCOLOGY™

G 5 toxicity:

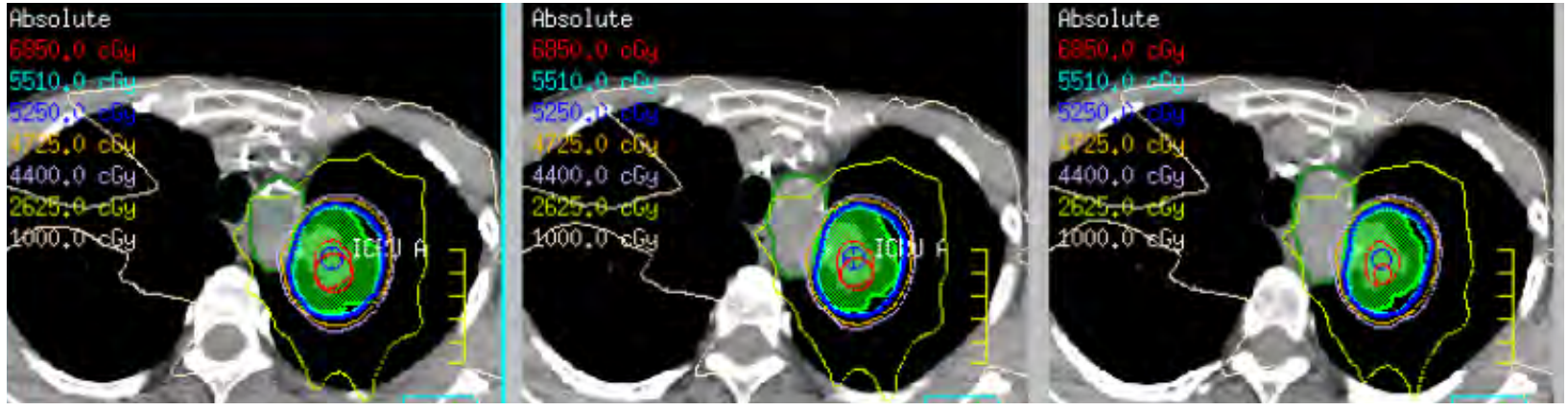
4 pts had Gr 5 toxicities

1 pt at 10.5Gyx5

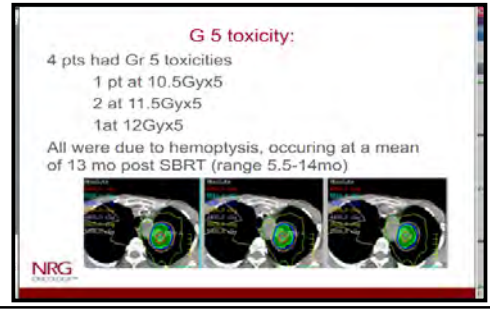
2 at 11.5Gyx5

1at 12Gyx5

All were due to hemoptysis, occuring at a mean of 13 mo post SBRT (range 5.5-14mo)



Tumeurs centrales: Fractionnement, dose totale, tolérance

NRG-Oncology **RTOG 0813** **IASLC 2015-Denver**		**G5: 4%** **12 Gy x 5**
Senthi, revue de la littérature **Radiother Oncol 2013**		**G5 2.8%** **3.6% si BED3> 210 Gy** **1.0% si BED3< 210 Gy**
Lagerwaard F, 2012, Pays Bas **Haasbeck CJ 2011**		**G5 0%** **7.5 Gy x 8**
Chang JY, MDACC, IJROBP 2014		**G5 0%** **10 Gy x 7**

BJR
Received: 12 January 2015 | Revised: 2 April 2015 | Accepted: 13 April 2015
doi: 10.1259/bjr.20150036
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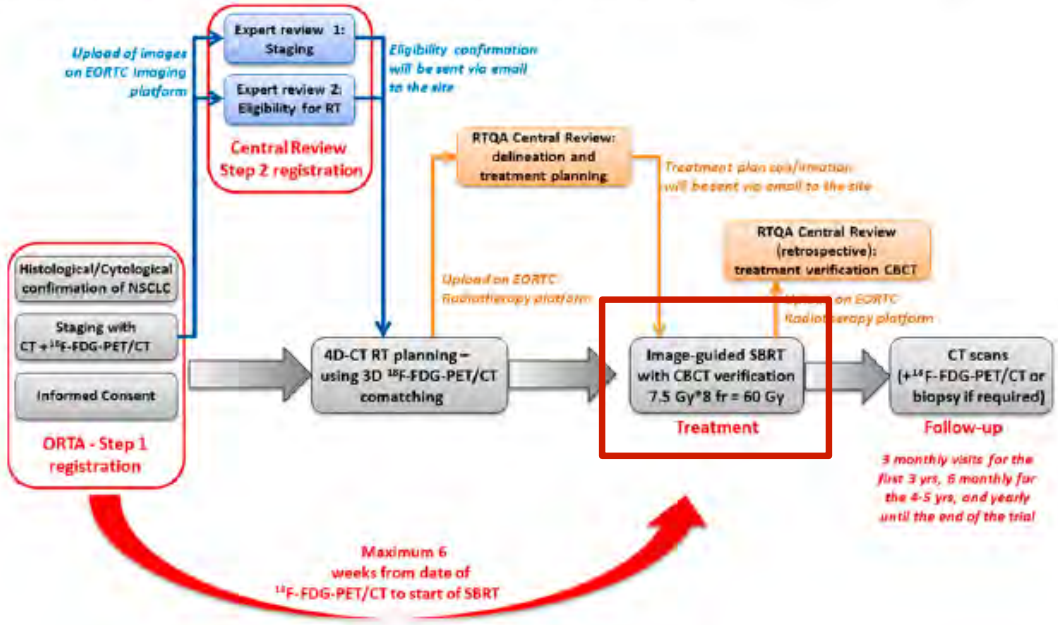
ADVANCES IN RADIOTHERAPY SPECIAL FEATURE: REVIEW ARTICLE

LungTech, an EORTC Phase II trial of stereotactic body radiotherapy for centrally located lung tumours: a clinical perspective

[1,2]S ADEBAHR, [3]S COLLETTE, [3]E SHASH, [4]M LAMBRECHT, [5]C LE PECHOUX, [6]C FAIVRE-FINN, [7]D DE RUYSSCHER, [8]H PEULEN, [8]J BELDERBOS, [9]R DZIADZIUSZKO, [10]C FINK, [11]M GUCKENBERGER, [4]C HURKMANS and [1,2]U NESTLE

Figure 4. Design of the LungTech trial [European Organization for Research and Treatment of Cancer (EORTC) 22113-08113]. 3D, three dimensional; 4D-CT, four-dimensional CT; ^{18}F-FDG, Fluorine-18 Fludeoxyglucose; CBCT, cone beam CT; fr, fractions; NSCLC, non-small-cell lung cancer; ORTA, online randomized trials access; PET, position emission tomography; RT, radiotherapy; RTQA, radiation therapy quality assurance; SBRT, stereotactic body radiotherapy; yrs, years.



TAKE HOME MESSAGE

SBRT for central tumors is a « double-edged sword »
that can kill cancer cells
but can also lead to severe, potentially life-threatening radiation sequelae due to the spatial proximity to serial OARs.

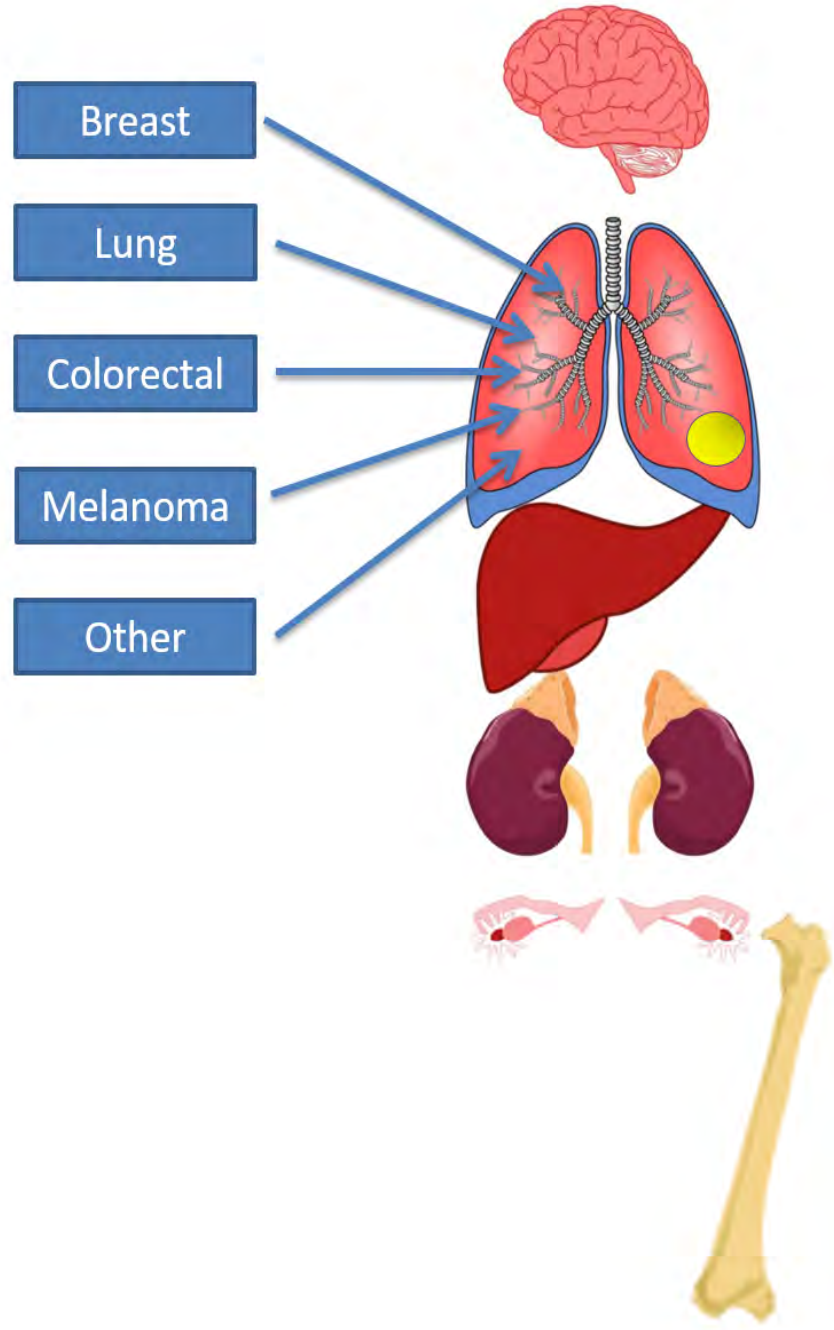
Prospective, multicentric data on the tolerance of mediastinal structures is limited.

3 categories of patients

1) Primary lung cancer

2) Lung OligoMTS from several primary tumors

3) Distant MTS from lung cancer.



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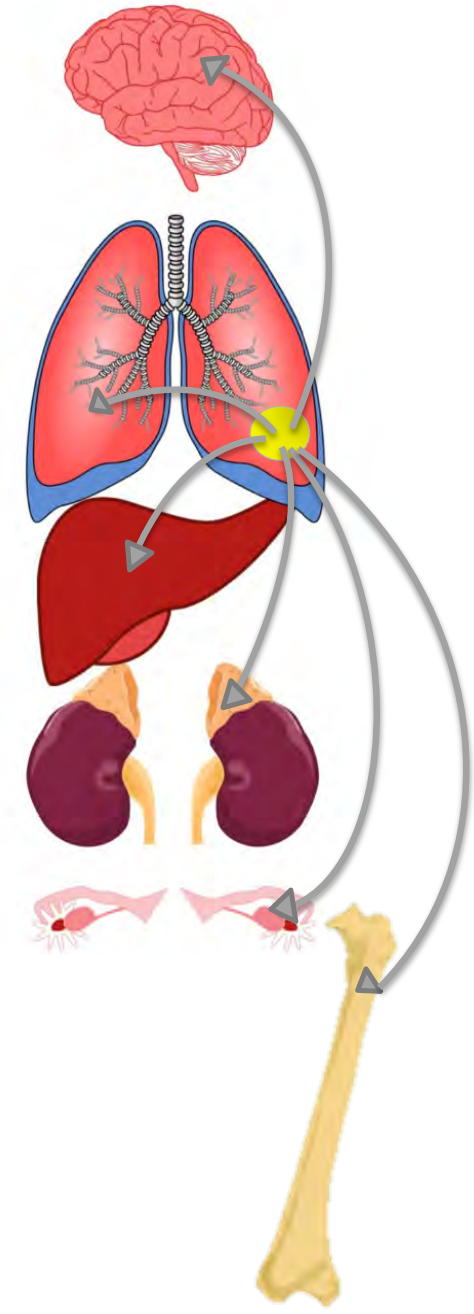


CONVERT trial

Concurrent ONce-daily VErsus twice-daily RadioTherapy: A 2-arm randomised controlled trial of concurrent chemo-radiotherapy comparing twice-daily and once-daily radiotherapy schedules in patients with limited-stage small cell lung cancer and good performance status

Corinne Faivre-Finn[1], Michael Snee[2], Linda Ashcroft[3], Wiebke Appel[4], Fabrice Barlesi[5], Adi Bhatnagar[6], Andrea Bezjak[7], Felipe Cardenal[8], Pierre Fournel[9], Susan Harden[10], Cecile Le Pechoux[11], Rhona McMenemin[12], Nazia Mohammed[13], Mary O'Brien[14], Jason Pantarotto[15], Veerle Surmont[16], Jan Van Meerbeeck[16], Penella Woll[17], Paul Lorigan[1], Fiona Blackhall[1]

*1. The University of Manchester, Institute of Cancer Sciences, Manchester, UK; 2. St James Hospital, Leeds, UK; 3. MAHSC-CTU, The Christie NHS Foundation Trust, UK; 4. Royal Preston Hospital, UK; 5. CHU de Marseille, France; 6.Southampton General Hospital, UK; 7.*Canadian Cancer Trials Group, Princess Margaret Cancer Center, Toronto, Canada*; 8. GECP , Institut Català d'Oncologia, Barcelona, Spain; 9. GFPC, Institut de Cancérologie de la Loire, France; 10. Addenbrookes Hospital, Cambridge, UK; 11. Institut Gustave Roussy, Villejuif, France; 12. Freeman Hospital, Newcastle-upon-Tyne, UK; 13. Beatson Cancer Centre, Glasgow, UK; 14. Royal Marsden Hospital, Surrey, UK; 15. Ottawa Health Research Institute, Canada; 16. Universiteit Gent, Belgium; 17. Weston Park Hospital, Sheffield, UK*

Presented by: Prof C Faivre-Finn

CONVERT

SCLC localisé:

La dose de radiothérapie
Le concept du bifractionnement

ASCO 2016 CHICAGO

ASCO ANNUAL MEETING
COLLECTIVE WISDOM
2016
THE FUTURE OF PATIENT-CENTERED CARE AND RESEARCH

June 3-7, 2016
McCormick Place | Chicago, Illinois | #ASCO16

IASLC

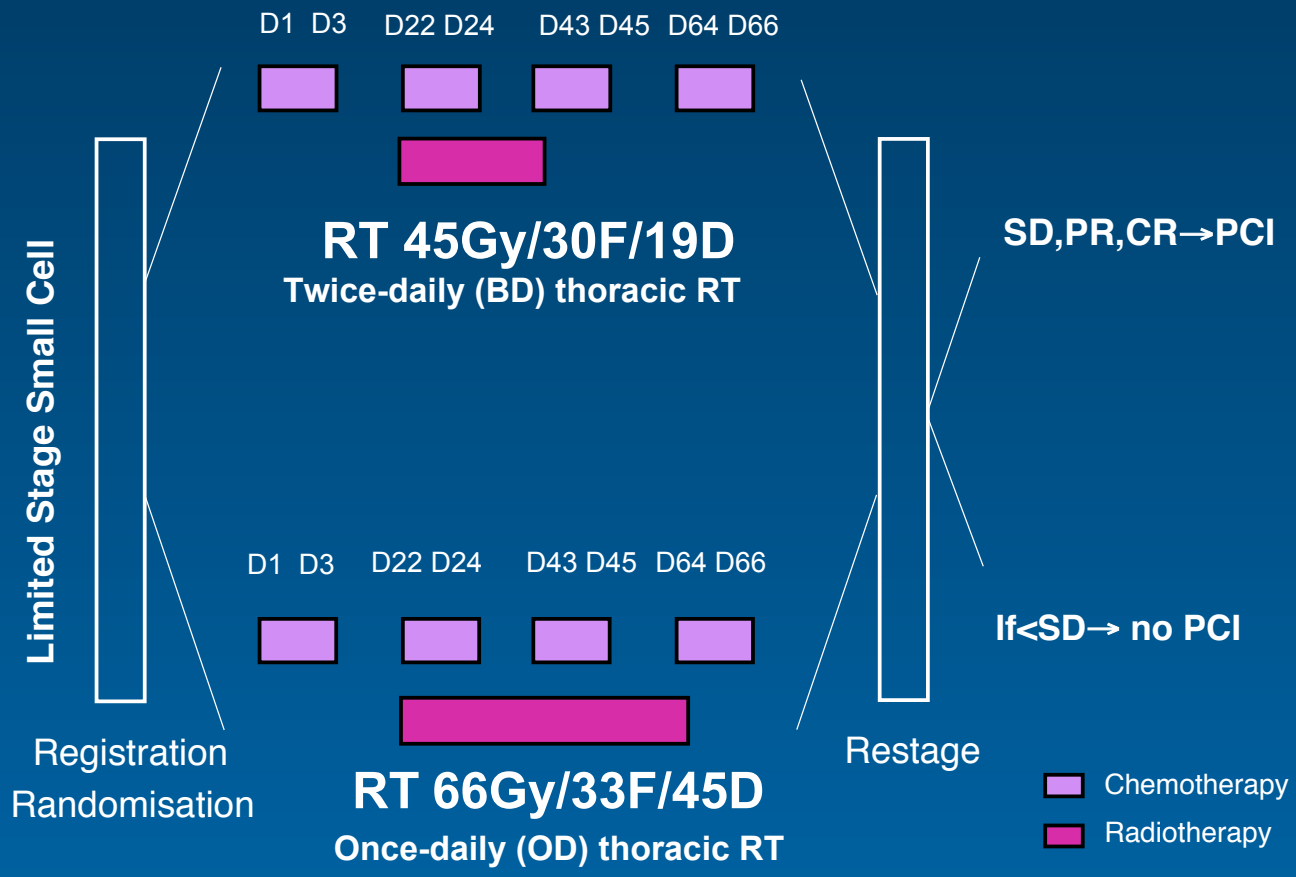
Study design
multinational, phase III randomised study

RTP after randomisation
RT started on D22 cycle 1
- **3DCRT or IMRT**
- **No ENI**

QA programme

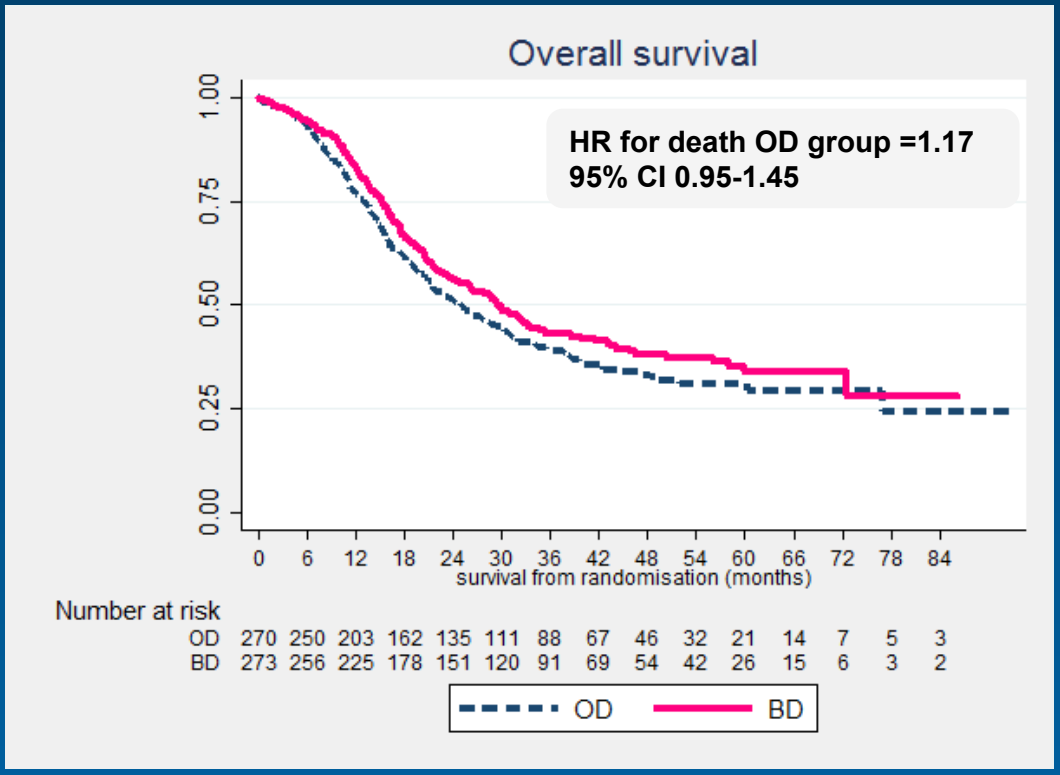
Chemotherapy
4 to 6 cycles
- **Cisplatin 25mg/m2 D1-3 or 75mg/m2 D1**
- **Etoposide 100mg/m2 D1-3**

Stratification factors
- **Centre**
- **No. of cycles chemo: 4 vs.6**
- **PS: 0,1 vs. 2**



Presented by: Prof C Faivre-Finn

Overall survival



Primary objective-survival at 2 years
Trial hypothesis

- **Expected survival BD arm 44%**
- **Projected survival OD arm 56%**

Median follow-up: 45 months

Overall survival (n=543)	BD	OD	Log-rank
Median (months)	30 (24-34)	25 (21-31)	p=0.15
1-year	83% (78-87)	76% (71-81)	
2-year	56% (50-61)	51% (45-57)	
3-year	43% (37-49)	39% (33-45)	

Presented by: Prof C Faivre-Finn

Acute Toxicity

Organ at risk	Arm	N	Median (Range)
Lung V5 (%)	BD	246	56.2 (7.2-88.5)
	OD	234	60.8 (7.0-91.6)
Lung V20 (%)	BD	252	23.2 (0.1-35.4)
	OD	240	28.8 (8.0-40.5)
Heart (% total dose)	BD	240	2.0 (0-45.3)
	OD	229	1.4 (0-36.2)
Spinal cord (max dose, Gy)	BD	251	32.0 (1.3-45.8)
	OD	241	41.7 (1.3-52.6)
Oesophagus (max dose, Gy)	BD	248	45.7 (0.7-64.4)
	OD	236	65.9 (2.2-71.7)
Oesophagus V35 (%)	BD	246	34.0 (0-76.5)
	OD	230	38.8 (0-82.8)

AE CTCAE v3.0	Arm	0 n (%)	1-2 n (%)	3-5 n (%)	p (0,1,2 vs 3,5)
Oesophagitis	BD	48 (18.9)	159 (62.6)	45 (18.5)	0.85
	OD	63 (25.7)	135 (55.1)	47 (19.2)	
Pneumonitis	BD	198 (78.0)	51 (20.1)	5 (2.0)*	0.70
	OD	187 (77.3)	49 (20.2)	6 (2.4)*	

1 patient in each arm not assessable for oesophagitis, 6 patients for pneumonitis
***1 patient in BD arm and 2 patients in OD arm (1 received sequential CTRT) died from radiation pneumonitis**

Presented by: Prof C Faivre-Finn

Late Toxicity

Symptom	Arm	0	1-2	3	4	p 0,1,2 vs 3,4
Dermatitis	BD OD	233 (94.0) 216 (92.7)	15 (6.0) 17 (7.3)	-	-	-
Oesophagitis	BD OD	219 (88.3) 191 (81.6)	29 (11.7) 39 (16.7)	- 4 (1.7)	-	 0.06
Oesophageal stricture/fistula	BD OD	240 (91.8) 226 (97.0)	8 (3.2) 6 (2.6)	- 1 (0.4)	-	 0.48
Pulmonary fibrosis	BD OD	125 (50.6) 120 (52.6)	119 (48.2) 106 (46.5)	3 (1.2) 2 (0.9)	-	 1.00
Pneumonitis	BD OD	171 (69.0) 154 (67.0)	71 (28.6) 70 (30.4)	5 (2.0) 5 (2.2)	1 (0.4) 1 (0.4)	 0.90
Myelitis	BD OD	247 (99.6) 223 (96.5)	1 (0.4)* 8 (3.5)*	-	-	-
Other	BD OD	92 (37.4) 99 (42.7)	131 (53.3) 113 (48.7)	20 (8.1) 18 (7.8)	3 (1.2) 2 (0.9)	 0.78

*** Myelitis all grade 1**

Presented by: Prof C Faivre-Finn

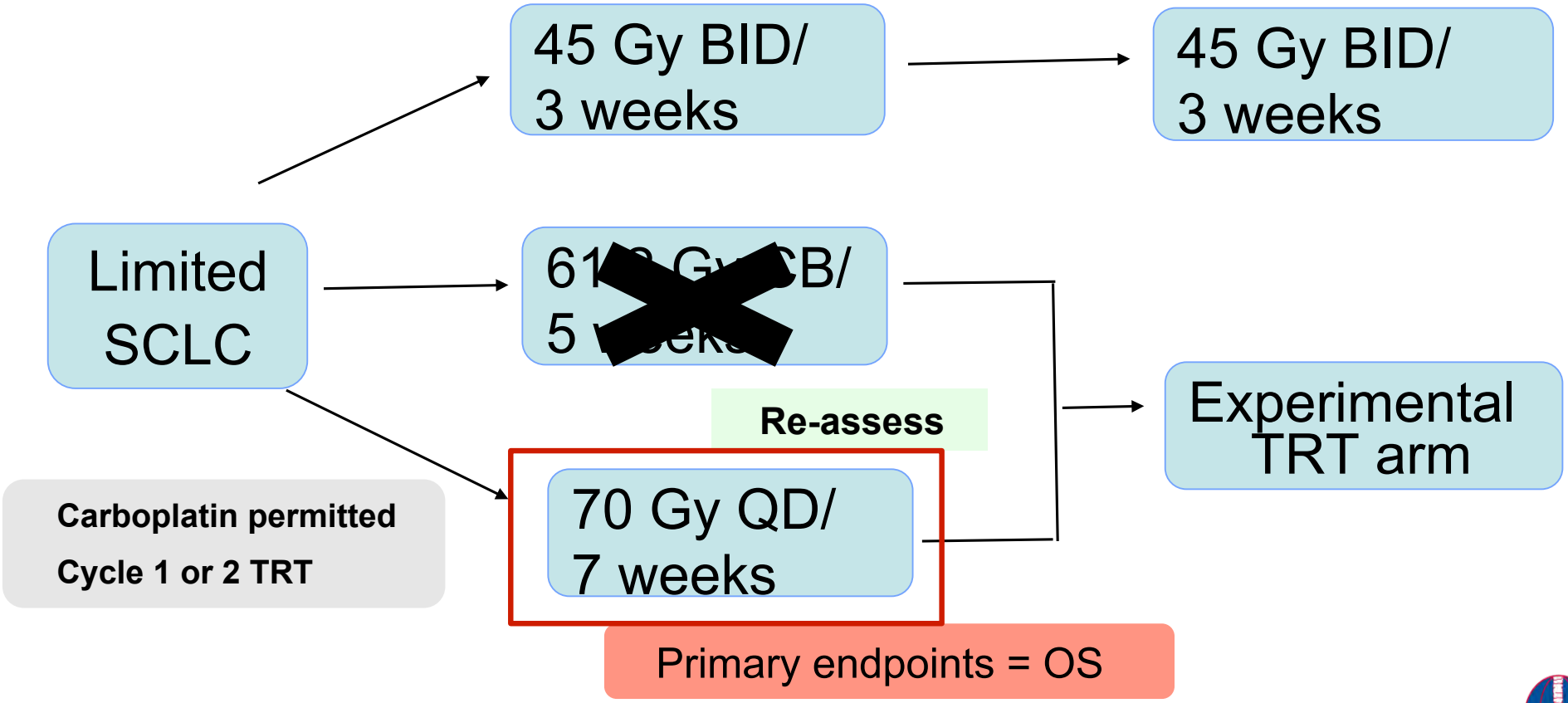
Conclusions

- Survival in both arms was higher than previously reported
- Radiation-related toxicities were lower than expected likely due to the use of modern RT techniques
- OD RT did not result in a superior survival or worse toxicity than BD RT
- The results of CONVERT support the regimen for standard of care treatmer good PS

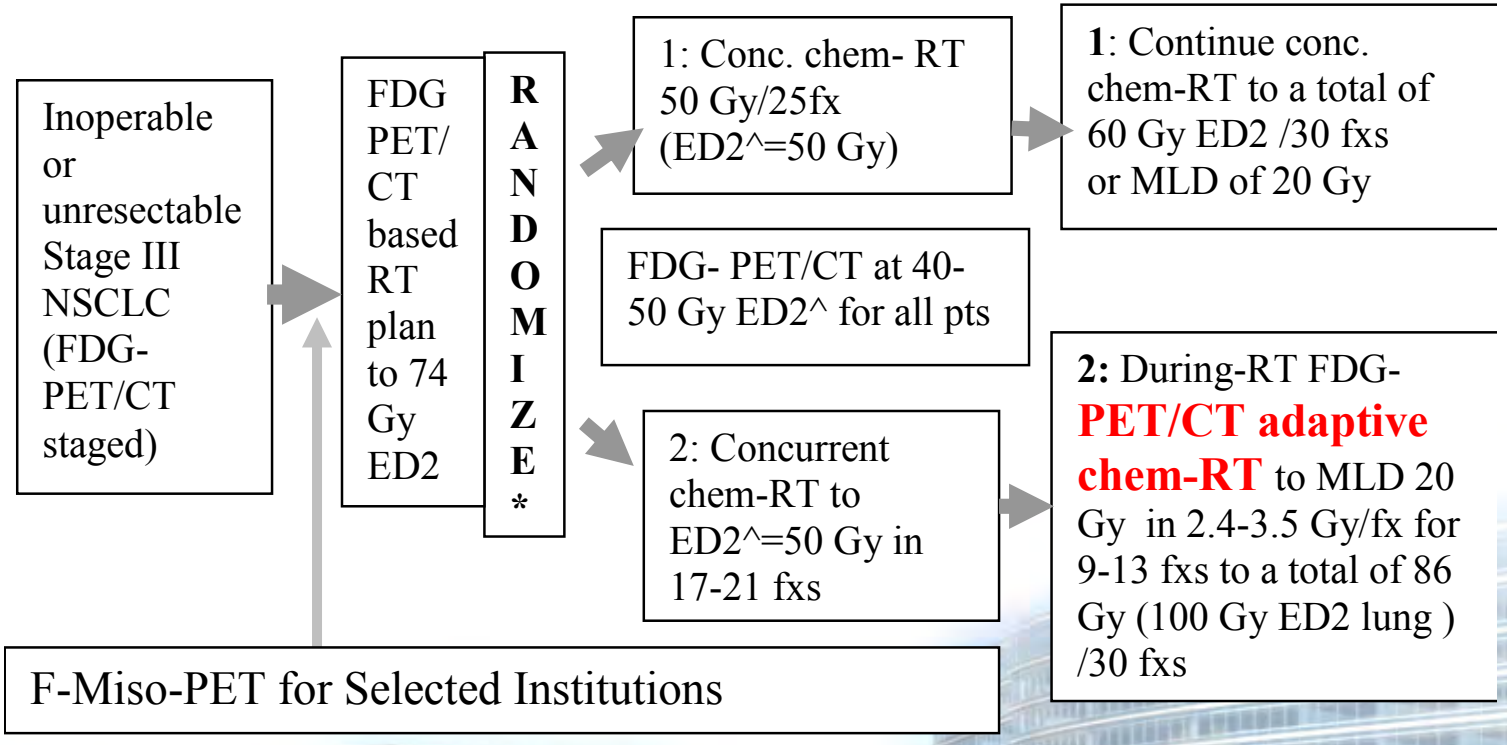
Si 1 Fx/jour, dose totale 66 Gy

Presented by: Prof C Faivre-Finn

Intergroup study
CALGB 30610-RTOG 0538



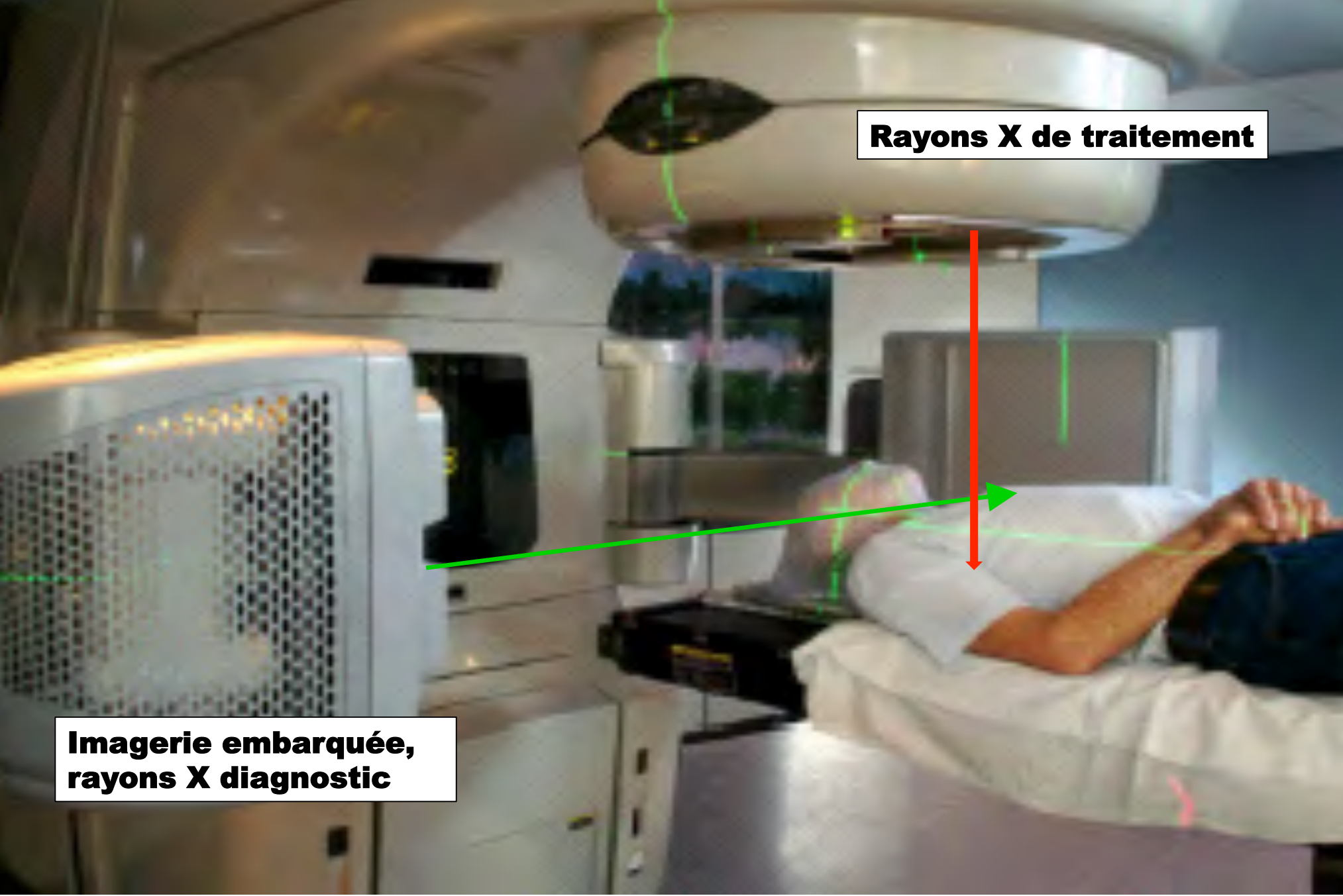
RTOG 1106/ ACRIN – Phase IIR



RTOG 0617 standard arm
Uniform dose prescription

Experimental arm:
Individualized adaptive RT

La radiothérapie guidée par l'image
IGRT


Rayons X de traitement
Imagerie embarquée,
rayons X diagnostic

The ExacTrac Snap Verification

XRays before AND DURING t he radiation de livery

La radiothérapie adaptative

ART

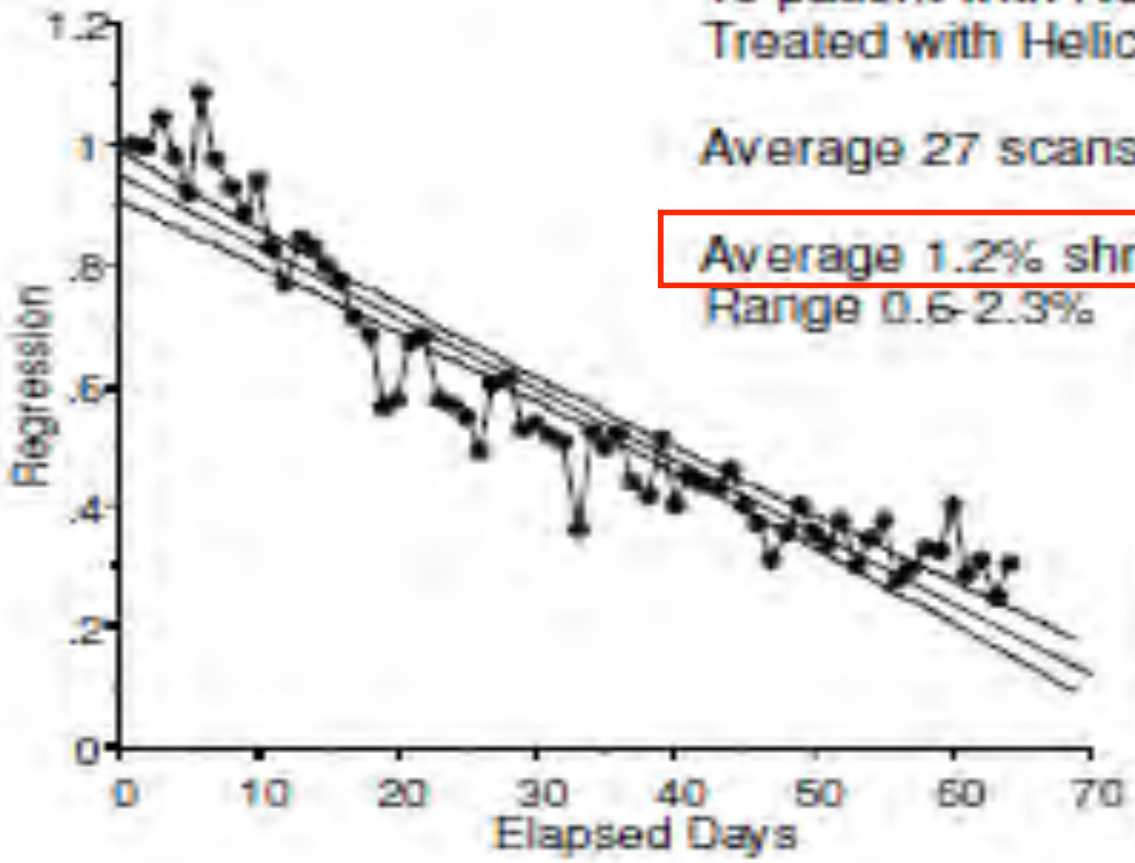
Lung Ca: Tumor Regression – Anatomic Changes

Kupelian et al., IJROBP, 2005

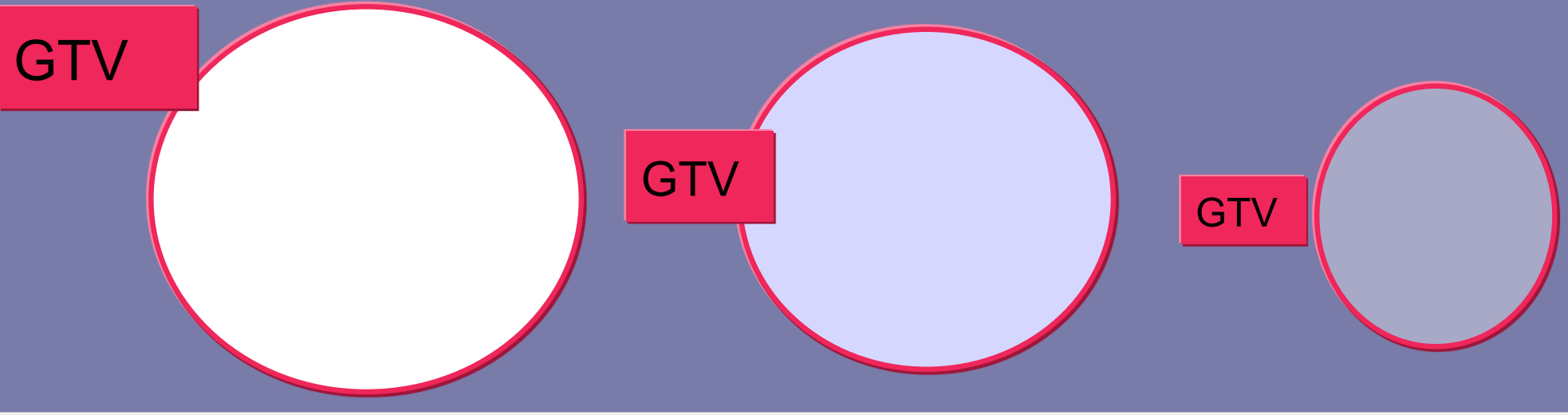
10 patient with NSCLC,
Treated with Helical Tomotherapy

Average 27 scans per patient

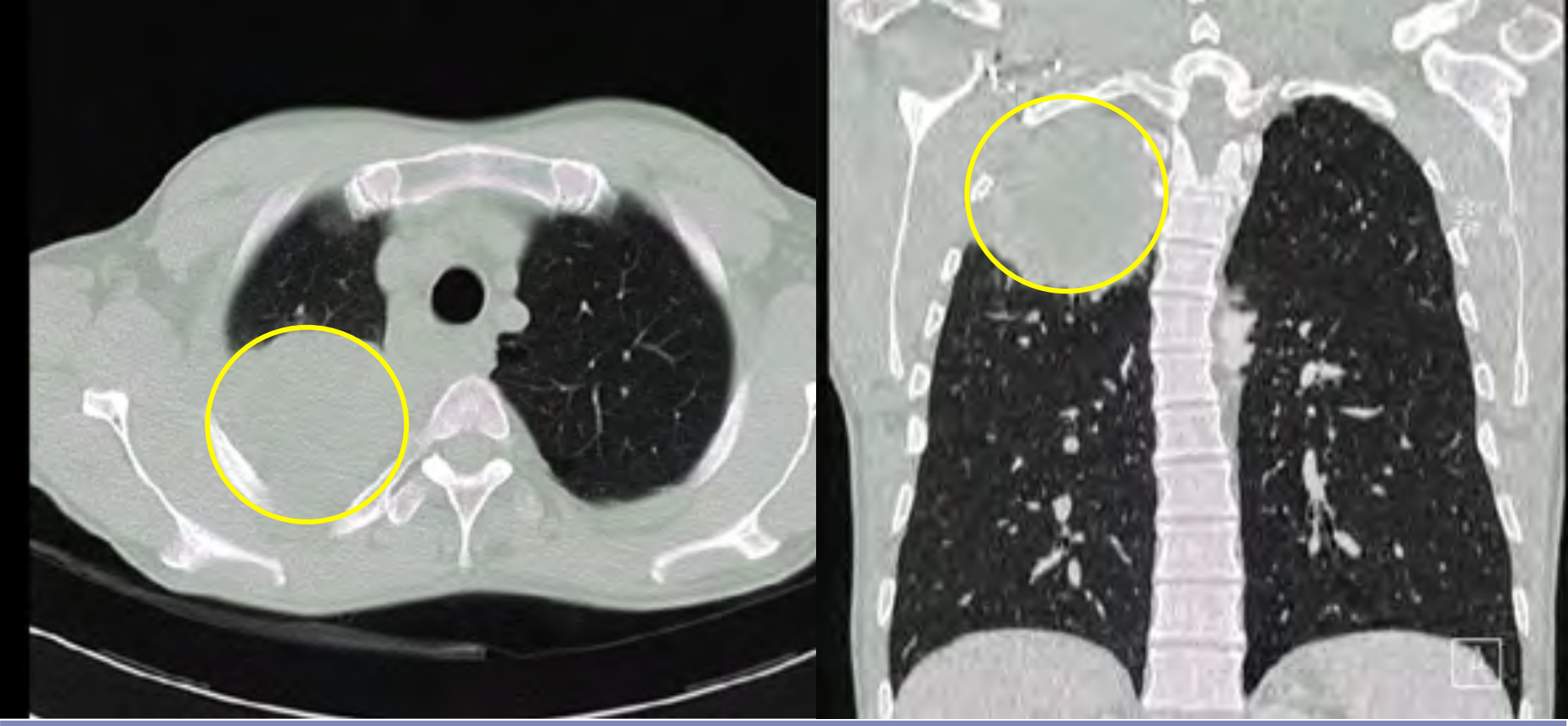
Average 1.2% shrinkage per day:
Range 0.6-2.3%



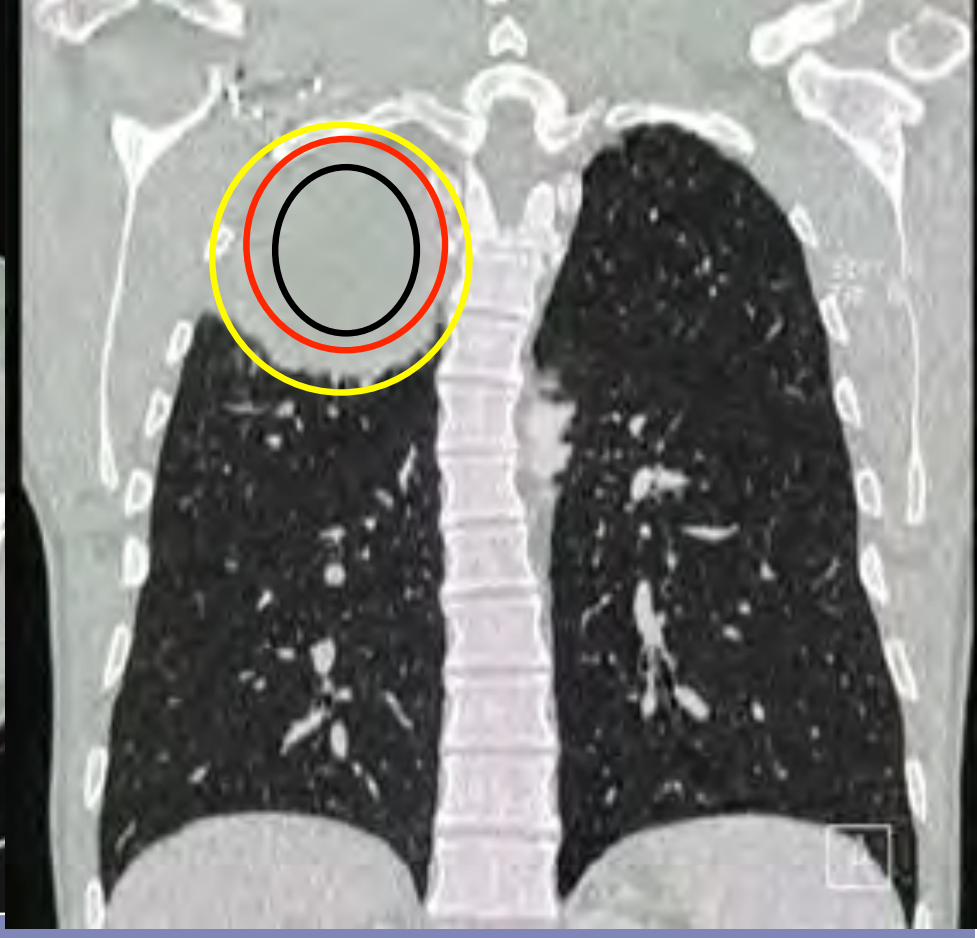
ART: Adaptive RadioTherapy



Week 1 4 6



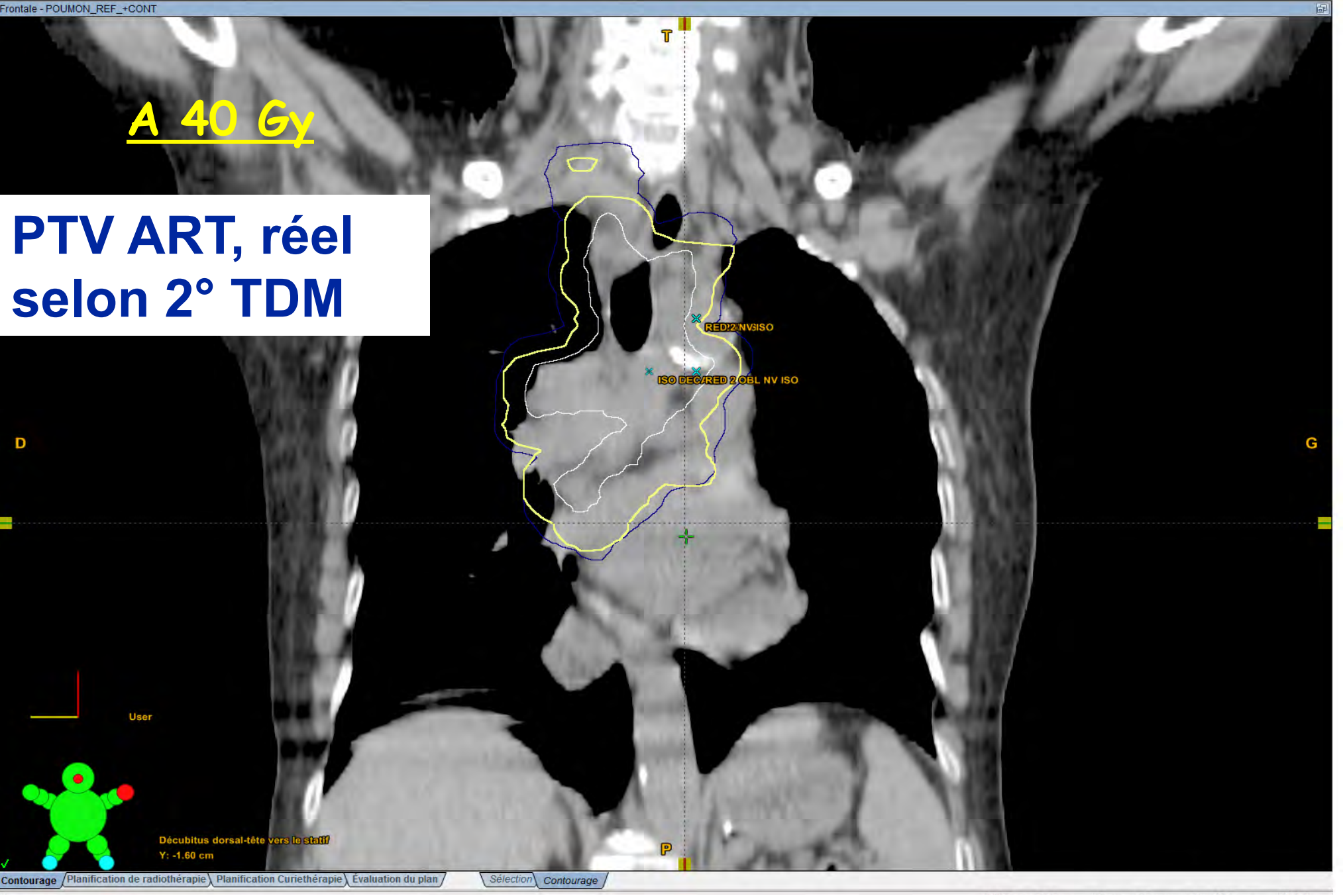
Volume tumoral initial, avant la radiothérapie



Volume tumoral initial, avant la RT

Volume tumoral après 4 semaines de RT

Volume tumoral après 5 semaines de RT


Frontale - POUMON_REF_+CONT
A 40 Gy
PTV ART, réel selon 2° TDM
T
D
G
P
RED!2 NV ISO
ISO DEC RED 2 OBL NV ISO
User
Décubitus dorsal-tête vers le statif
Y: -1.60 cm
Contourage
Planification de radiothérapie
Planification Curiethérapie
Évaluation du plan
Sélection
Contourage

Radiothérapie adaptative

Grâce à la mise à disposition d'imagerie de réévaluation, le volume tumoral peut être adapté à l'image réelle:

TDM de contrôle :

- **Diagnostique**
- **Dosimétrique**
- **Imagerie embarquée dans la machine**

Contribution du PET-CT

RT et PET-CT

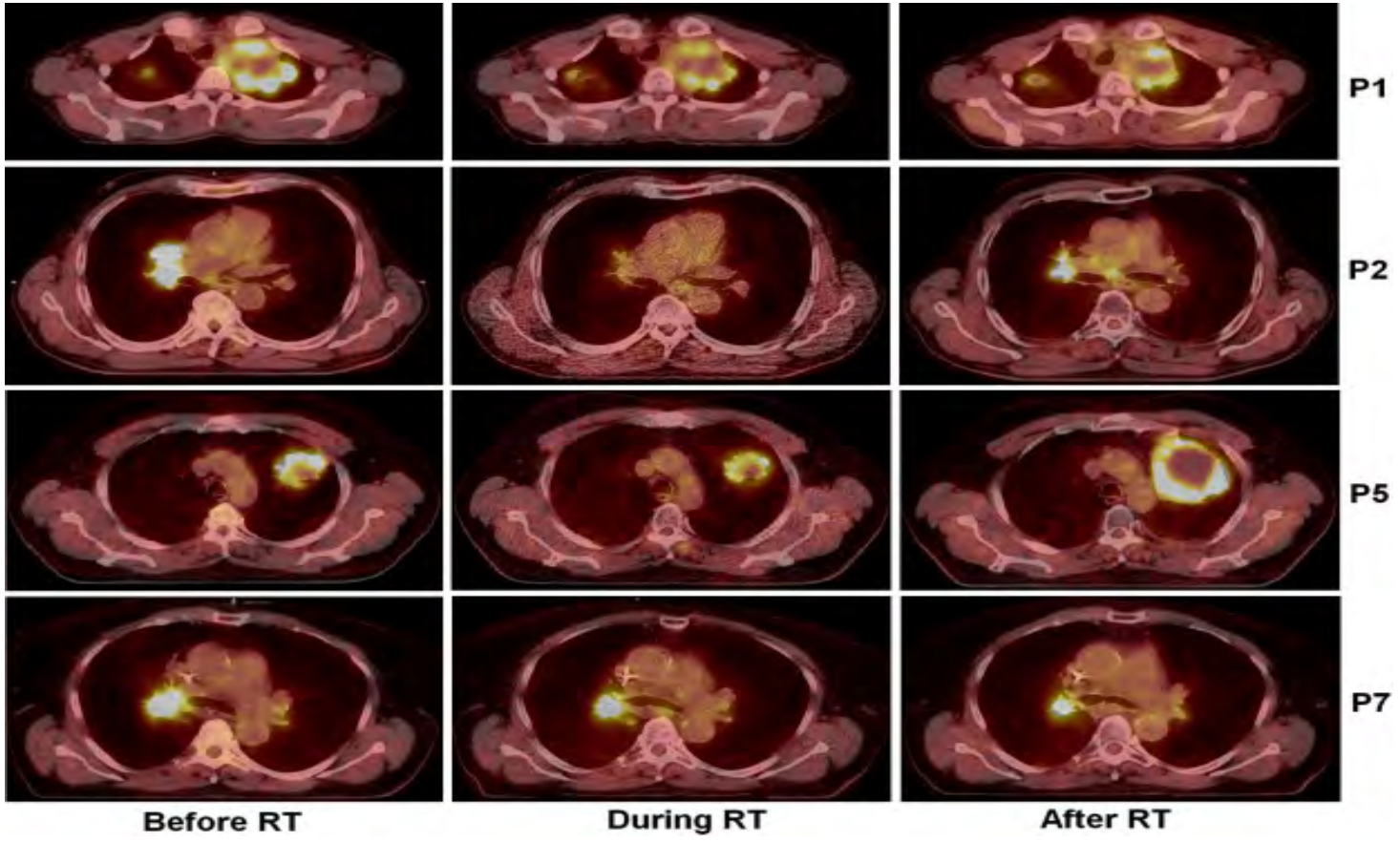
Les zones hypermétaboliques ont été montrées
radiorésistantes, suggérant la nécessité
d'une dose de radiothérapie plus élevée.

La tumeur peut être segmentée en plusieurs sous-volumes,
qui recevront une dose différente
selon l'intensité de leur métabolisme :

Escalade de dose

sur les zones restant hypermétaboliques.

Local Failure Appears Most Common in the Primary Tumor Volume with the Highest FDG Uptake



Abramyuk A et al, 2009

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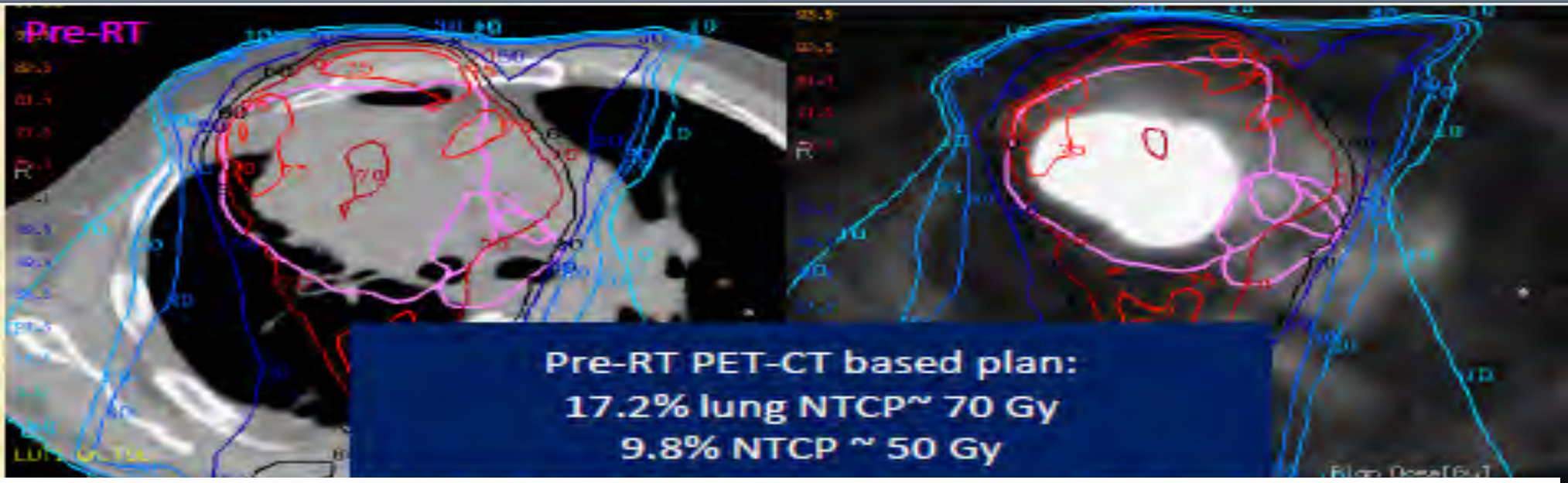
Adaptive Radiation Therapy planning based on PET/CT♪



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MINISTÈRE DES AFFAIRES SOCIALES ET DE LA SANTÉ

Appel à projets national en cancérologie

Programme hospitalier de recherche clinique en Cancérologie
PHRC-K 2014
Dossier de candidature

Le projet doit être rédigé en anglais
Date limite de soumission en ligne : 8 septembre 2014 minuit
http://www.e-cancer.fr/aap/recherche/phrck2014

Titre du projet :	
RTEP7-IFCT14.01 : Etude de phase II-III randomisée évaluant l'intérêt d'une redistribution de dose personnalisée chez des patients atteints d'un cancer pulmonaire non à petites cellules inopérables et ayant une TEP-FDG positive à 42 Gy de la radiochimiothérapie pulmonaire à visée curative.	
Project title :	
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	
Mots clés *Key words* **:**	Radiotherapy, nuclear medicine, lung cancer
Discipline, spécialité du projet *Project area* **:**	Nuclear medicine, Radiotherapy
Organe, localisation anatomique de la tumeur *Organ, tumor location :*	Lung cancer,
Autre (libre) *Other* **:**	FDG-PET, Radiotherapy, Functional imaging, adaptive radiation therapy and dose redistribution
Titre, Prénom & Nom du coordonnateur *Title, First name and Name of co-ordinator:*	**Professor Pierre Vera**
Fonction et spécialité *Position and specialty :*	PU-PH, Nuclear Medicine Physician, MD, Ph.D.
Service ou département *Unit or Department* **:**	Department of Nuclear Medicine
Nom de l'établissement hospitalier *Hospital name* **:**	Henri Becquerel Cancer Center and QuantIF (EA4108 – FR CNRS 3638), 1 rue d'Amiens, 76038 Rouen cedex, France
Téléphone *Phone number* **:**	+33 (0)2 32 02 22 58
Adresse électronique *e-mail :*	**pierre.vera@chb.unicancer.fr**
Titre, Prénom & Nom du co-coordonnateur *Title, First name & Name of co-coordinator:*	**Professor Philippe Giraud**
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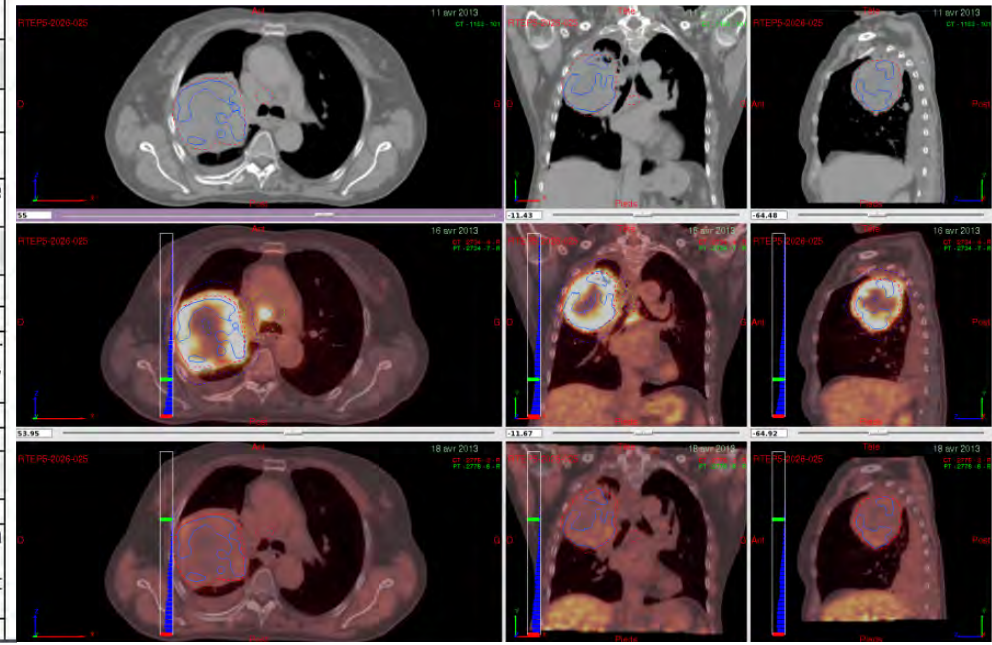
Téléphone *Phone number* **:**	+33 (0)1 56 09 33 22

RTEP7
Cancer bronchique

PHRC 2014 : 917 763 €



MAASTRO/NKI Phase IIr Trial

. T2-4N0-3M0
. Primary tumor diameter 4 cm or more
. MaxSUV>5
. Eligible for radical treatment

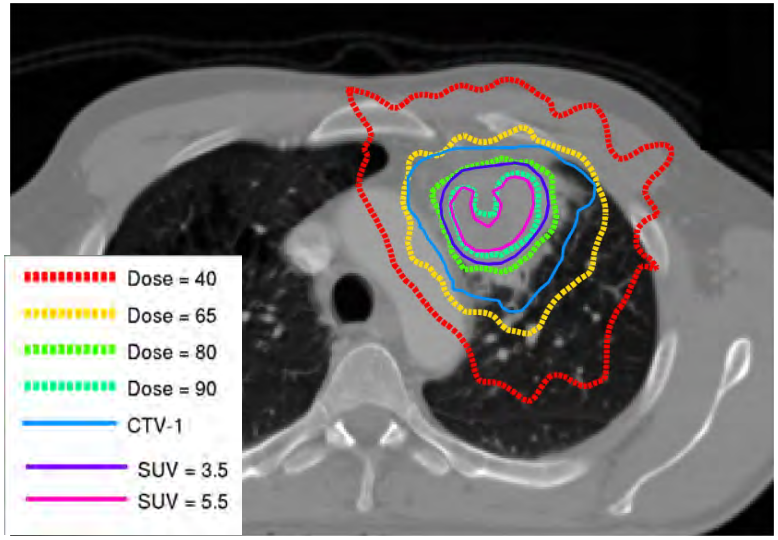
→ Register → Dose calculation

→ Dose escalation not possible → Chemo-radiotherapy to tolerance

→ Dose escalation possible → RANDOMIZE

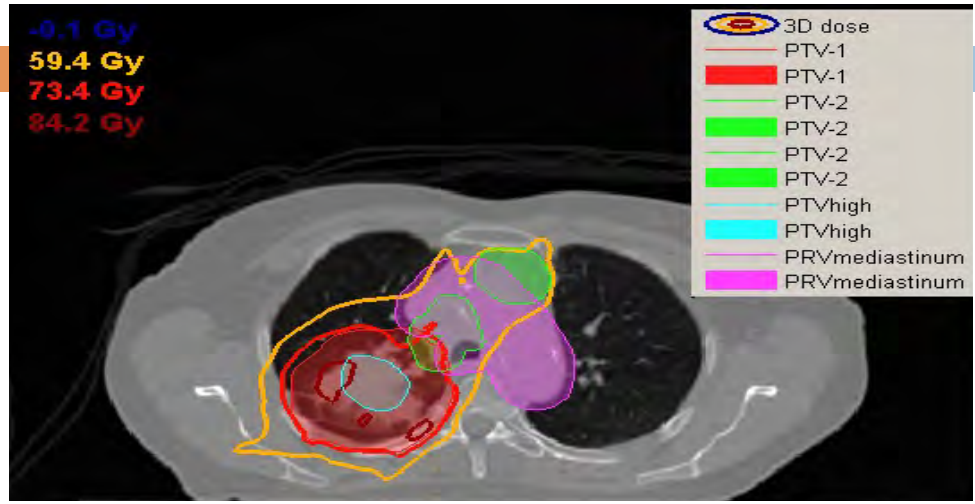
→ Homogeneous boost

→ Inhomogeneous boost

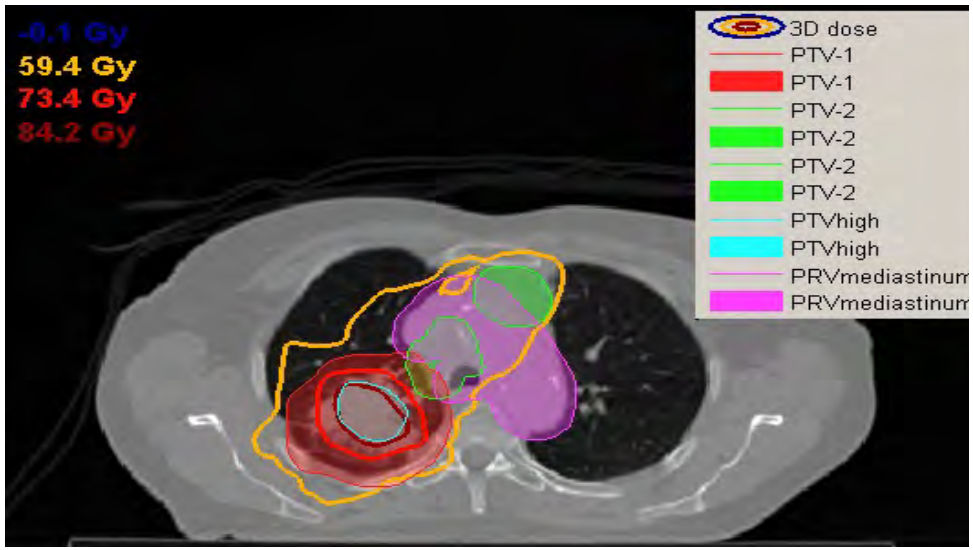


De Ruysscher D, Belderbos J et al 2010

MAASTRO/NKI Phase IIr Trial



66 Gy given in 24 fractions of 2.75 Gy with an integrated boost to the primary tumor as a whole to 81.6 Gy.
MLD 19 Gy

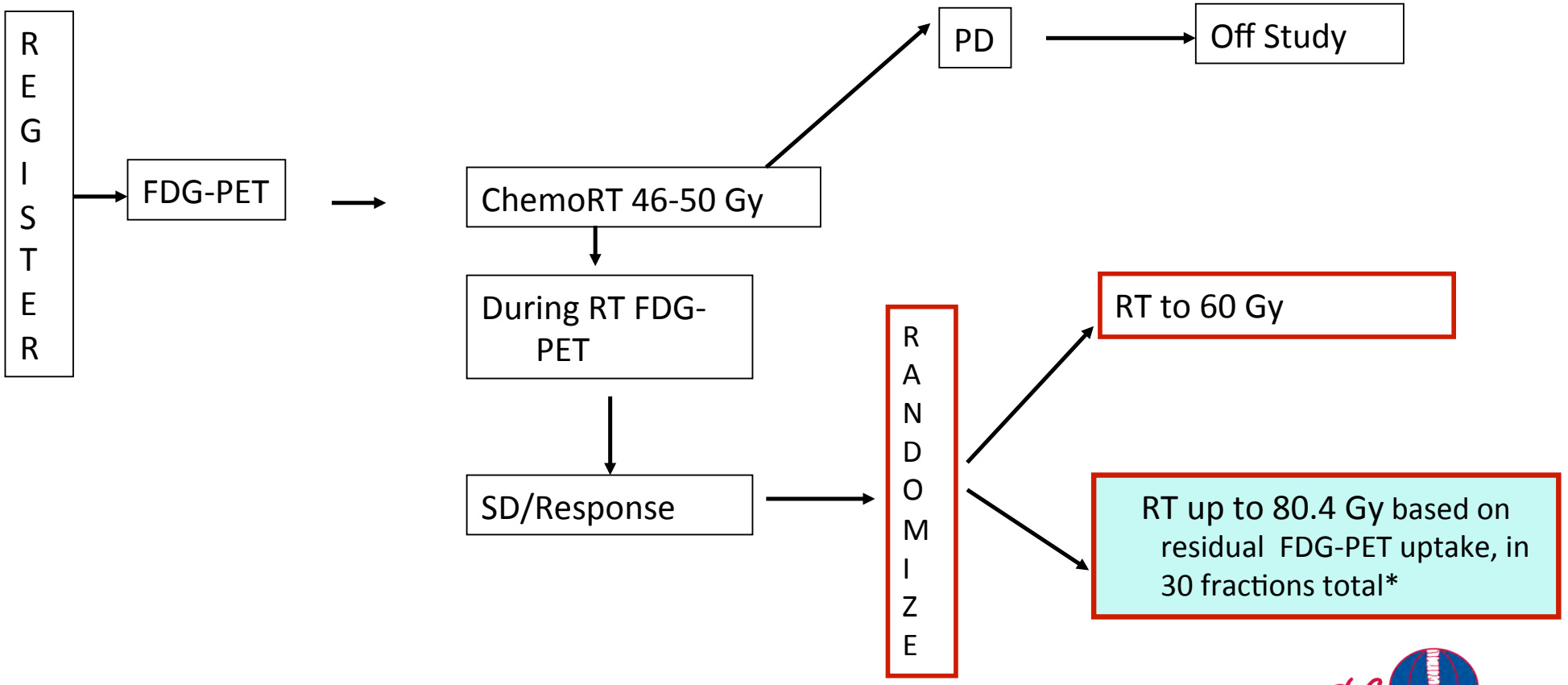


66 Gy given in 24 fractions of 2.75 Gy with with an integrated boost to the 50% SUVmax area to 93.6 Gy.
MLD 19.9 Gy

Primary endpoint:
local progression-free survival at 1 yr

Courtesy A VanBaardwijk 2010

RTOG 1106: PET-based Adaptive RT for Stage III NSCLC: Phase II Randomized Trial



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RTEP7
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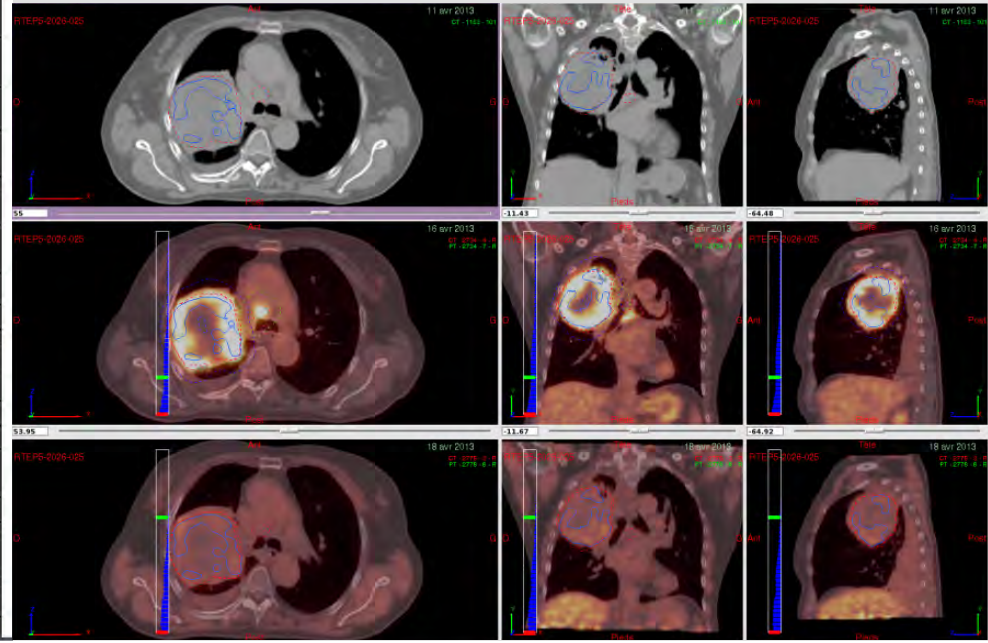
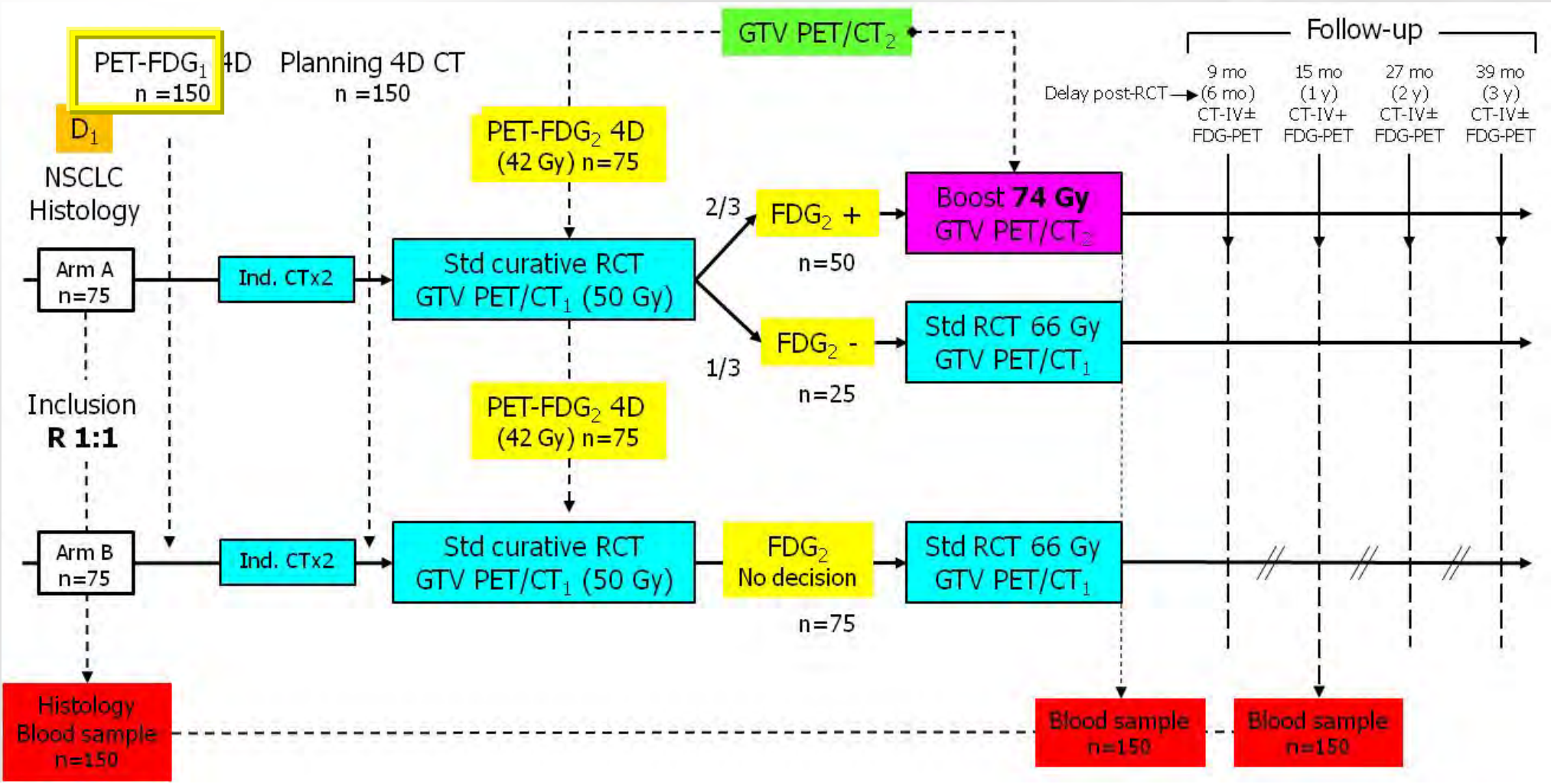
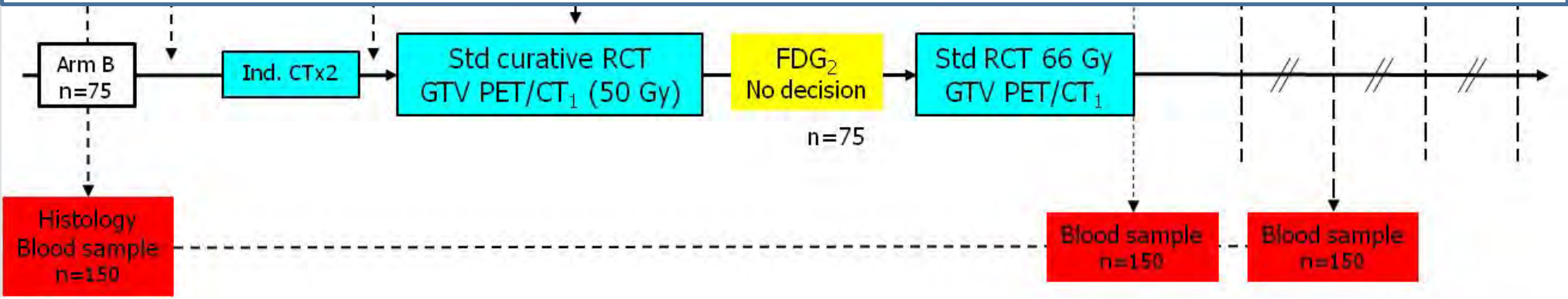
PHRC 2014 : 917 763 €



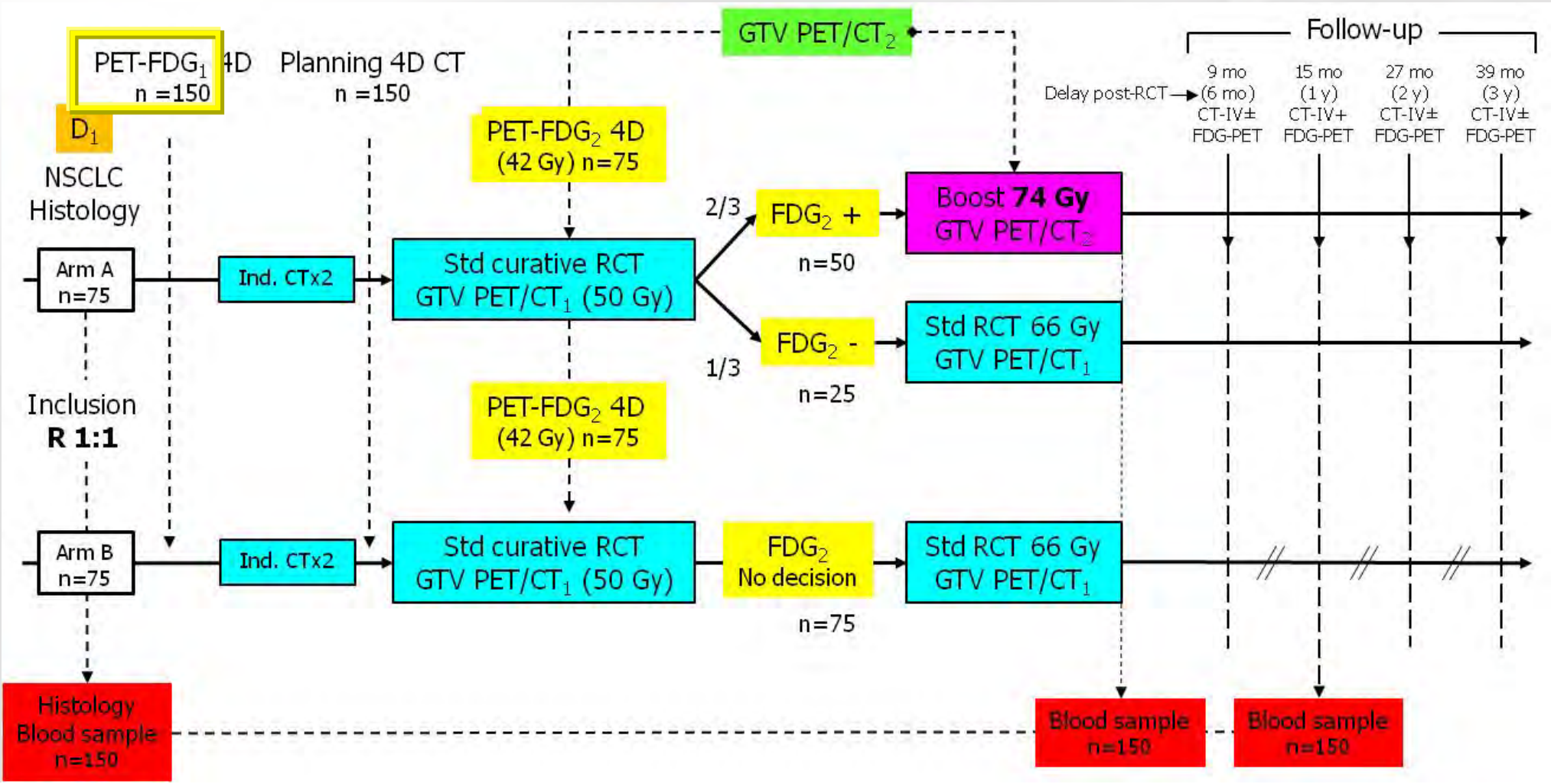
RTEP7 / IFCT 1401



RTEP7 / IFCT 1401



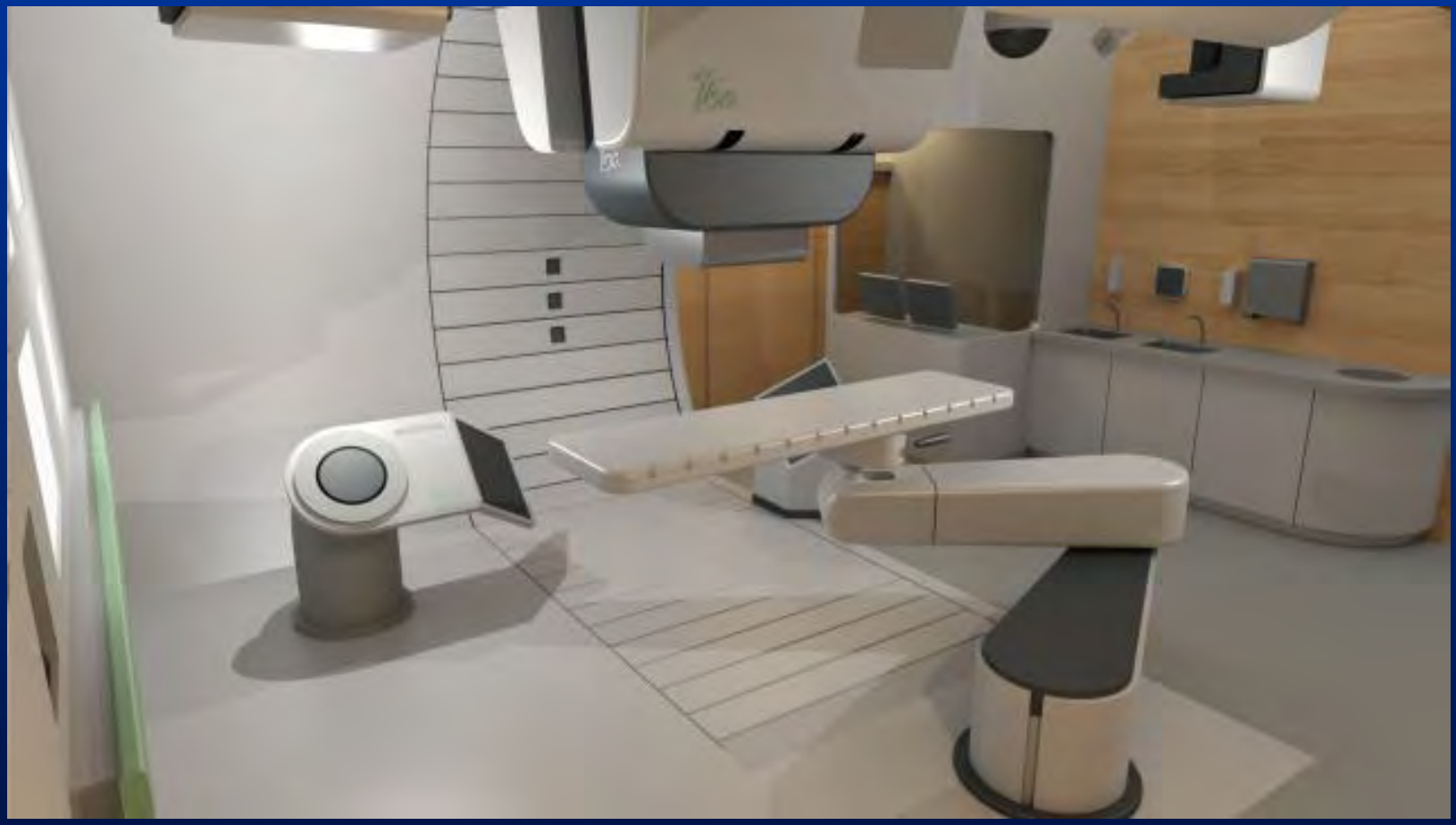
RTEP7 / IFCT 1401



Rôle potentiel des protons dans le traitement du cancer bronchique

Will Protons Provide Improvement?

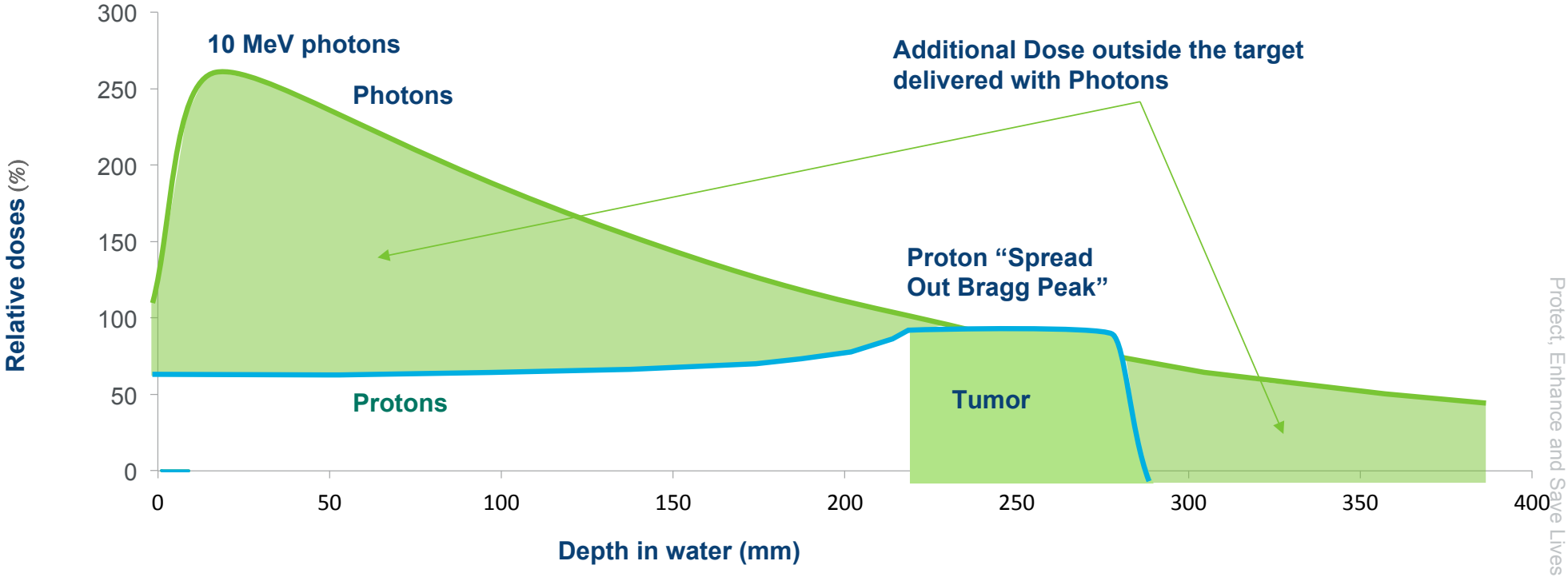
Salle de traitement



The physics of Protons

Le pic de Bragg!!

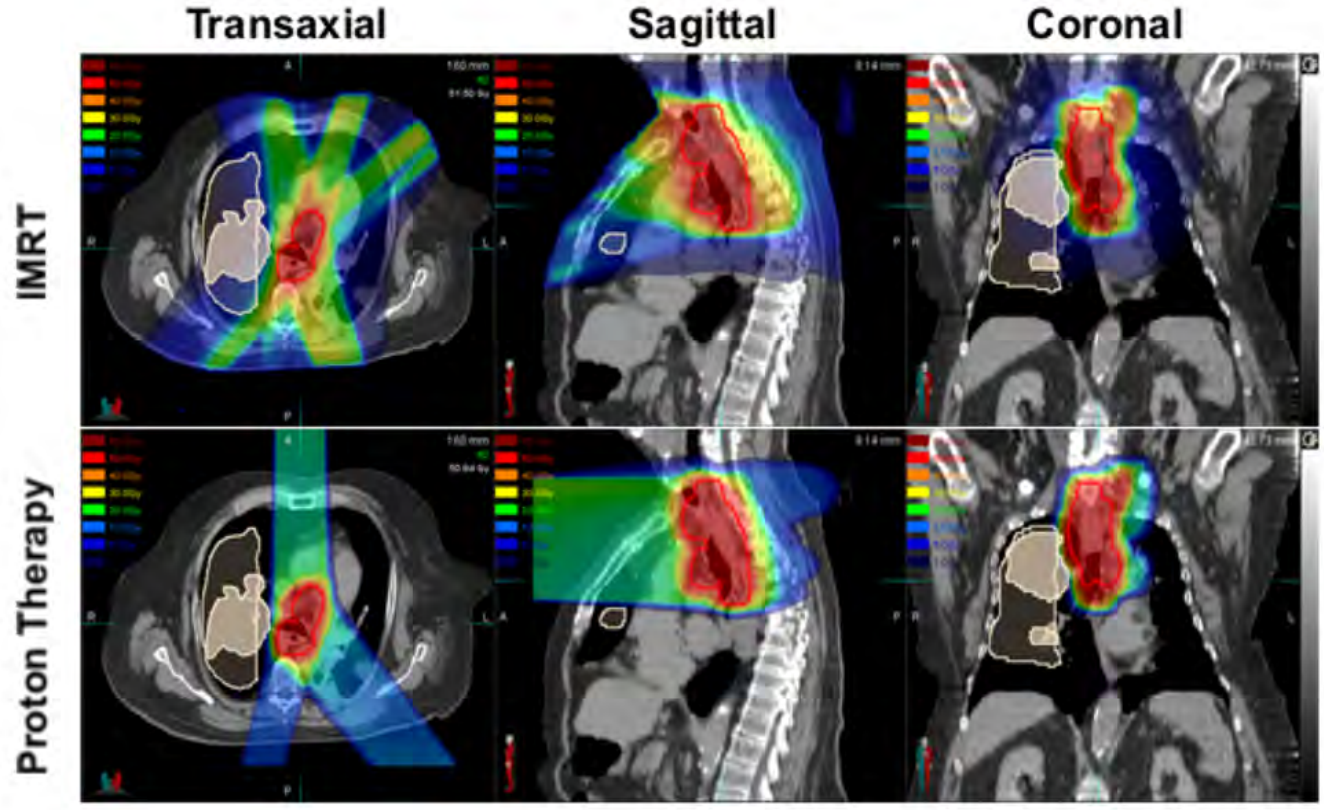
Depth dose curves for protons and photons.



Thoracic Focus Group

Functional Lung Avoidance RT Planning

Avoid « high functional zones » when delivering Radiation dose

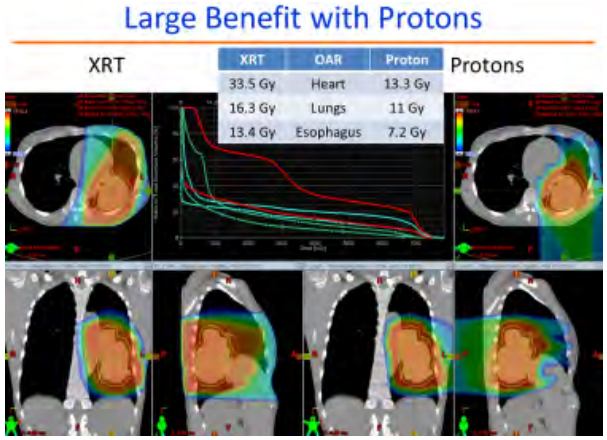


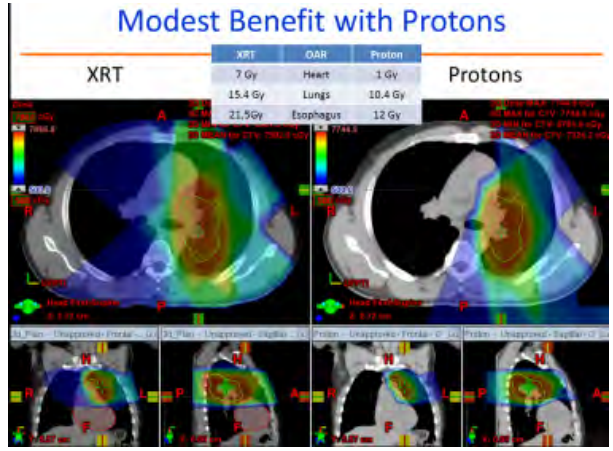
Courtesy of Stephen Bowen, PhD

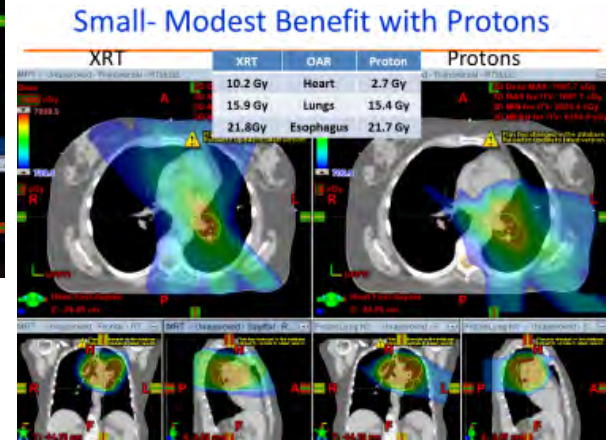
NCT01982123, PI Zeng

DEBATE ON ROLE OF PROTONS IN LA-NSCLC

- **Do all stage III NSCLC patients will benefit from PT?**
  - Depends







Thoracic Focus Group

A Bayesian Phase II Randomized Trial of Image-Guided Adaptive Conformal Photon (IMRT) vs Passive Scattering Proton (PSPT) Therapy, with Concurrent Chemotherapy, for Locally Advanced NSCLC: Treatment Related Pneumonitis and Locoregional Recurrence (2008-0133)

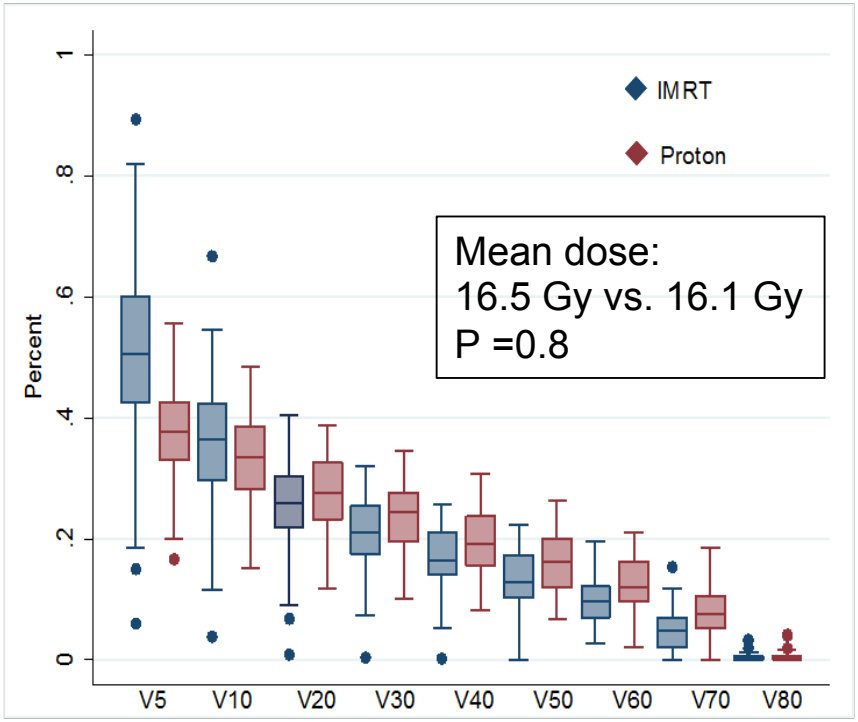
MDACC: Zhongxing Liao, M.D.

MGH: Noah Choi, M.D.

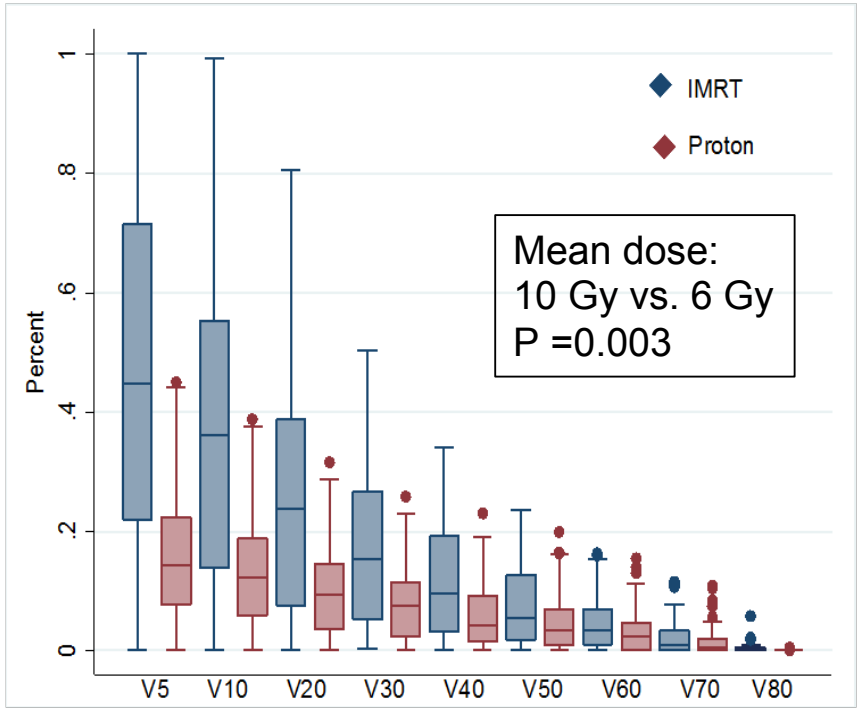
Supported by the NCI Grants

Abstract ID: 8050

Results: Mean Doses to Lung and Heart



Lung



Heart

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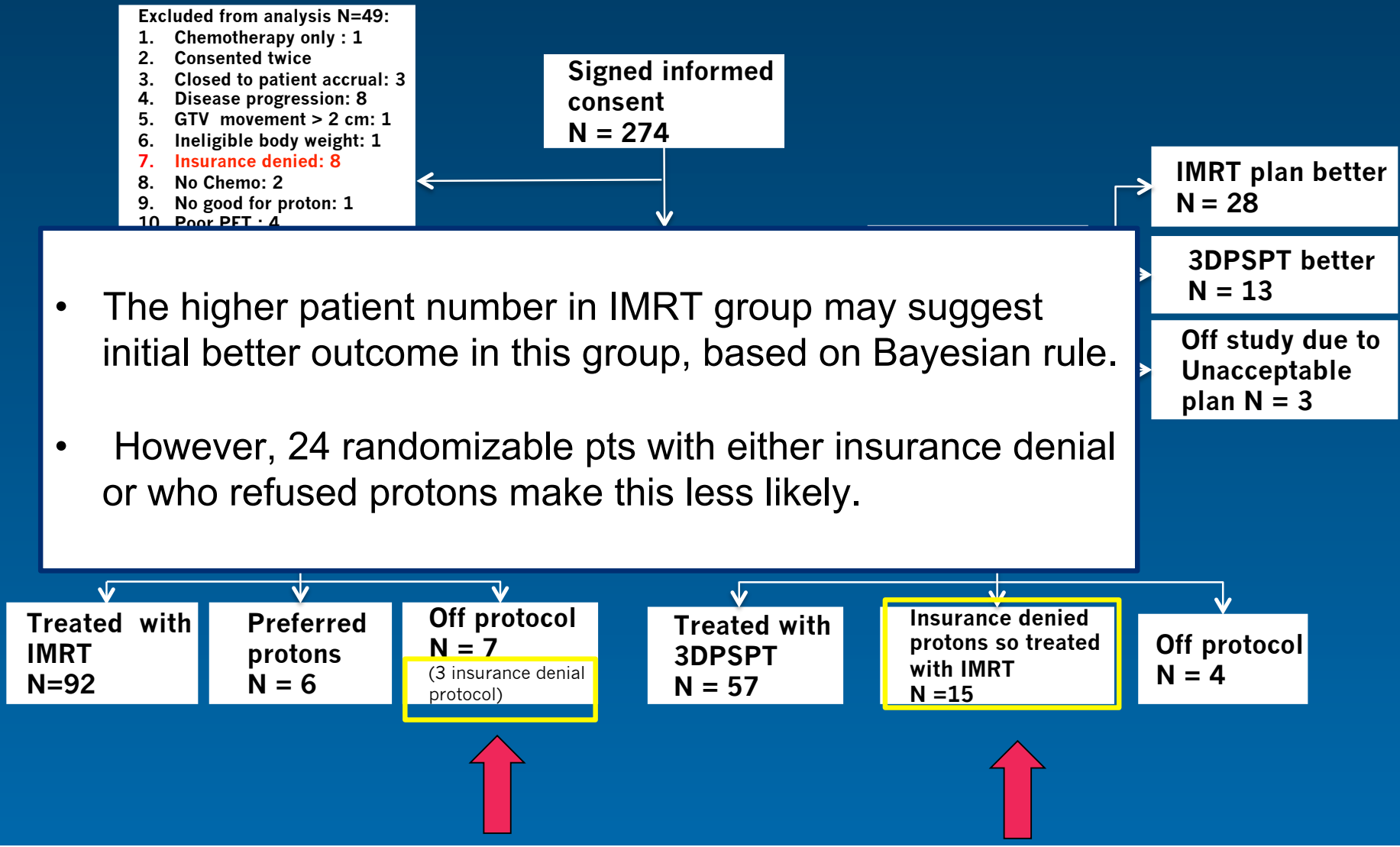
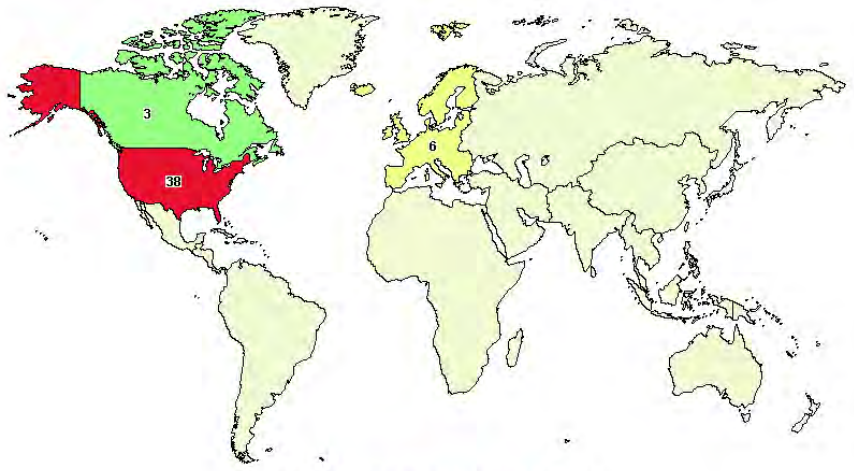
Consort Diagram



Clinical Trials in Lung Cancer and Protons



Source http://ClinicalTrials.gov

Region Name	Number of Studies	
World	47	
Europe [map]	6	
North America	39	
Canada [map]	3	[studies]
United States [map]	38	[studies]

Hints:

Click on a [map] link to show a map of that region.

Click on a [studies] link to search within your current results for studies in that region. Use the back button to return to this list and try another region.

Studies with no locations are not included in the counts or on the map.

Studies with multiple locations are included in each region containing locations.

- Only four trials for Stage III are randomized (protons vs. photons):
  1. MDACC/MGH Bayesian
  2. RTOG 1308
  3. Dresden/Heidelberg
  4. MDACC 11-1058 (IMRT vs. IMPT)
- (worldwide, only 4% of all disease sites trials will randomize between photons vs. protons*)

Mishra M et al, 2014

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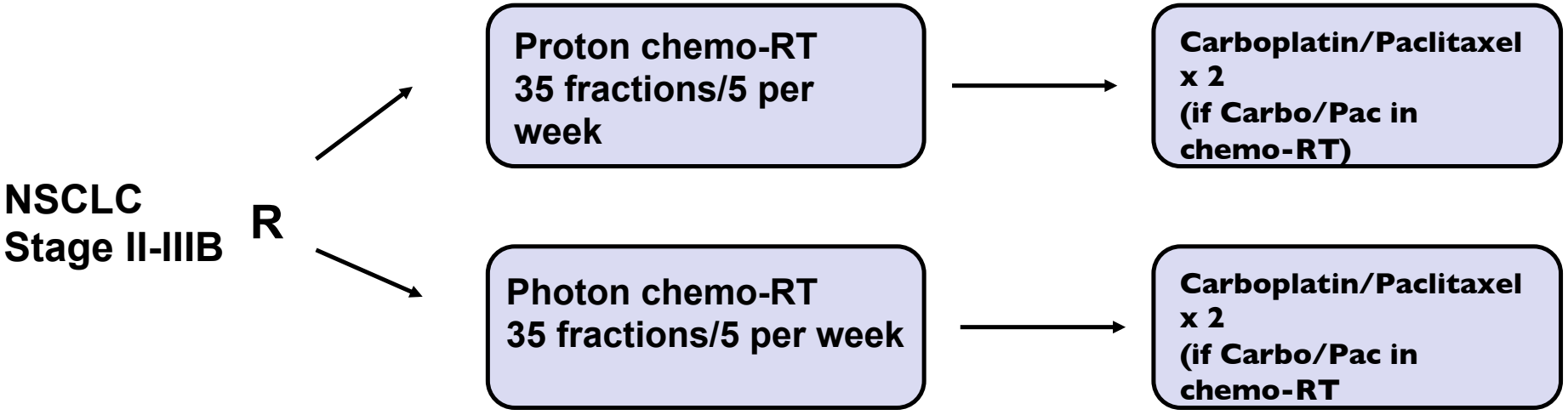
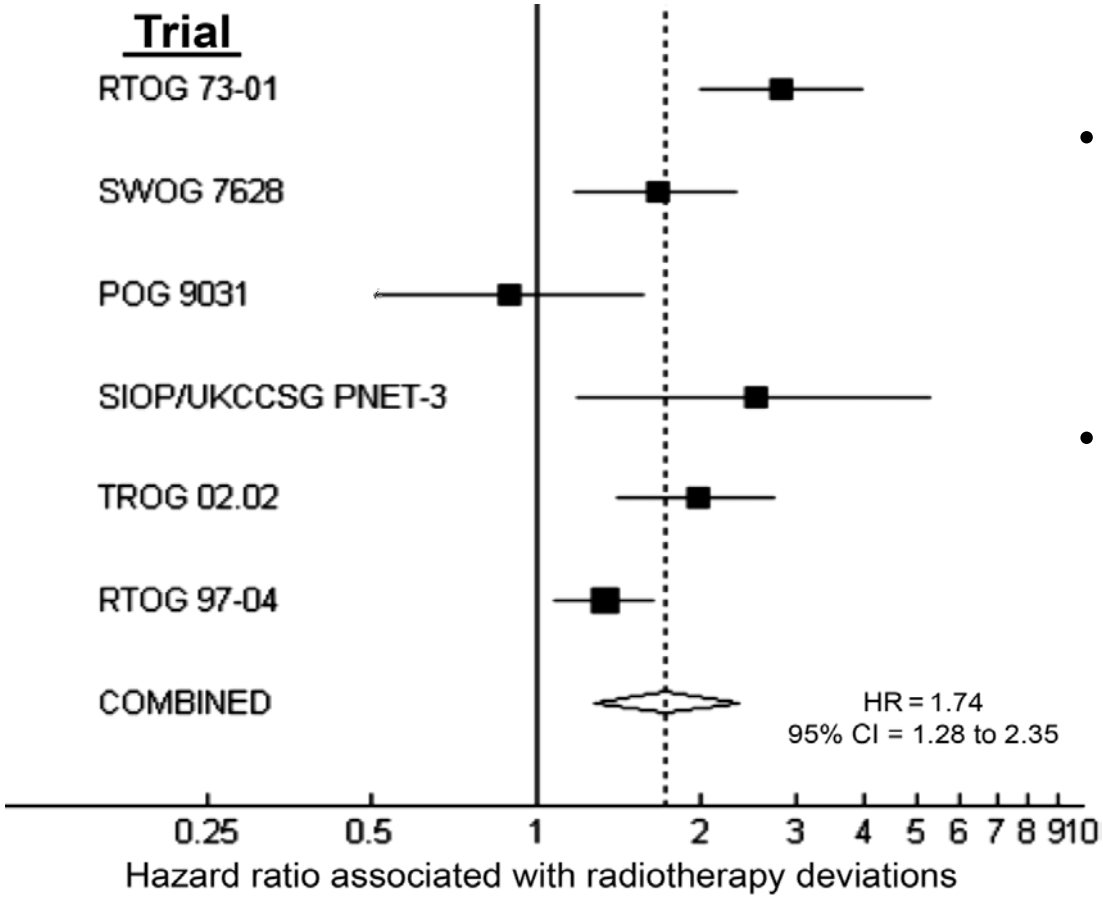
Phase III study RTOG 1308 (n=560, NCT01993810)(USA)



Primary endpoint: OS

In clinical trials, RT protocol deviations are associated with increased risks of treatment failure and overall mortality.



- Meta-analysis of cooperative group trials to examine the association between RT quality assurance deviations and OS.
- "These findings raise the possibility that strict adherence to RT planning guidelines might benefit all cancer patients treated with RT."

Ohri N et al, 2013

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Merci