Role de la Radiothérapie des Carcinomes Bronchiques à Petites Cellules

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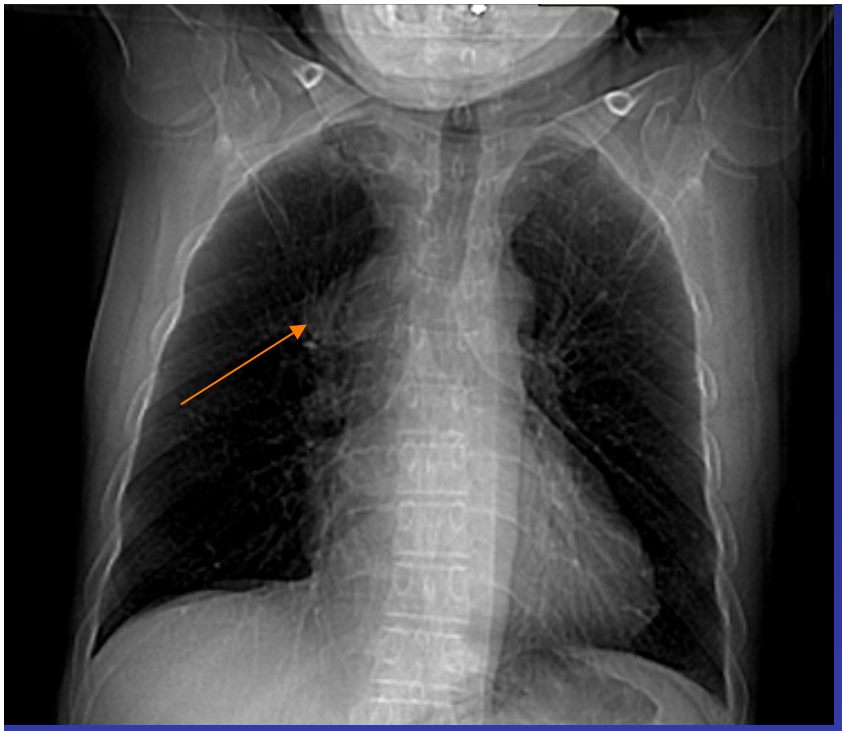
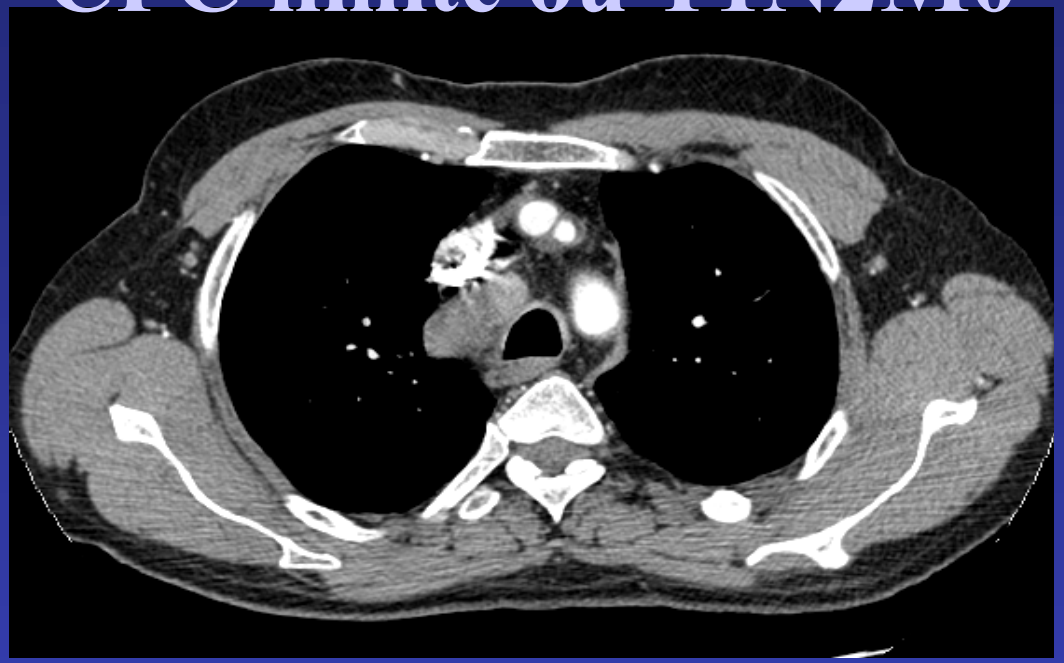
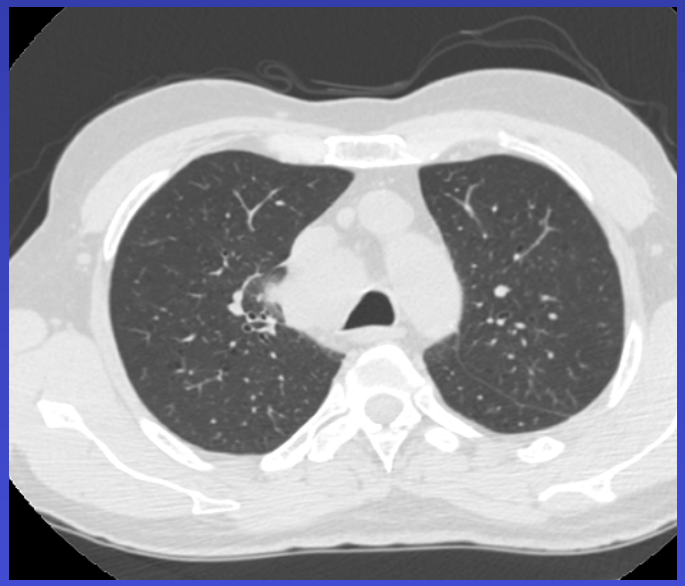
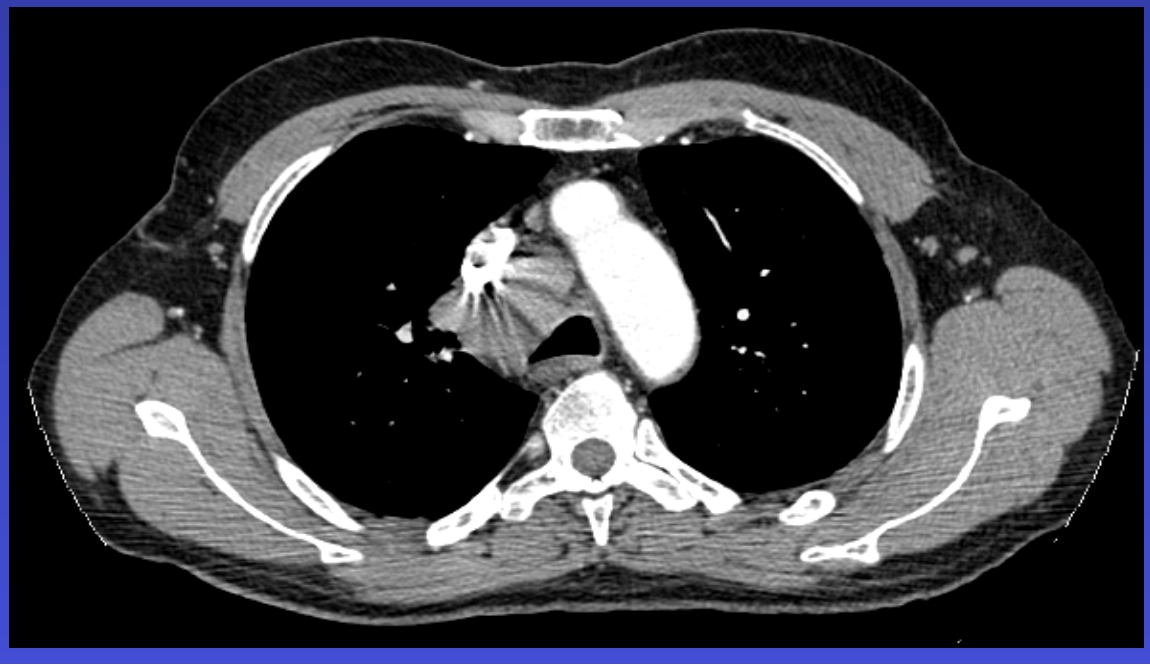
IOT
Institut d' Oncologie Thoracique

CPC limité ou T1N2M0









CPC Chimiothérapie en 1ere ligne

- Principal traitement des CPC
- Associations les plus utilisées
  - Cisplatine-Etoposide
  - Carboplatine-Etoposide
  - Cisplatine Irinotecan ou carboplatine Irinotecan (Asie)
- En concomitant à RTT
  - Cisplatine-Etoposide
  - Carboplatine-Etoposide

Role de la RT thoracique dans les CPC limités

Méta-analyse: 13 essais (2 140 pts) comparant CT-RT à CT exclusive :

5% de la survie à 3 ans en associant la RT

(10% avec CT, 15 % avec CT-RT)

Pas de différence entre

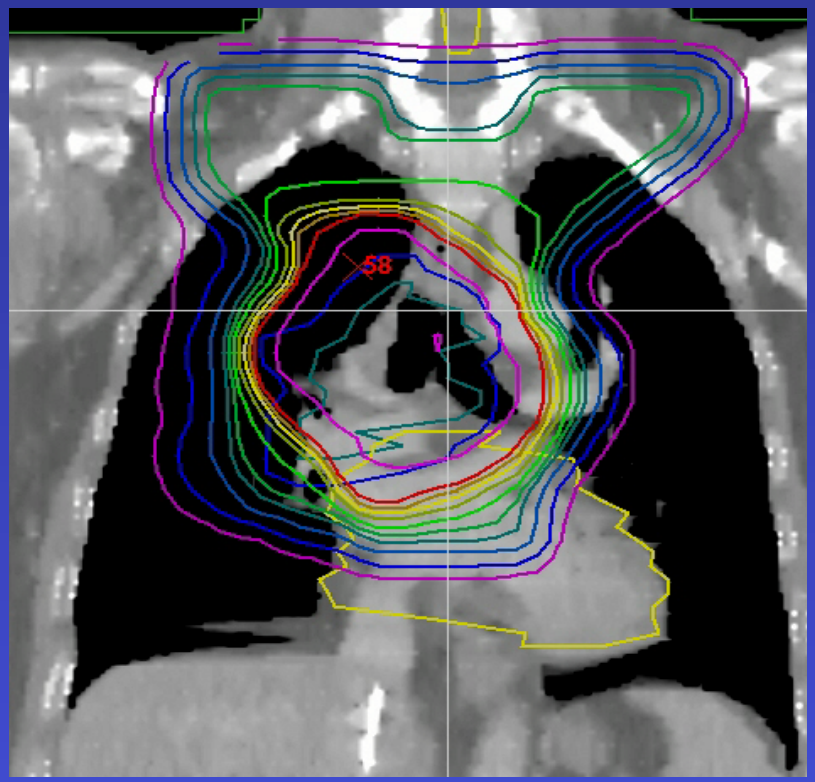
- RT précoce et tardive
- Schémas Séquentiels, concomitants ou alternés

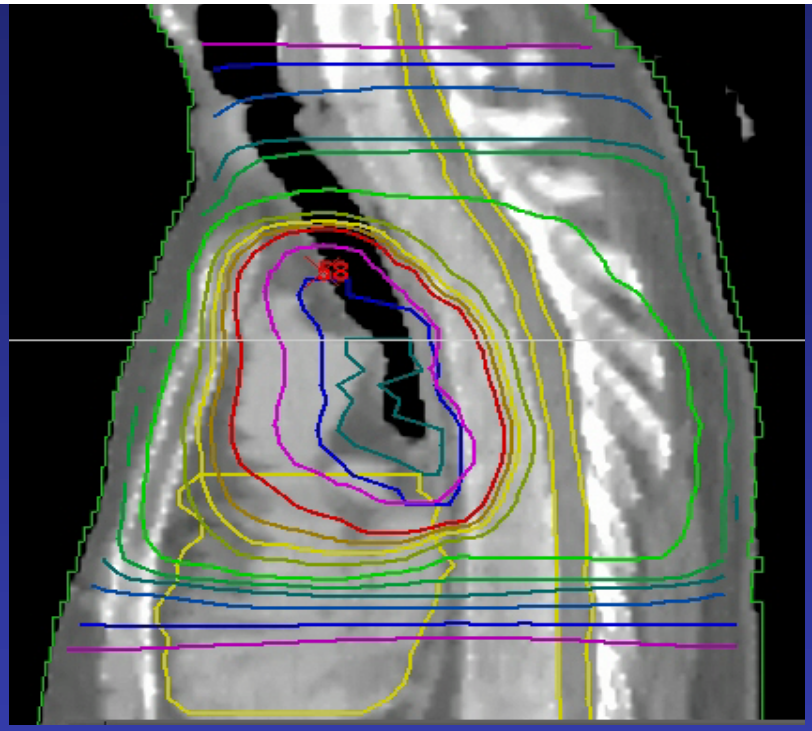
Bénéfice de CT-RT, surtout chez les pts jeunes < 55 ans

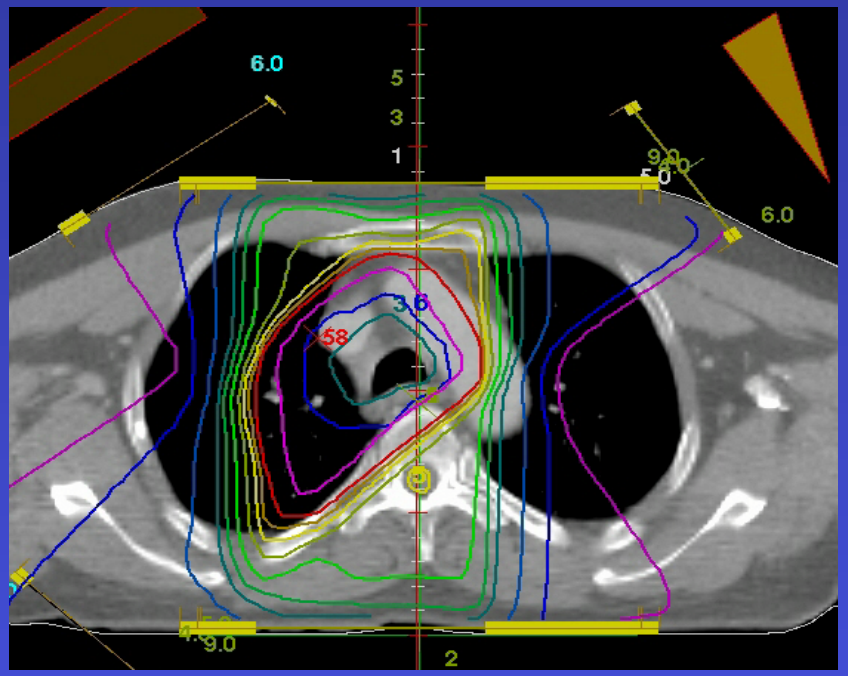
Survie à 3 ans : 9% (CT) et 17 % (CT-RT)

Pignon et al, NEJM 1992, 327

Exemple de traitement par radiothérapie thoracique classique d'un CPC limité







CPC limité : y-a-t-il eu des avancées dans la prise en charge ?

- Association CT-RT est le traitement standard
- Taux de réponse bons
  - Taux de réponses objectives 64-95%
  - Taux de réponses complètes 45-75%
- IPC en cas de RC

- Mais risque de rechute précoce élevé
  - Survie médiane 14-23 mois
  - Survie à 2 ans 25 to 47%
  - Survie à 5 ans 10 to 25%

25-30 mois

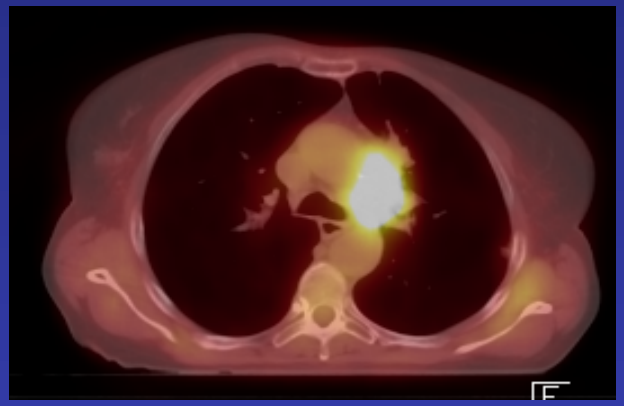
51-56%

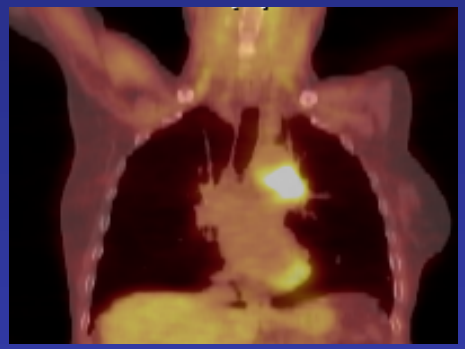
31-36%

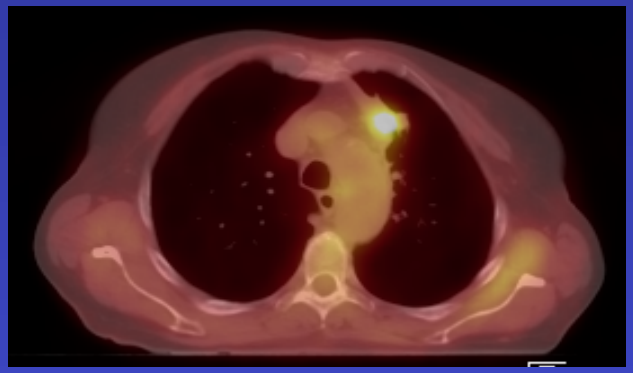
Kubota, Faivre-Finn

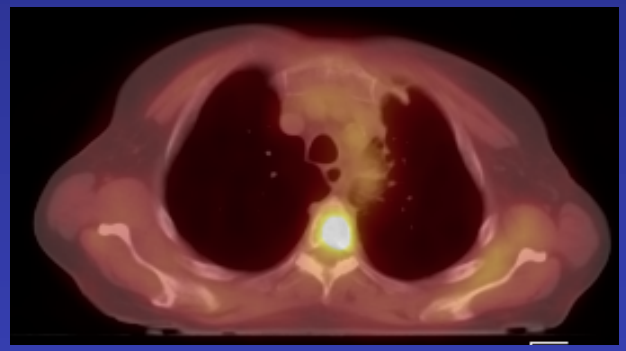
Progrès prise en charge CPC liés surtout à l'intégration de la RTT, IPC (Murray et al, 2003) mais aussi selection patients (PET Scan, IRM)

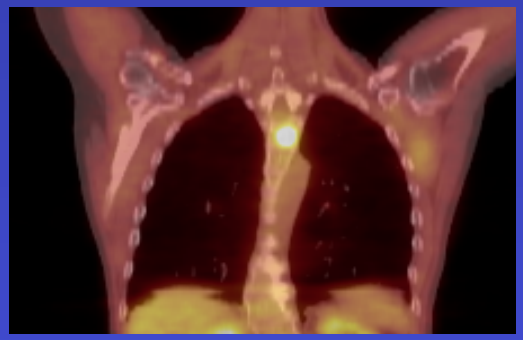
Surprise du TEP-scan: lesion en D4











Importance croissante TEP et toujours l'imagerie cerebrale dans le bilan d'extension +++

CPC limité: Comment améliorer les traitements combinés

- Meilleure modalité d'association CT-RT (séquentielle, alternée, concomitante) ?
- RT conformationelle sans irradiation ganglionnaire prophylactique ? IMRT ?
- Meilleur fractionnement de la RT? classique ou fractionné accéléré?
- Timing ?
- Dose optimale ?
- Nouvelles drogues associées?

RT-CT dans les CPC localisés Modalité optimale?

- Séquentiel versus concomitant (228pts)

SM	**19.5 mois**	**27.2 mois**
Survie à 3A	**21%**	**31%**
Tox oesoph >gr3	**3.5%**	**8.8%**

Takada 2002

- Alterné versus séquentiel (335 pts)

SM	**15 mois**	**15 mois**
Survie à 3A	**12%**	**15%**
Rechute locale	**60%**	**60%**
Tox oesoph >gr3	**3%**	**3%**

Gregor JCO 97

- Alterné versus concomitant (156 pts)

SM	**13.5 m**	**14 m**
Survie à 3 A	**6%**	**11%**
Fibrose pulm	**2**	**7**

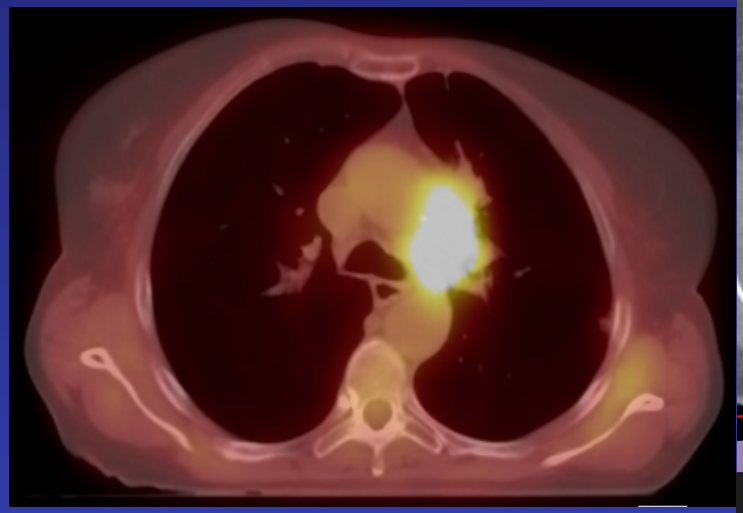
Lebeau Cancer 2000

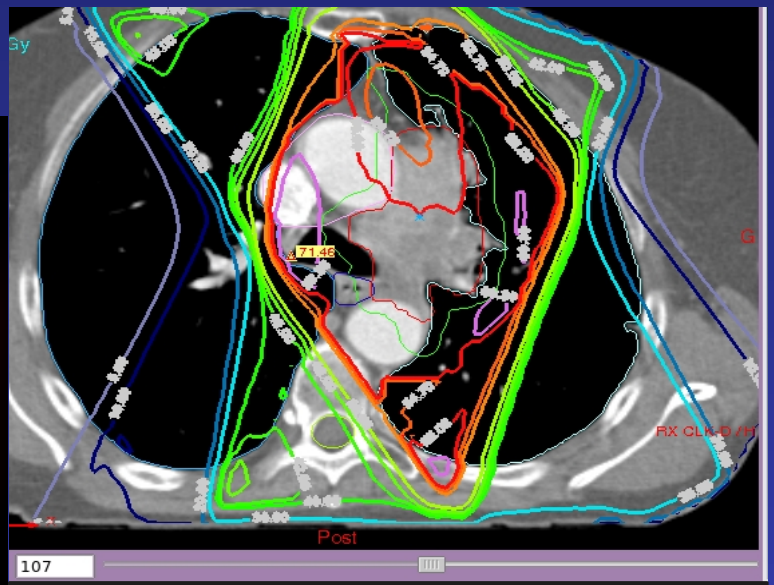
Traitement de première ligne pour les patients en bon etat general

- Patients should be considered for concomitant CTRT, taking into consideration the feasibility of radiation treatment plan and good planning target volume coverage while maintaining normal tissue dose constraints

Strength of recommendation: A
Level of evidence: II

De Ruysscher, et al. EORTC recommendations for planning and delivery of high-dose, high precision radiotherapy for lung cancer. J Clin Oncol 2010.
Baas et al. Concurrent CT (carboplatin, paclitaxel, etoposide) and involved field RT in LD SCLC: a Dutch multicenter phase II study. Br J Cancer 2006
Yuen et al. Similar outcome of elderly patients in intergroup trial 0096: EP, and TRT administered once or twice daily in LD SCLC. Cancer 2000




Gy
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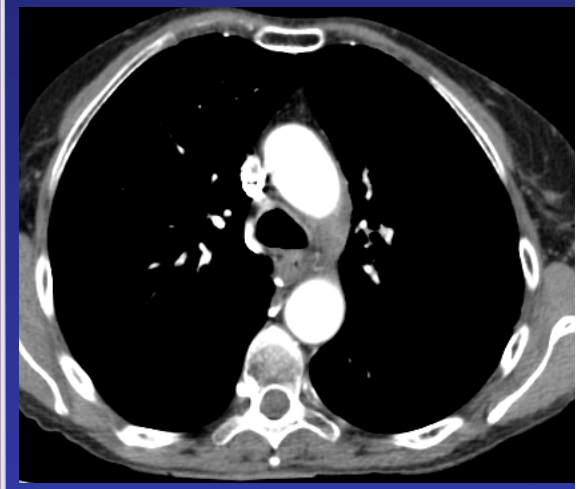
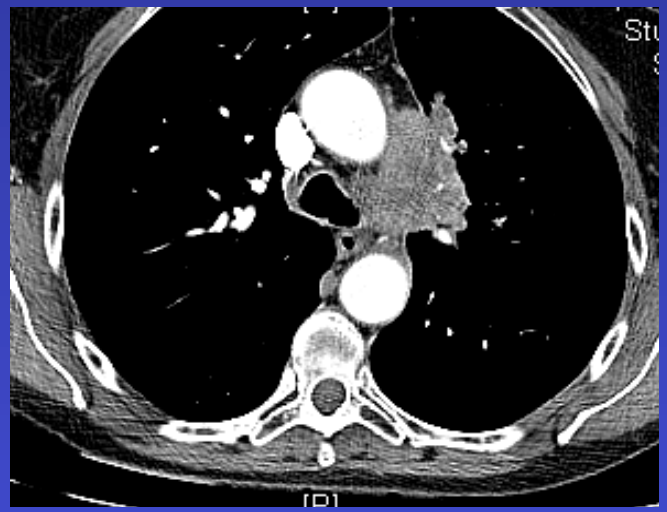
RX CLK-D /H
Post
107

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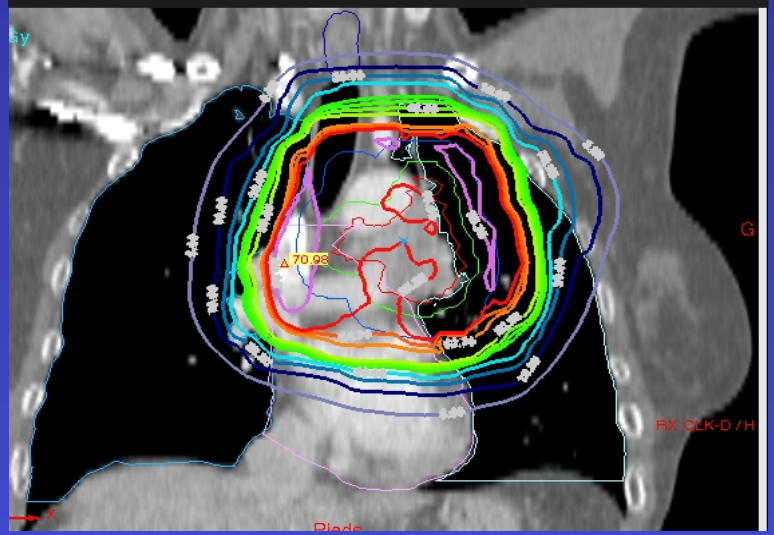
Gy
70.98
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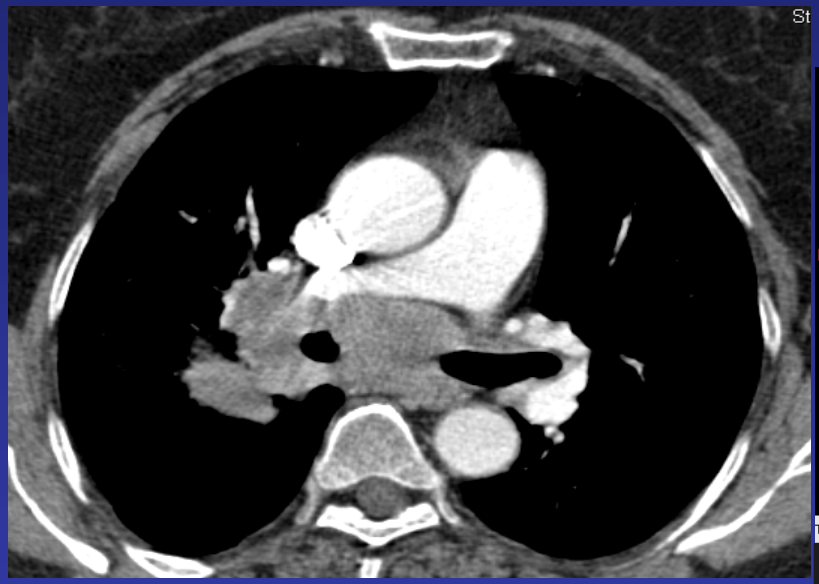
RX CLK-D /H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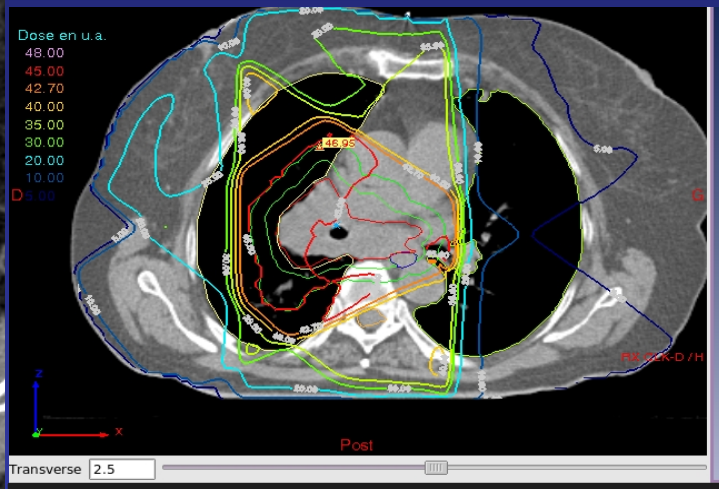
Dose en u.a.
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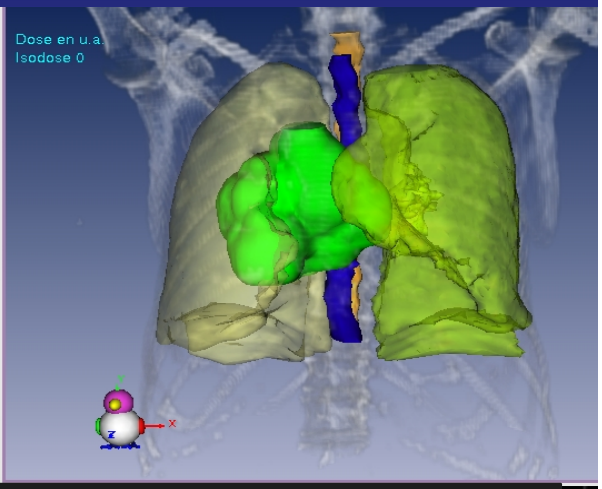
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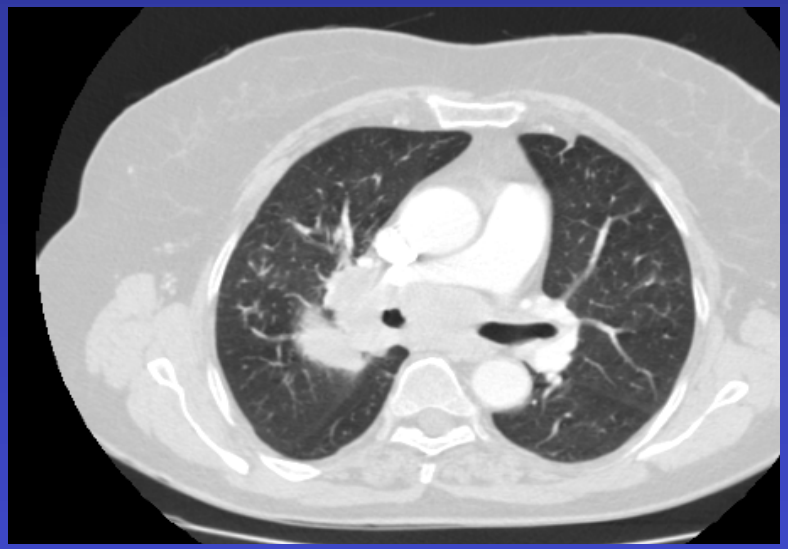

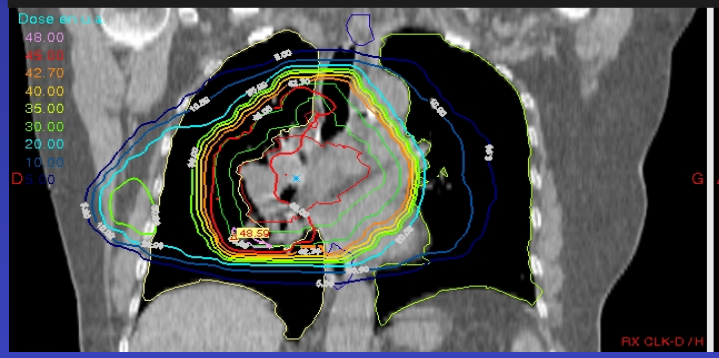
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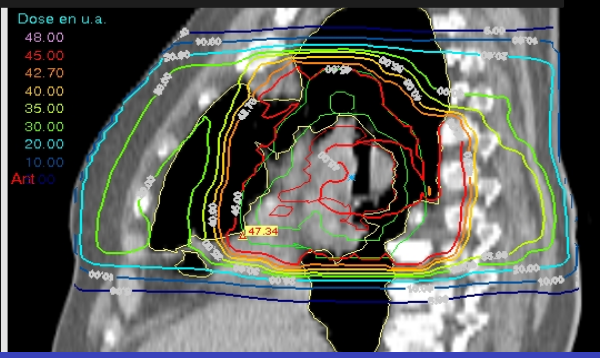
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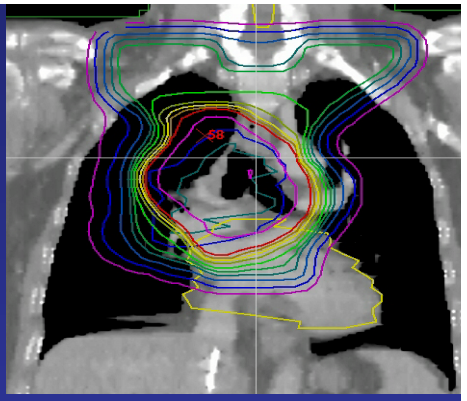
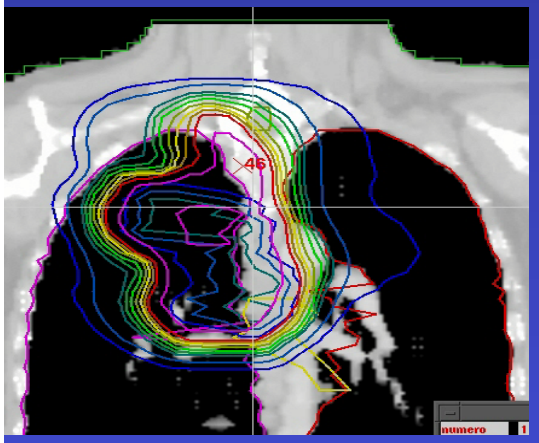
CPC limité: Comment améliorer les traitements combinés

- Meilleure modalité d'association CT-RT (séquentielle, alternée, concomitante) ?
- Volume: RT conformationelle sans RT ganglionnaire prophylactique ? pre CT ou post CT?
- Meilleur fractionnement de la RT? classique ou fractionné accéléré?
- Timing ?
- Dose optimale ?
- Nouvelles drogues associées?

Optimal volume: Elective nodal irradiation or not?

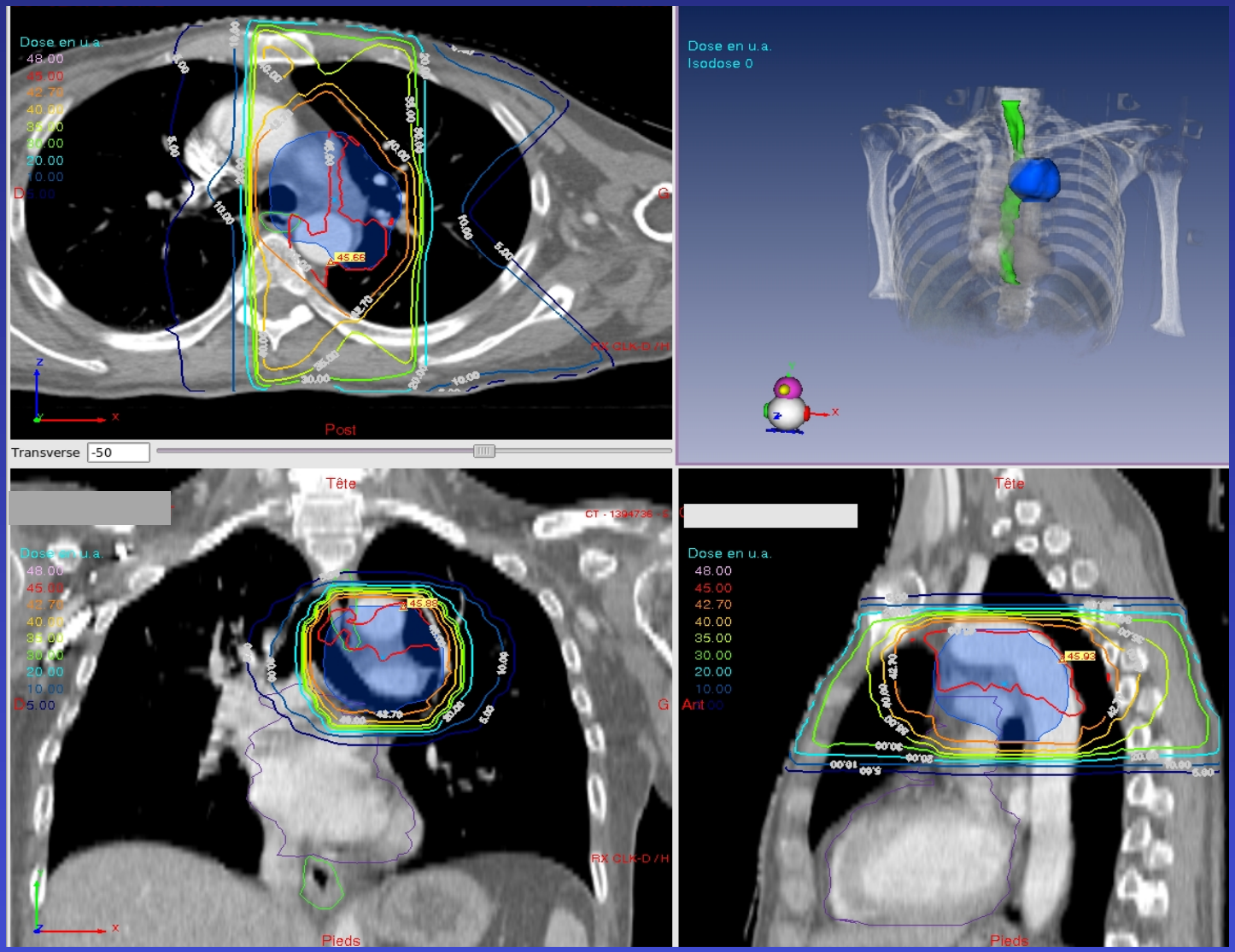


- No evidence to support ENI in NSCLC (Phase III trial Yuan 2007)
- Few studies
- On-going randomized studies with no ENI
- PET-CT can help avoid geographic misses when using an involved-field approach (3% vs 11% isolated nodal failures)
- Baas 16% nodal failures



Yuan et al, 2007; Baas et al 2006; De Ruysscher et al; 2006; Van Loon et 2010

No elective Nodal Irradiation



Site de rechute

- Rechute locale en general en plein volume de RT
- RT 3D
  - Etude randomisée de Hu(85 pts): taux de RL: 36% dans les 2 bras : volume pré-CT ou volume post 2 cycles CT
  - 2.4% des pts rechute hors champs toujours dans la region sus-claviculaire homolaterale
  - Risque de tox pulm gr 2-3: 16% vs 3% (NS)

Hu et al, Cancer 2011

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Concurrent CT-RT : Conventional versus Hyperfractionated Accelerated TRT with 4 EP

Results :	RT(45Gy/5wks)	HFRT(45Gy/3wks)	P
CRR	49 %	56 %	ns
ORR	87 %	87 %	
MST	19 m	23 m	
2-5-Year S	41%/16 %	47 %/26%	0.04
2-Year DFS	24 %	29 %	0,10
LR	52 %	36 %	0.06
LR + Dist R	23%	6%	0.01

Turrisi et al,NEJM 1999

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Timing of radiotherapy

Trials assessing timing of radiotherapy.

Author	Year	n	Dose/fr (Gy)	CT	TR timing	MS	2-(	p
Perry et al. [4]	1987	270	50/2 OD	6 cycles of CVE every 3 weeks then CAV alternating with CVE during 18 months (with limit on adriamycin dose)	conc C1 (D1)	13	24	NS
					conc C4 (D64)	14.5	31.	p= 0.144
Murray et al. [15]	1993	308	40/2.67 OD	CAV alternating with PE (3 cycles of each)	conc C2 (D22)	21.2	40	S
					conc C6 (D106)	16	33.	p= 0.008
Work et al. [17]	1997	199	40–45/2 OD	PE x 2, then CAV x 4, then PE x 1, then CAV x 2	seq C1 (D1)	10.5	20.	NS
					seq C6 (D127)	12	19	
Jeremic et al. [16]	1997	107	54/1.5 BD	CbE during RT, then 4 PE	conc C1 (D1)	34	71.	
				CbE during RT with PE before and after RT	conc C3 (D36)	26	52.	
Skarlos et al. [18]	2001	81	45/1.5 BD	CbE x 6	conc C1 (D1)	17.5	35.	NS
					conc C4 (D63)	17	28.	
Spiro et al. [19]	2006	325	40/2.67 OD	CAV alternating with PE (3 cycles of each)	conc C2 (D22)	13.7	22	p= 0.052
					conc C6 (D106)	15.1	31	

2 meta-analyses Fried JCO 2004 et De Ruysscher 2006
Plutôt en faveur RT précoce mais NS ou marginalement S

NS

NS

Paumier Lung cancer 2010

Impact of time between D1 of CT and last day of chest TRT on Survival and LC

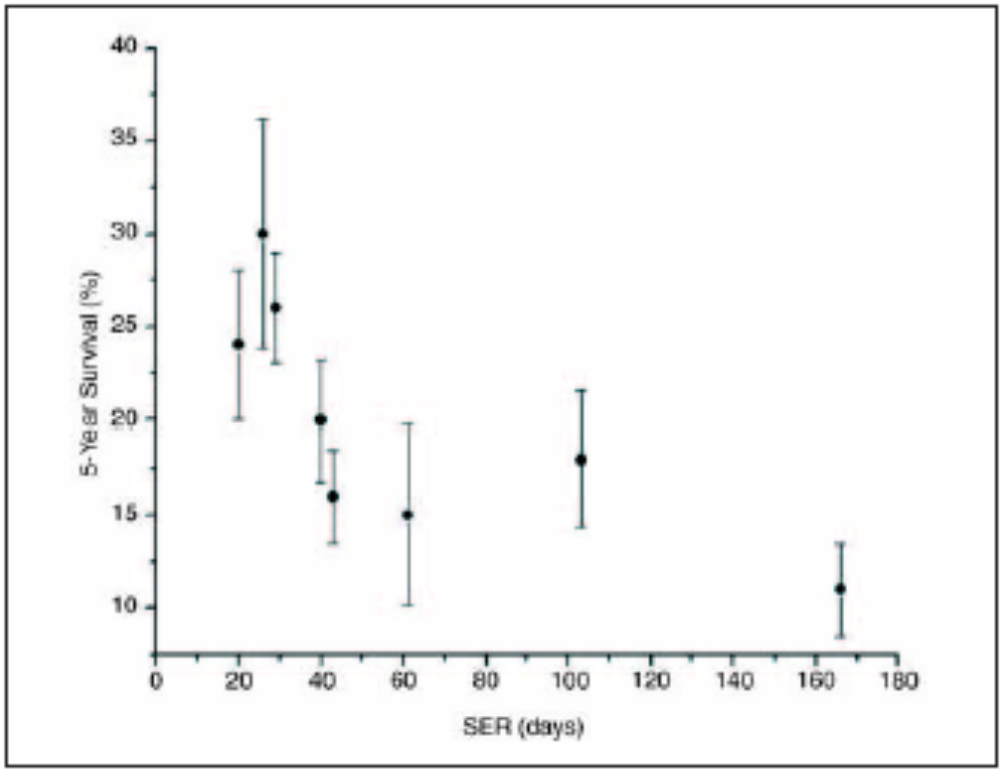


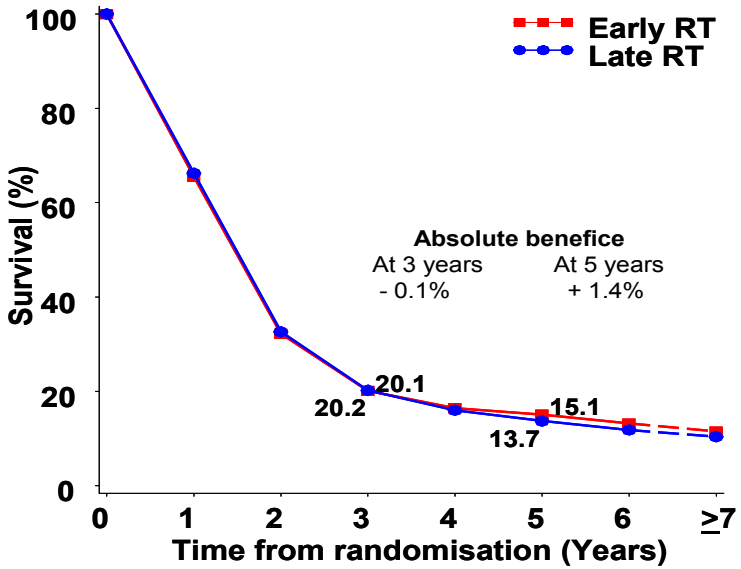
Fig 5. The survival at 5 years as a function of the time from the start of any treatment and the end of radiotherapy (SER). Each dot represents a single trial ± SE.

Overall duration of RT as well as timing to be considered

5 Year OS of 20% reached if SER<30 days

De Ruysscher et al, JCO 2006

Meta analysis based on Individual data
Overall survival



Trial	No. Deaths / No. Entered Early RT	Late RT	O-E	Variance	Hazard Ratio	HR [95% CI]
CALGB8083	127/138	146/154	12.1	66.0		1.20 [0.94;1.53]
BR.6	146/168	149/164	-20.6	72.1		0.75 [0.60;0.95]
CCCWFU62286	55/57	52/56	1.2	26.4		1.05 [0.71;1.53]
03PCL88	83/88	71/76	10.1	37.9		1.30 [0.95;1.79]
ECOG3588	190/211	194/206	-17.5	94.8		0.83 [0.68;1.02]
EORTC08877	166/175	161/174	15.3	80.3		1.21 [0.97;1.51]
JCOG9104	88/114	96/117	-11.5	45.3		0.78 [0.58;1.04]
HE1A95	37/42	35/39	-1.3	17.6		0.93 [0.58;1.48]
LLCG93	135/159	136/166	9.8	67.0		1.16 [0.91;1.47]
Total	**1027/1152**	**1040/1152**	**-2.4**	**507.4**		**1.00 [0.91;1.09]**

Test for heterogeneity: p=0.006

0.5 1.0 2.0

Early RT better | Late RT better

Early RT effect: p = 0.915

De Ruysscher et al, IASLC 2011

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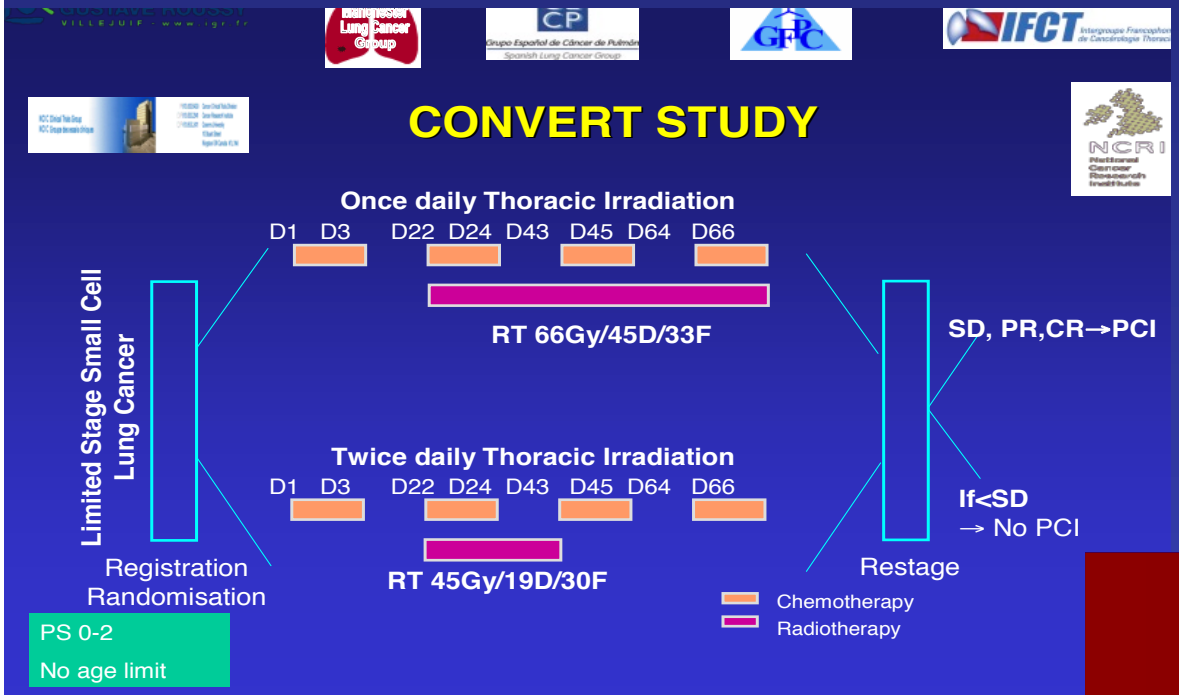
CPC localisé Radiothérapie Thoracique

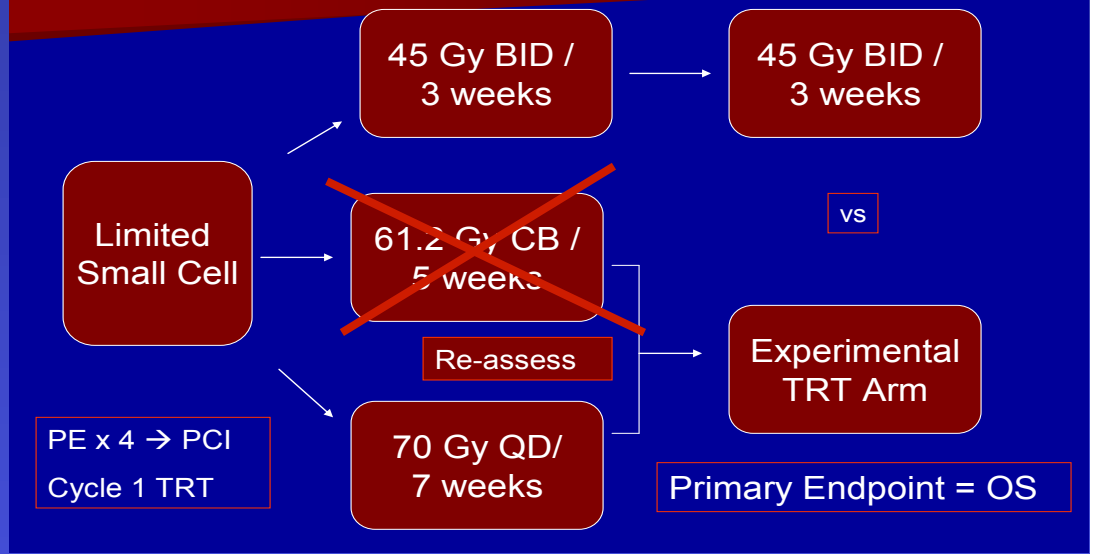
- RT conventionnelle: 50 Gy à 66 Gy en 25 à 33 séances (Dose par séance 1.8 à 2 Gy)
- RT hyperfractionnée accélérée : 45 Gy/30 seances/3 semaines avec 2 séances de 1.5 Gy par jour à 6 h d'intervalle (schema validé par etude de Turrisi et Etudes Japonaises
  - Particulièrement adaptée à la cinétique tumorale rapide
- Effet dose mal connu mais 2 essais l'ont étudié

Optimal RT dose in SCLC



- Two ongoing trials: 1 in Europe and 1 in the US

Intergroup Phase III trial CALGB 30610-RTOG 0538



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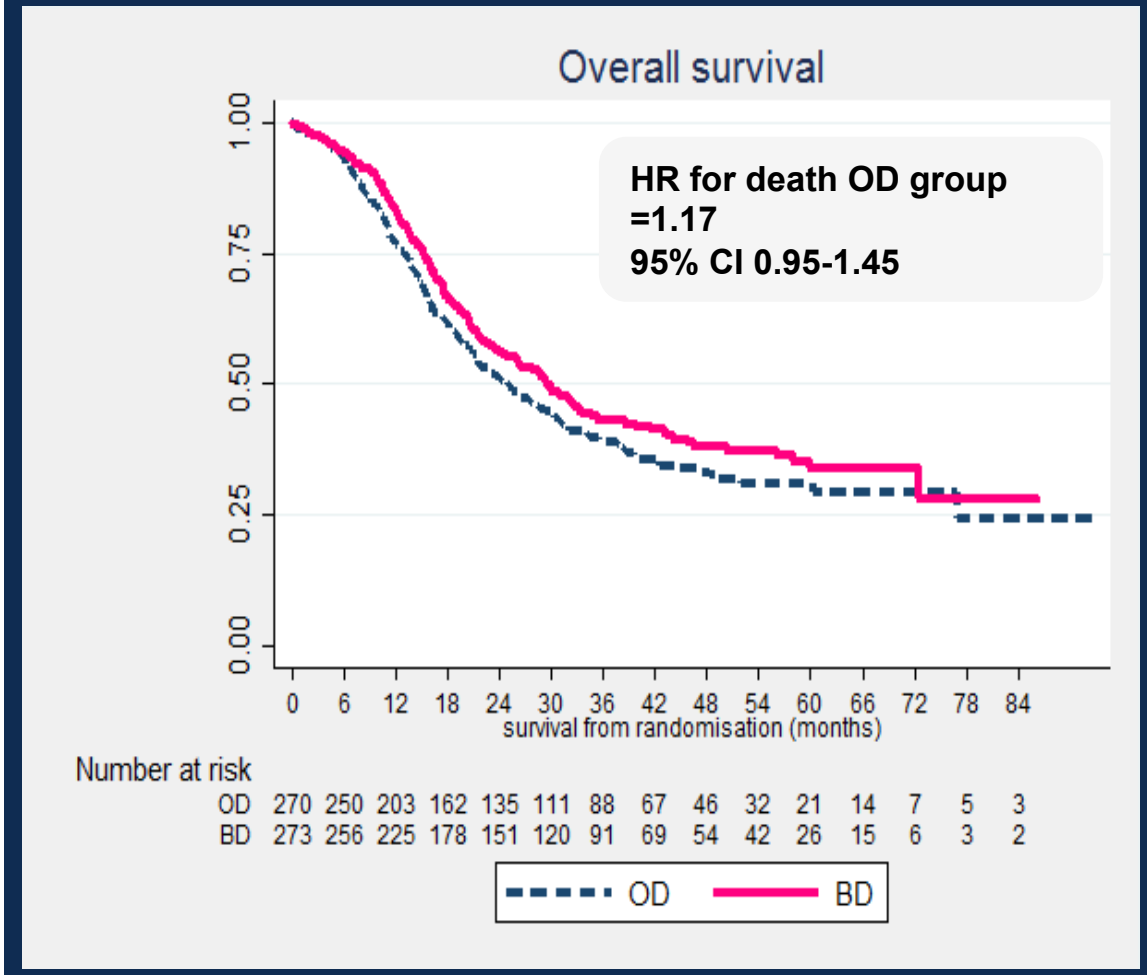


Primary objective-survival at 2 years
Trial hypothesis

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

Median follow-up: 45 months
PET/CT staging in 57% pts

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)	
5-year	34%(27–41)	31%(25–37)	

Faivre-Finn ASCO 2016; Lancet Oncol 2017

Summary

- With median FU of 45 months (for those alive), 2-year survival = 56% (95% CI 50-61) in the BD arm (n=274) vs. 51% (95% CI 45-57) in the OD arm (n=273) (HR 1.17, 95% CI 0.95-1.45; p=0.15)
- Median OS=30 months (95% CI 24-34) in the BD arm vs. 25 months (95% CI 21-31) in the OD arm
- RT treatment delivery was higher in the BD arm
- Toxicities were comparable except for significantly more grade 3/4 neutropenia in the BD arm
- There was no difference in grade 3/4 acute oesophagitis (19% BD, 19% OD), and grade 3/4 acute radiation pneumonitis was rare (2.5% BD,2.2% OD)

CPC limité: Comment améliorer les traitements combinés

- Meilleure modalité d'association CT-RT (séquentielle, alternée, concomitante) ?
- Meilleur fractionnement de la RT? classique ou fractionné accéléré?
- Timing ?
- Dose optimale ?
- Nouvelles drogues associées?
- RT conformationelle sans irradiation ganglionnaire prophylactique ?

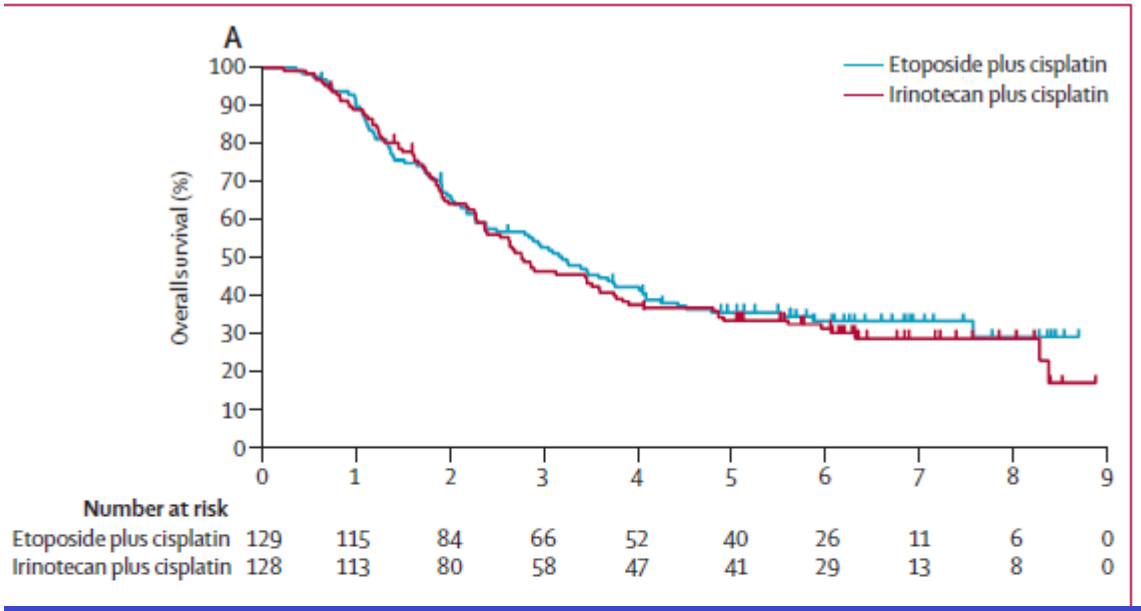
Irinotecan in Limited Small Cell Lung Cancer ?

- Japanese Phase III trials in ED (Noda et al, NEJM 2002)
  - IP vs EP: Very significant improved survival rate
  - 2-Yr Survival Rate: 19,5% vs 5,2%
- JCOG 9903 (31 pts 99-00): EP and concomittant twice-daily TRT followed by IP (Kubota et al, Clin Cancer Res 2005)
  - EP (1 cycle) and cc HFRT (D1-D21) followed by 3 monthly IP (starting on D29)
  - 2 / 3 Yr Survival:41/38%
  - Gr 3 and 4 Toxicities: Haematol (++) and diarrhea (8%), emesis
  - Only 9 pts received the planned dose of IP
  - No isolated local recurrence, 2 pts had local and distant relapse
  - On-going Phase III trial JCOG 0202 (EP vs IP as consolidation)
  - IP and HFRT vs RT as phase I study in RTOG

Etoposide and cisplatin versus irinotecan and cisplatin in patients with limited-stage small-cell lung cancer treated with etoposide and cisplatin plus concurrent accelerated hyperfractionated thoracic radiotherapy (JCOG0202): a randomised phase 3 study

Kubota et al, Lancet Oncol 2014

Kaoru Kubota, Toyoaki Hida, Satoshi Ishikura, Junki Mizusawa, Makoto Nishio, Masaaki Kawahara, Akira Yokoyama, Fumio Imamura, Koji Takeda, Shunichi Negoro, Masao Harada, Hiroaki Okamoto, Nobuyuki Yamamoto, Tetsu Shinkai, Hiroshi Sakai, Kaoru Matsui, Kazuhiko Nakagawa, Taro Shibata, Nagahiro Saijo, Tomohide Tamura, on behalf of the Japan Clinical Oncology Group



- 1cycle EP avec HFART

R

3 cycles EP	3 cycles IP
129 pts	129 pts
3yS=52,9%	3yS=46,6%
5yS=35,8%	5yS=33,7%

p=0,7

Cc CT and HFRT based on 4 cycles of EP remains standard treatment

IPC dans les CPC Introduction

- Risque de rechute cérébrale : problème majeur dans les carcinomes à petites cellules (CPC)

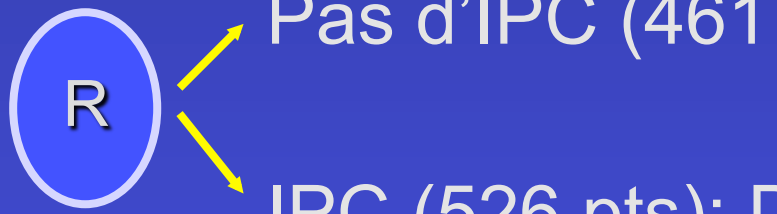
45% à 2 ans chez des pts mis en RC

- Survie médiane après découverte de métastases cérébrales (MC) malgré traitement : 4.5 mois

(Arriagada et al, JNCI 1995)

Controverse autour de l ’IPC
Survie

- Le «Prophylactic Cranial Irradiation Overview Collaborative Group» a entrepris une méta-analyse pour déterminer si l’IPC pouvait conduire à une amélioration modérée de la survie globale
- 7 essais (987 patients en RC)



PCIO Méta-analyse

Résultats **(Aupérin et al, NEJM 1999;341:476)**

- Diminution du taux cumulé de MC à 3 ans

  58.6% versus 33.3% dans le bras IPC **(p<0.001)**

- Amélioration de la survie globale à 3 ans (5.4%)

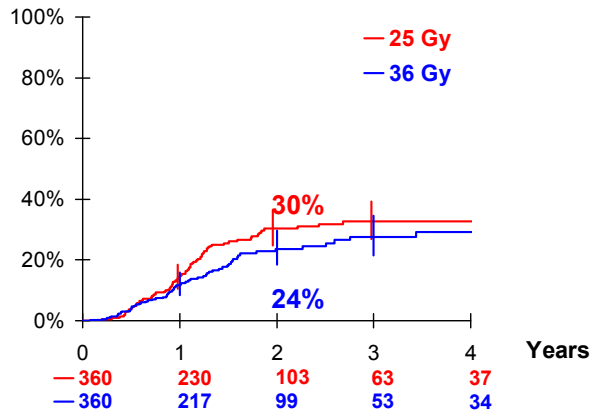
  15.3% versus 20.7% dans le bras IPC **(p=0.01)**

- Amélioration de la survie sans récidive à 3 ans

  13.5% versus 22.3% dans le bras IPC **(p<0.001)**

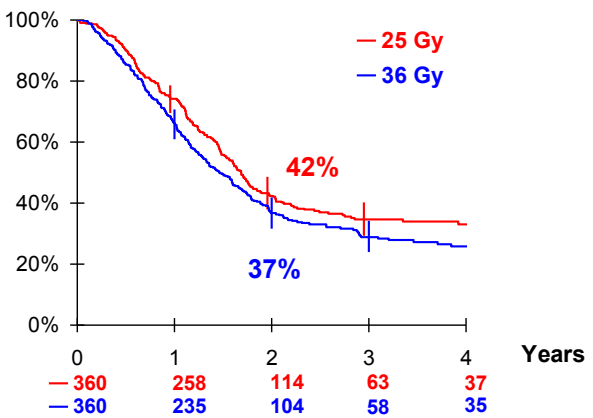
Dose optimale IPC: 25 Gy/10 fr

Brain metastasis incidence



143 brain metastases observed before March 1st 2007
HR of brain metastasis in 36 Gy versus 25 Gy: 0.77 (0.55-1.08), p=0.13

Overall survival



466 deaths observed before March, 1st 2007
HR of death in 36 Gy versus 25 Gy: 1.22 (1.02-1.47), p=0.03

PCI with a total dose of 25 Gy remains the standard of care in limited-stage SCLC.

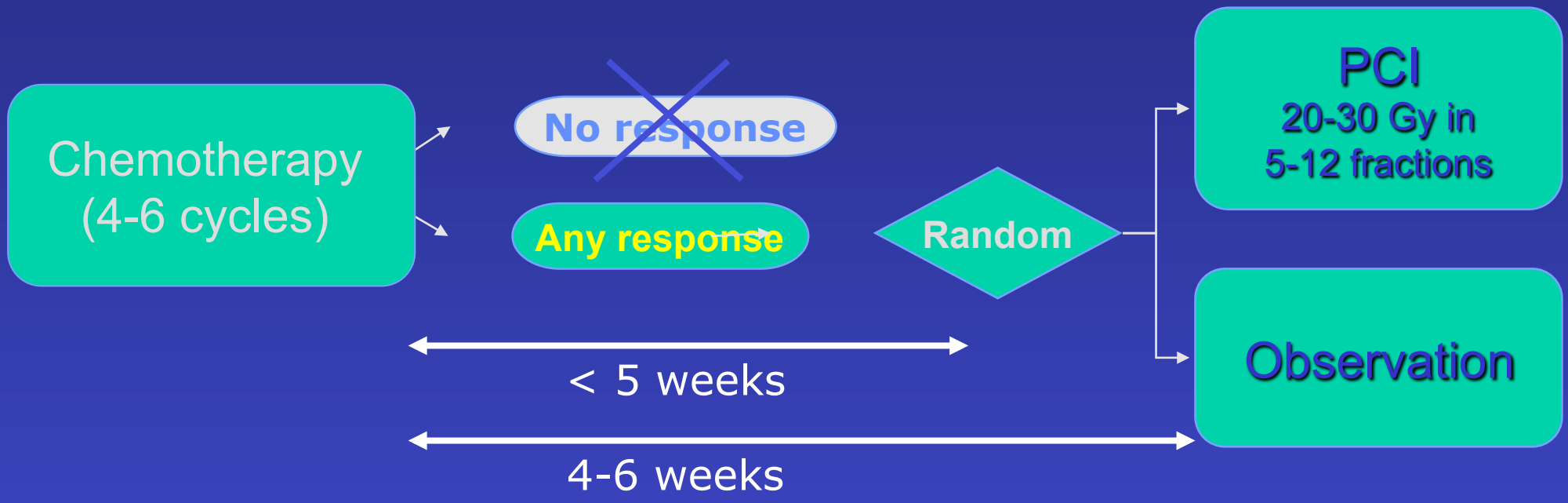
Le Pechoux et al, Lancet Oncol 2009

Role RT dans les CPC metastatiques TxNXM1

IPC?

Radiotherapie Thoracique?

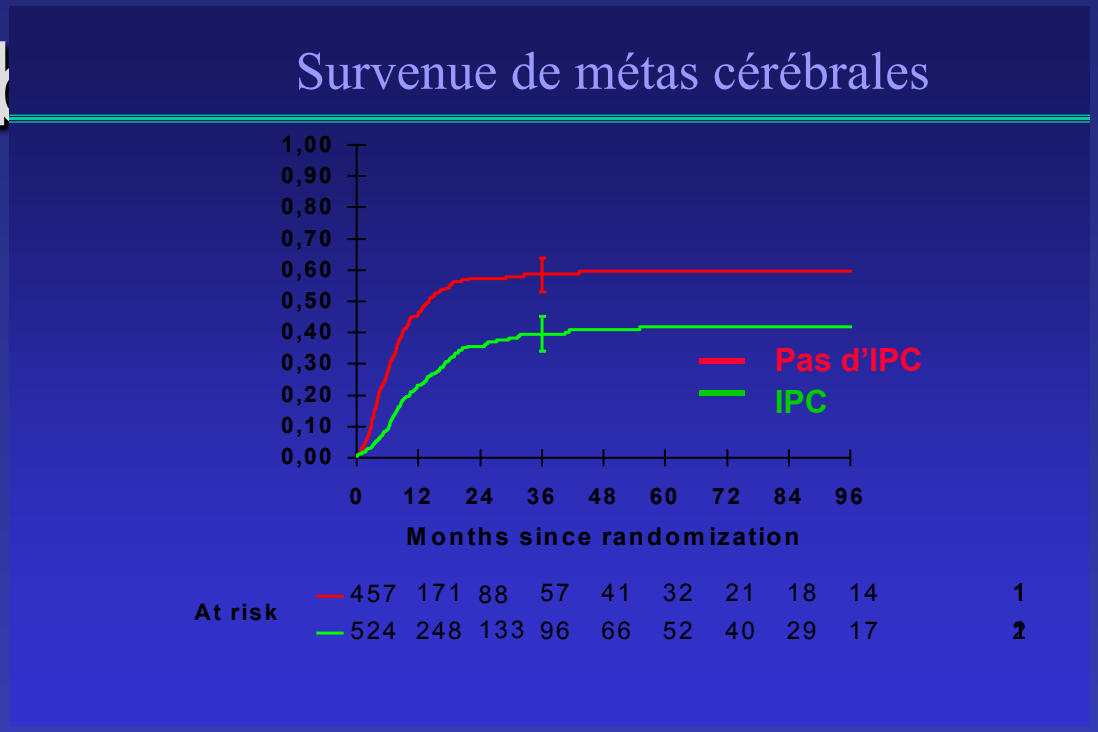
PCI in extensive disease small cell lung cancer (EORTC 08993-22993)



Stratification: WHO and Institute

Slotman et al, NEJM 2007

Symptomatic B

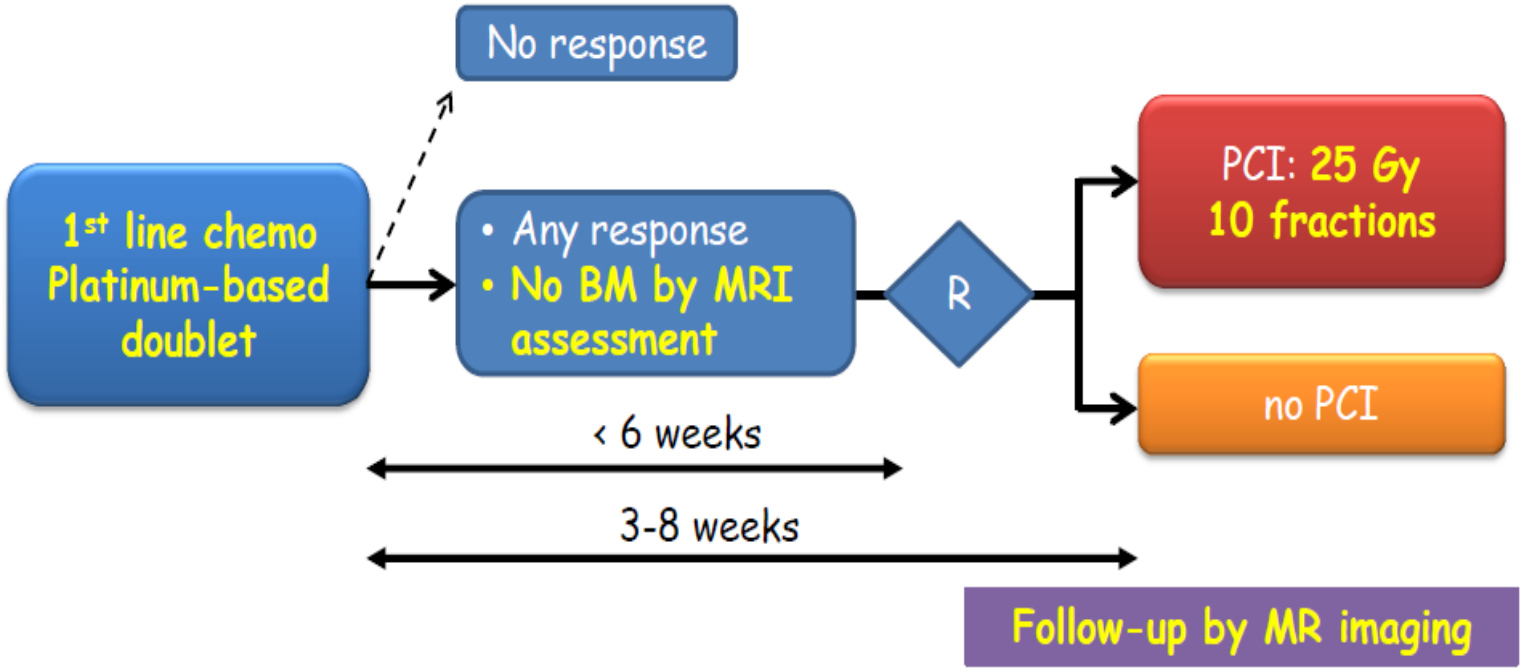


Slotman et al, PASCO 2007

Autre étude ayant évalué IPC dans CPC métatstatiques Takahashi Etude Japonaise

Resultats très differents…

Design of this study



Stratification by Age (70≦ / <70), PS (0-1 / 2), Response (CR / PR+MR), Institutions

Primary endpoint: Overall Survival

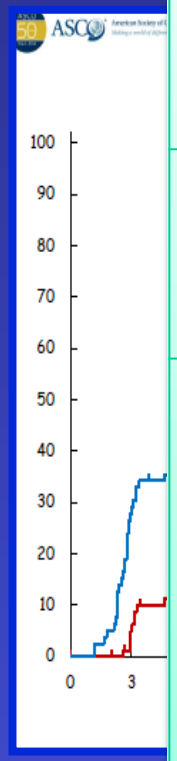
Secondary endpoints: Time to BM (evaluated every 3 months)
Progression-Free Survival (PFS)
Safety
Mini Mental State Examination (MMSE)

Seto, ASCO 2014; Takahashi 2017

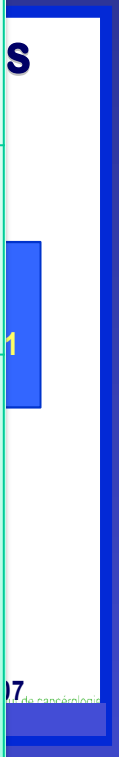
SCLC: emergence of detectable BM can be prevented and not just delayed with PCI!

Phase III SETO study
100% ED SCLC

Phase III EORTC study, Slotman et al
100% ED SCLC

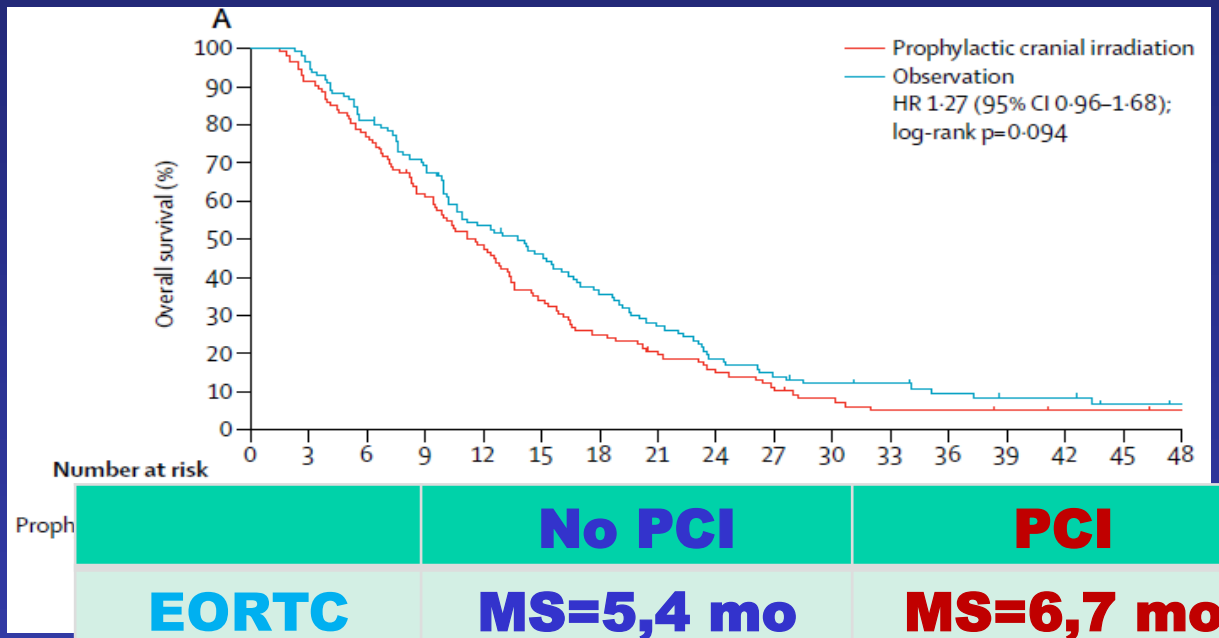


	No PCI	PCI	p
Symptomatic BM			
At 1yr (Slotman)	40,4%	14,6%	<0,0001
Detected BM on MRI			
At 6 months	46,2%	15%	
At 1 yr (Takahashi)	59%	32,9%	<0,0001
At 18 mo	63,8%	40,1%	



Slotman NEJM 2007,Seto ASCO 2014, Takahashi 2017

Overall Survival in M1 SCLC: Impact of PCI ?



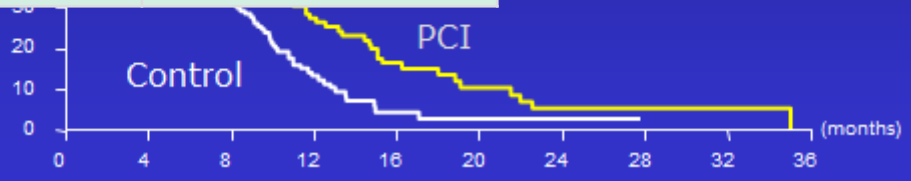
	No PCI	PCI	p
EORTC	MS=5,4 mo 1yrS=13,3%	MS=6,7 mo 1yS=27,1%	=0,003
Japan	MS=13,7 mo 1yS=53,6% 2yS=18,8%	MS=11,6 mo 1yS=48,4% 2yS=15%	=0,094

Takahashi , 2017

	PCI Arm	p
	6,7mo	<0,003

27.1% vs. 13.3%

52-0.88) p=0.003



Slotman, NEJM 2007

Place de la RT thoracique CPC M+ ??
Essai CREST

ES-SCLC, WHO 0-2

4-6 platinum-based chemotherapy

Any response

RANDOMIZE

TRT (30Gy in 10fx)

PCI

No TRT

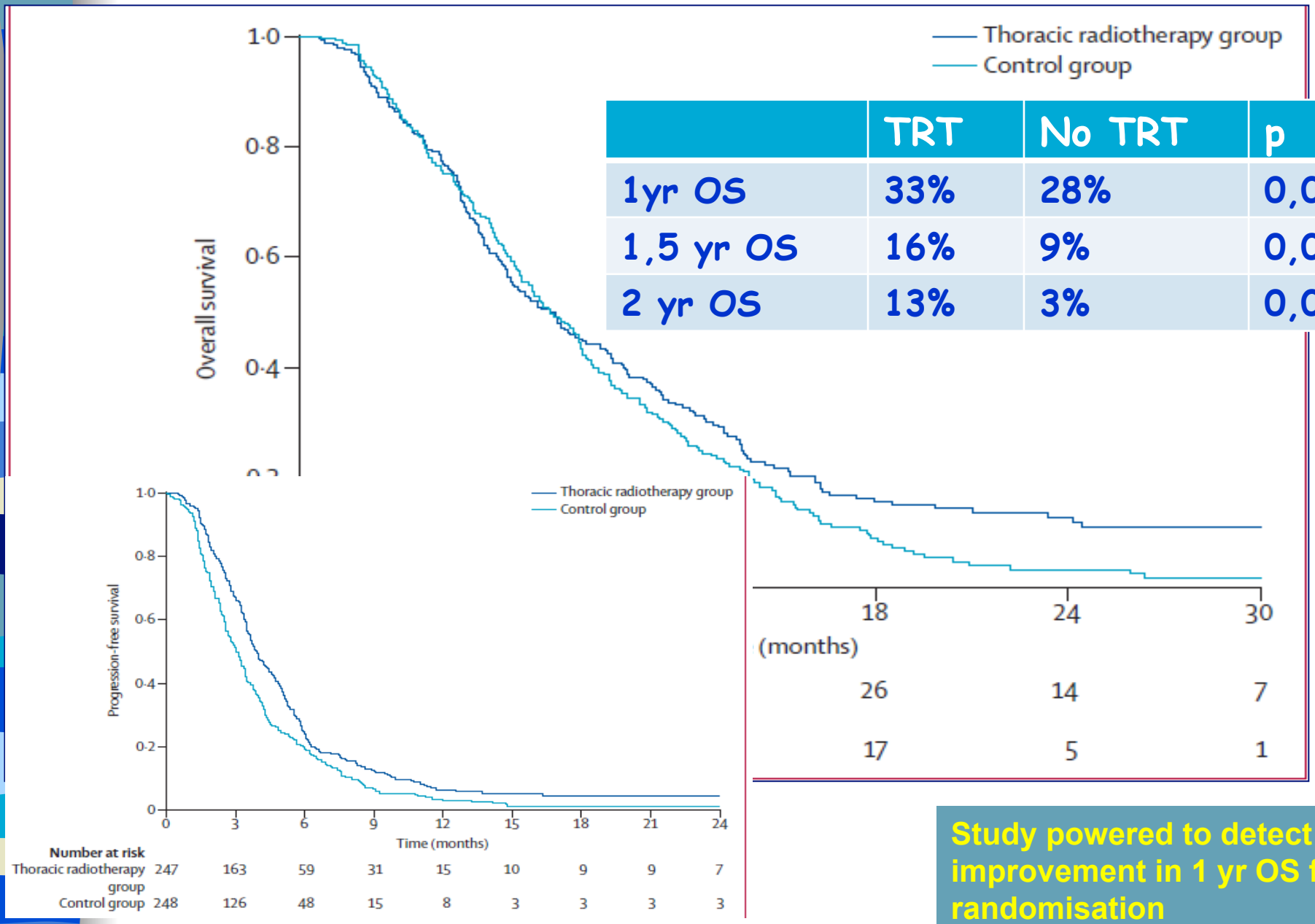
PCI

498 pts from 2009 to 2012
Study powered to detect a 10% improvement in 1 yr OS from randomisation
Control arm:27%

Stratification:

- Institute
- Presence of intrathoracic disease

Kindly provided by Ben Slotman ASCO 2014, Lancet 2014



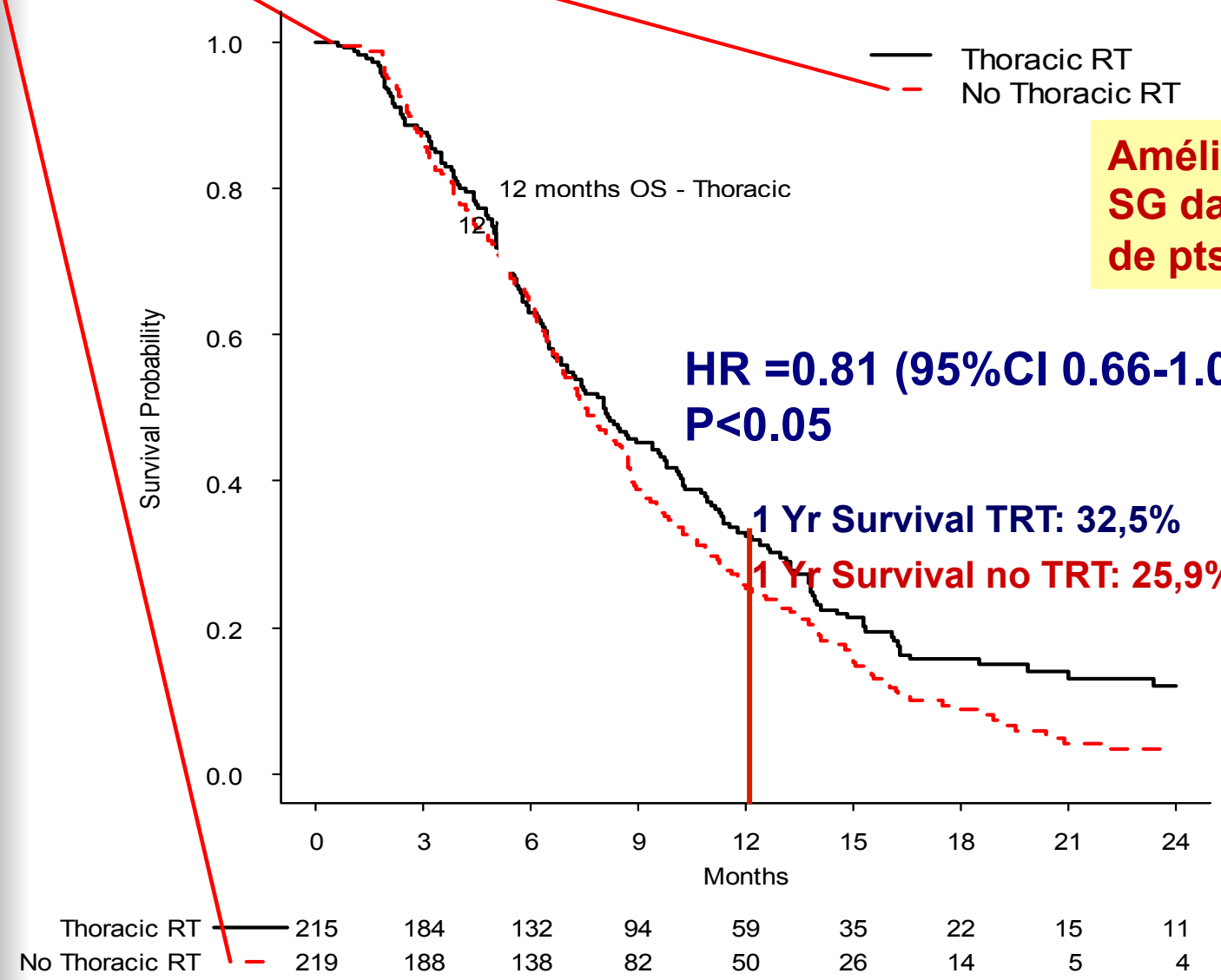
	TRT	No TRT	p
1yr OS	33%	28%	0,066
1,5 yr OS	16%	9%	0,03
2 yr OS	13%	3%	0,04

Study powered to detect a 10% improvement in 1 yr OS from randomisation
Control arm: 27%

Slotman et al, CREST trial Lancet 2014

Overall survival

Pts with residual intrathoracic disease (n=434)



Amélioration significative SG dans ce sous groupe de pts

HR =0.81 (95%CI 0.66-1.00)
P<0.05

1 Yr Survival TRT: 32,5%
1 Yr Survival no TRT: 25,9%

Slotman IASLC 2015

CPC limité: Associations RT-CT

- Association RT-CT : Amélioration de survie de 5% (9% CT seule vs 14% CT-RT)
- RT thoracique doit être plutôt précoce
- RT-CT concomitante ou RT-CT alternée> RT-CT séquentielle
- Pas de diff entre RT accélérée hyperfractionnée accélérée (45 Gy/30 fr/3sem et RT 66 Gy/33fr/ 6sem
- CT optimale reste EP ou CP
- Etude en cours evaluant immunotherapie en consolidation (Stimuli)

IPC Conclusions

- IPC Diminution significative du taux de MC
- Nécessité d ’une méta-analyse pour montrer une amélioration de la survie de 5% à 3 ans après IPC (15% à 20%)
- Partie intégrante du traitement standard des pts bonne reponse et de moins de 70 ans
- Neurotoxicité liée a age
- Dose optimale: 25 Gy en 10 séances dans les CPC limités
- IPC dans les CPC metastatiques?? Sujet de controverse