UNIVERSITÀ DEL PIEMONTE ORIENTALE

Il trattamento associato radiochemioterapico nel tumore polmonare localmente avanzato

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SCDU di Radioterapia

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"Maggiore della Carità", Novara

Claudia, 53 y

Heavy smoker, BPCO

Rx→ CT

FBS + BAL + CT guided byopsy

Adenocarcinoma G3

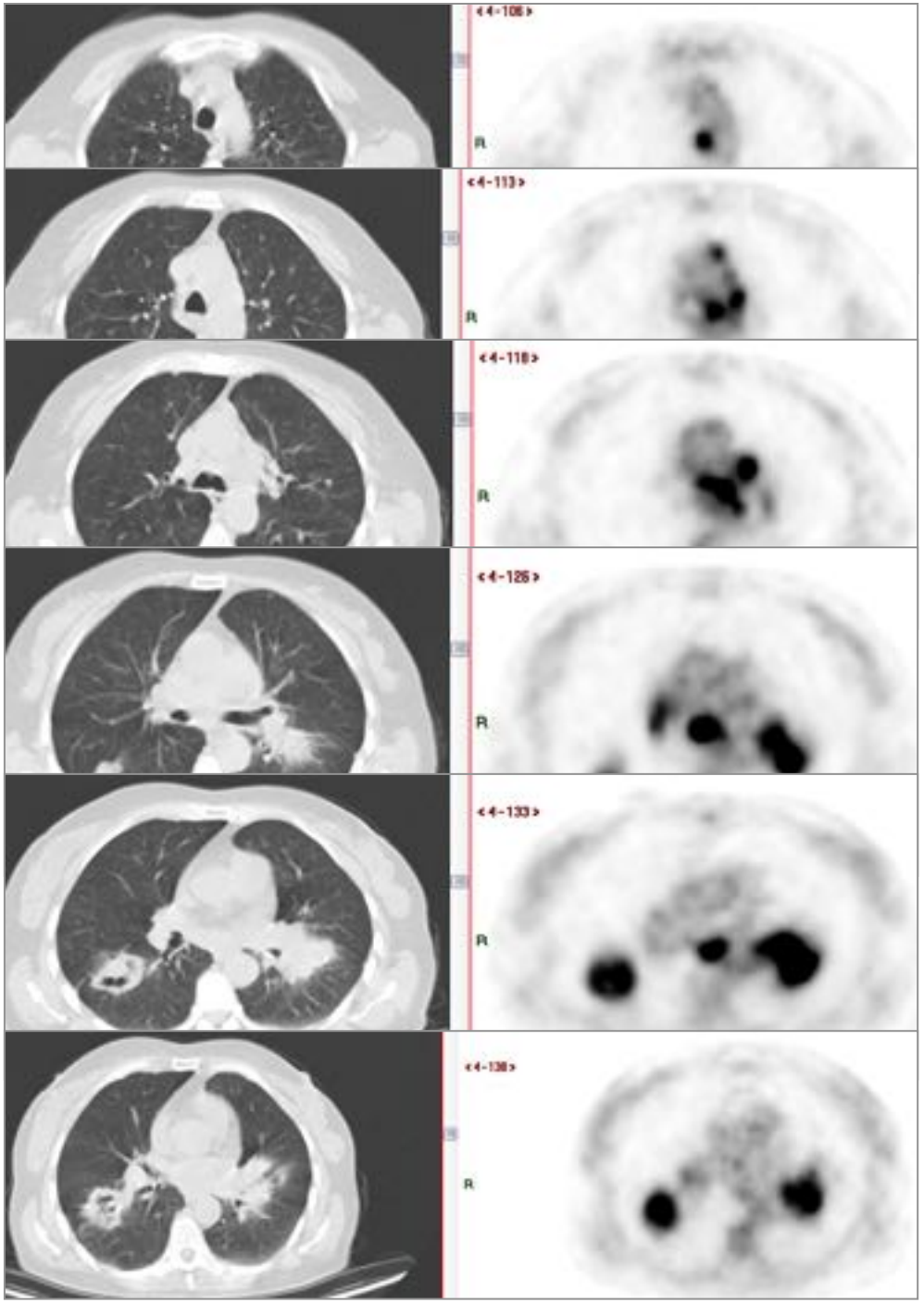
EGFR wild type

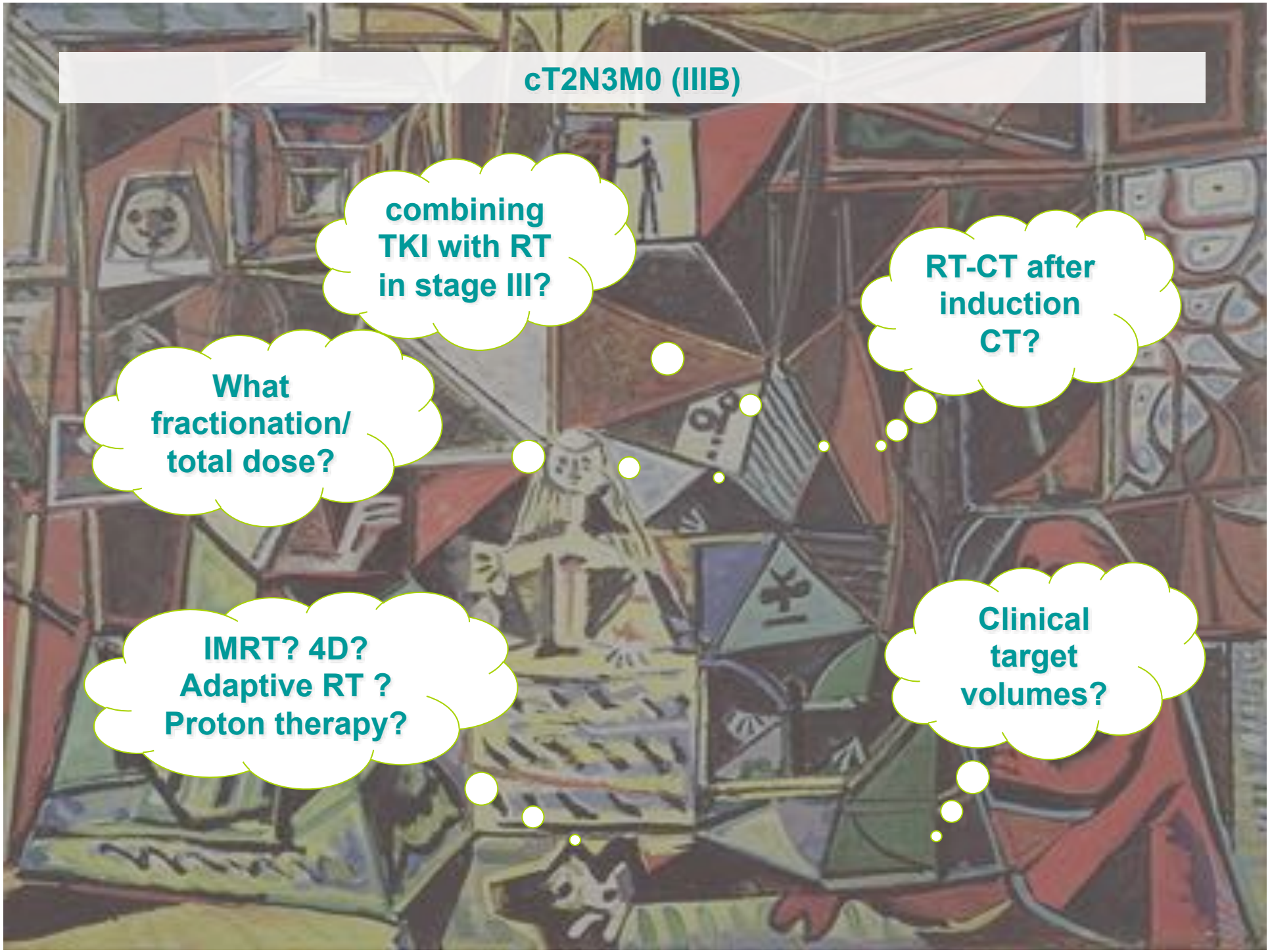
Staged as M1b (?!)

CT CDDP + Gem q21 5 cycles

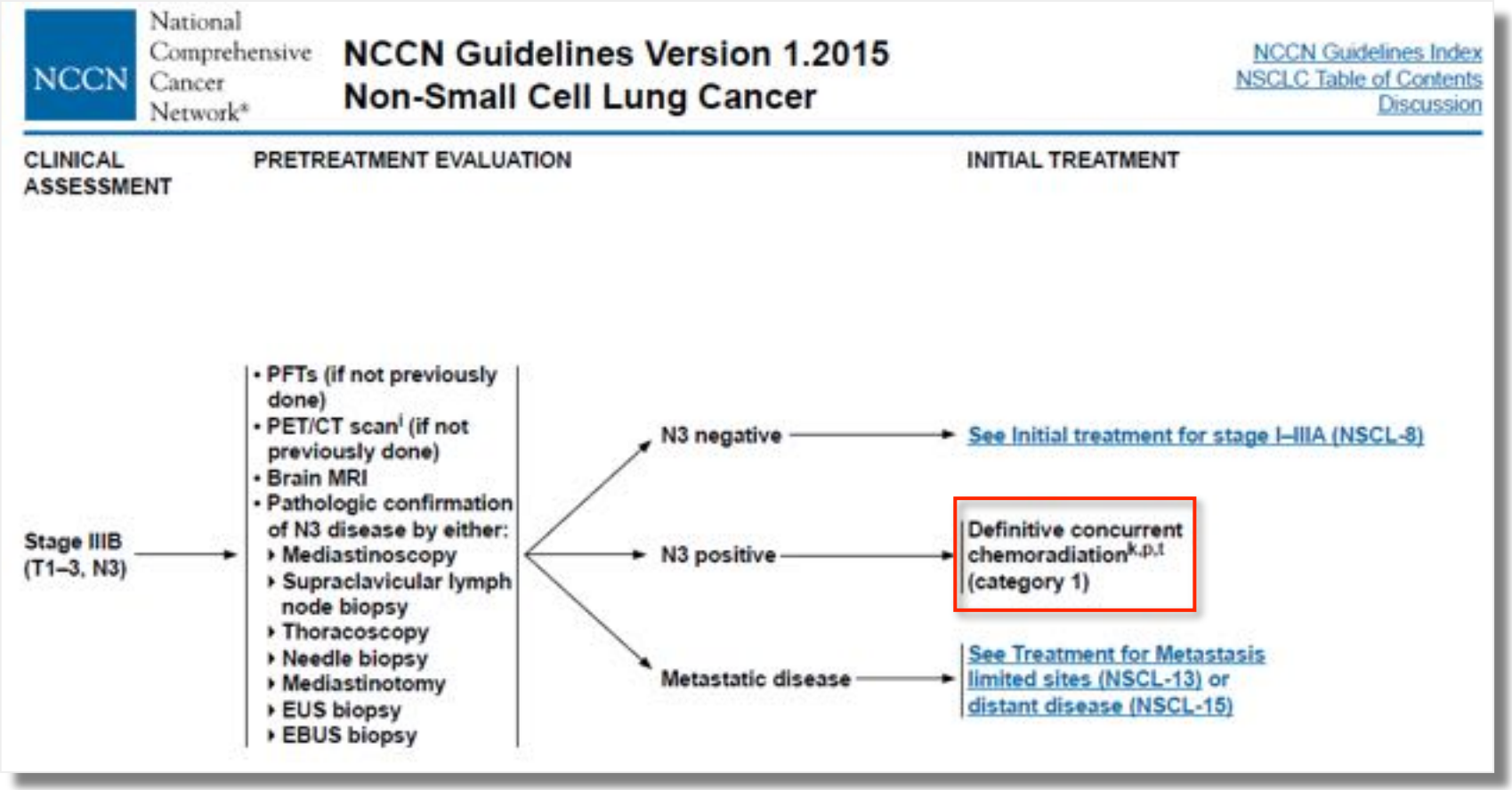
G4 haematologyc toxicity

post CT FDG PET : no change!!



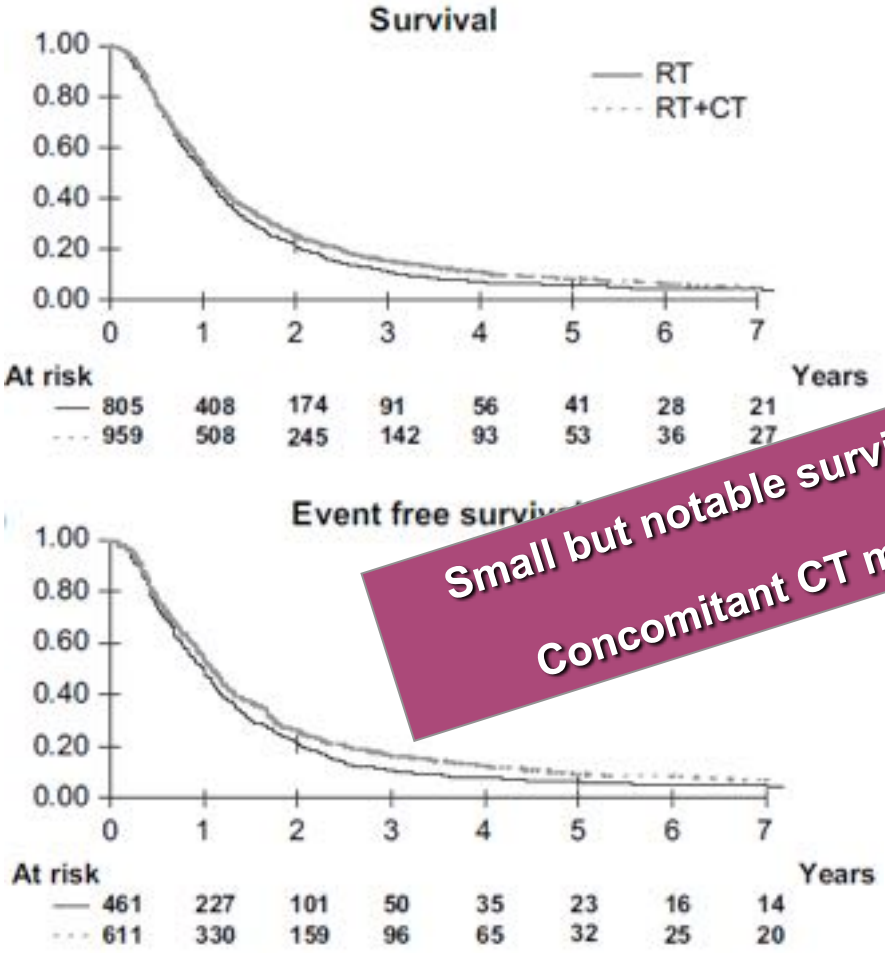

cT2N3M0 (IIIB)
combining TKI with RT in stage III?
RT-CT after induction CT?
What fractionation/ total dose?
IMRT? 4D? Adaptive RT ? Proton therapy?
Clinical target volumes?

What's the best option for C.?

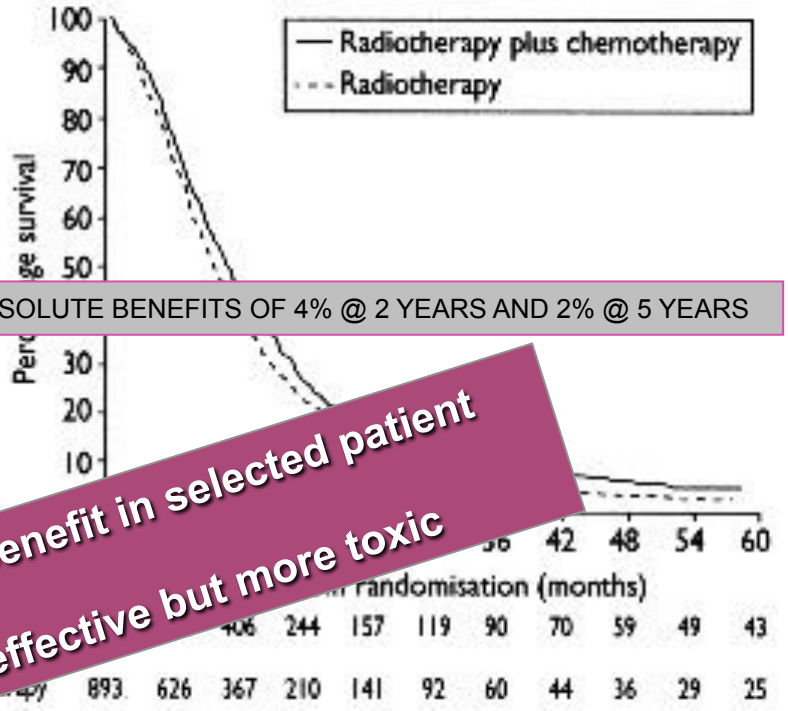


Combining Chemo and Radiation Therapy

Survival in trials of radical radiotherapy versus radical radiotherapy plus chemotherapy (only 11/22 trials using regimens based on cisplatin)



Non–Small Cell Lung Cancer Collaborative Group meta-analysis 1995



ABSOLUTE BENEFITS OF 4% @ 2 YEARS AND 2% @ 5 YEARS

Small but notable survival benefit in selected patient

Concomitant CT more effective but more toxic

9 trials (1764 patients)

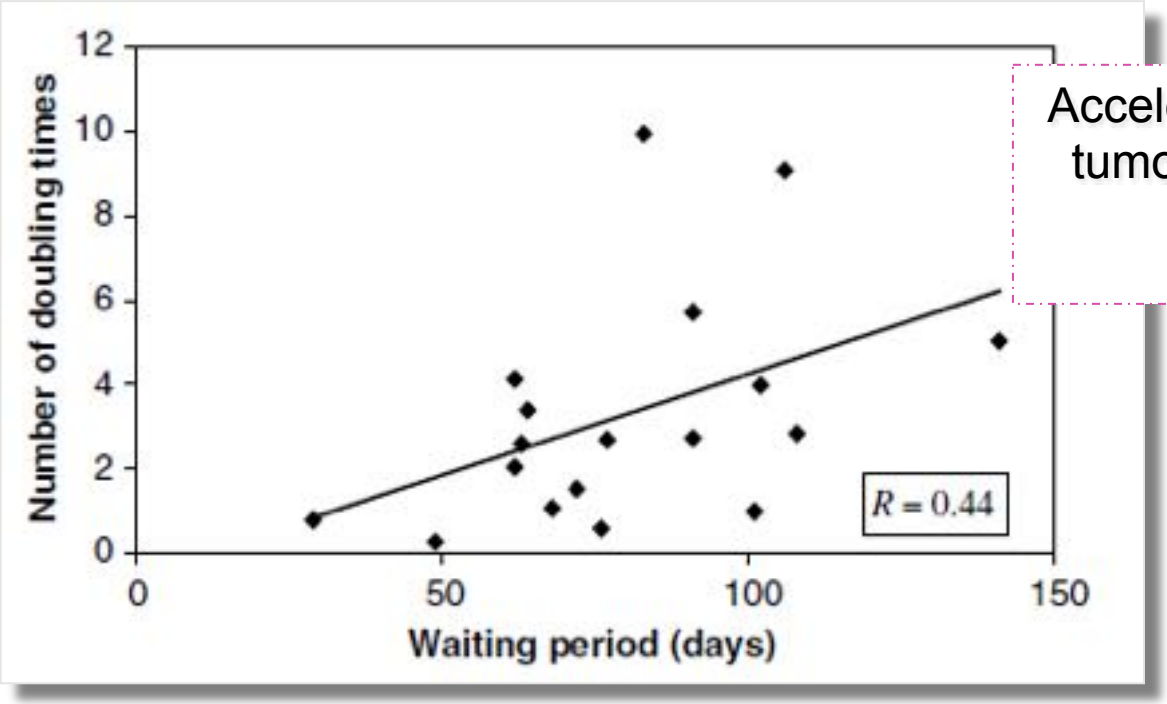
cisplatin- or carboplatin-based chemotherapy

Platin with etoposide more effective than platin alone

Auperin 2006- MAC3-LC

Sequential vs Concomitant CT-RT

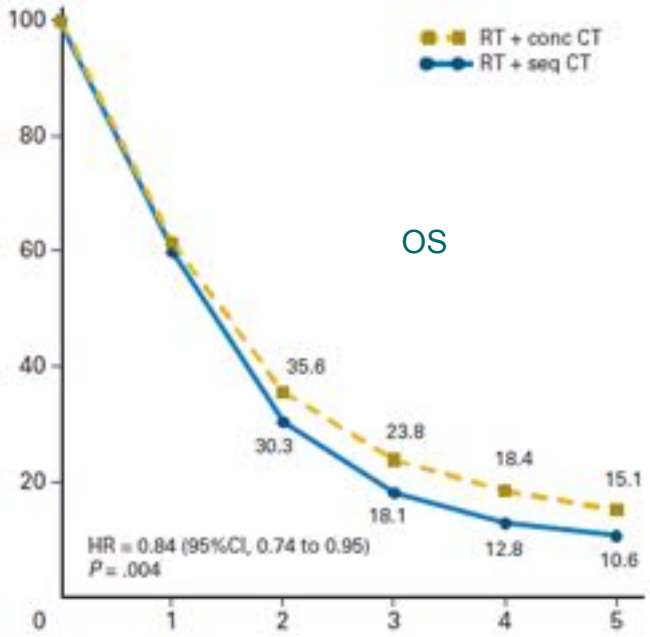
	PRO	AGAINST
SEQUENTIAL	Safe delivery full dose CT	•Accelerated repopulation •Emerging radioresistance •Delayed delivery RT
CONCOMITANT	•No delay in RT delivery •Decreased tumour ripopulation •Possible radiosensibilization	Increased acute toxicity



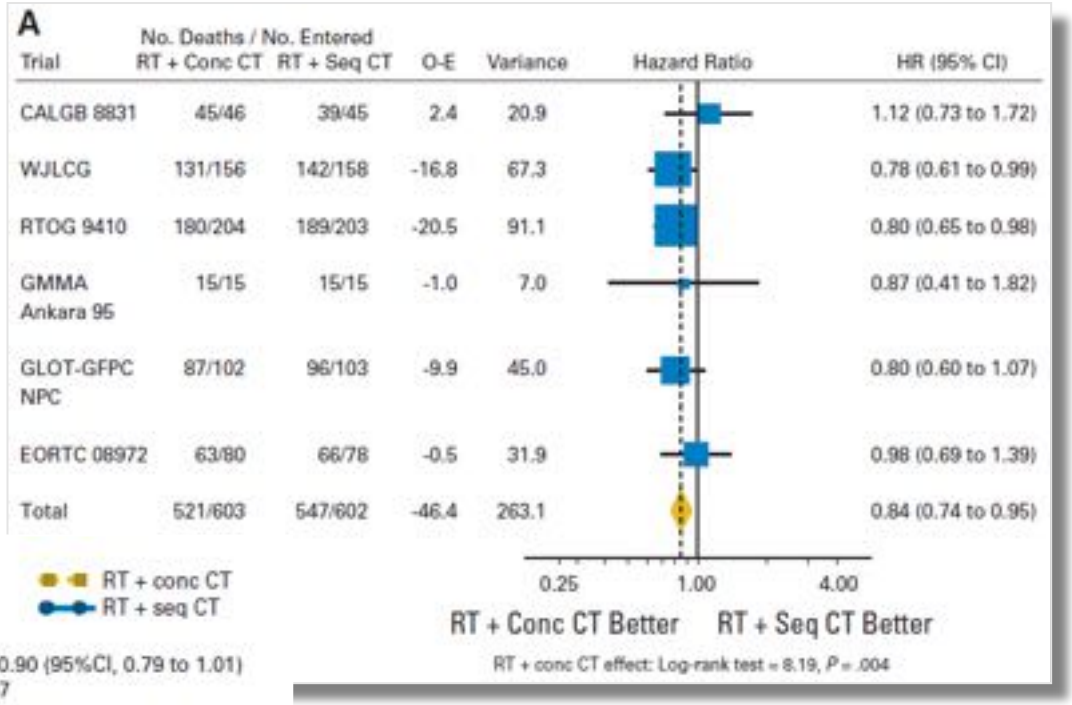
Accelerated regrowth of NSCL tumours after chemotherapy

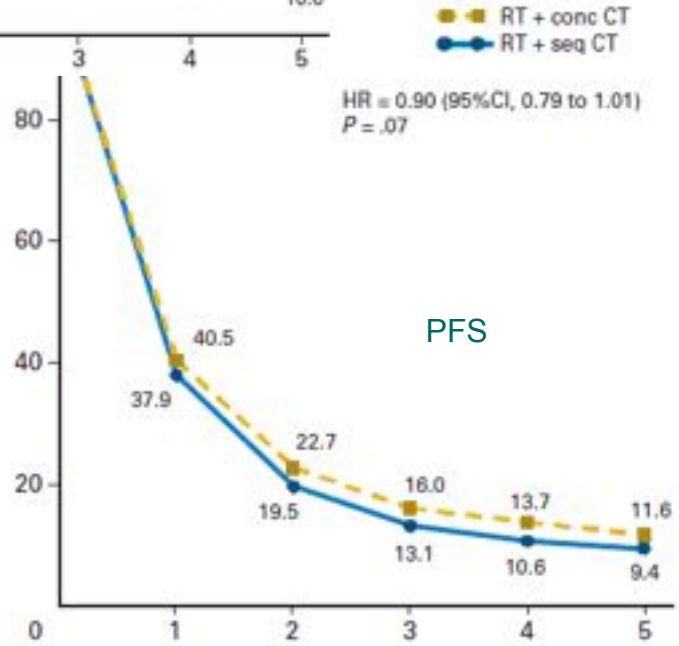
El Sharouni et al 2003

Sequential vs Concomitant CT-RT



OS

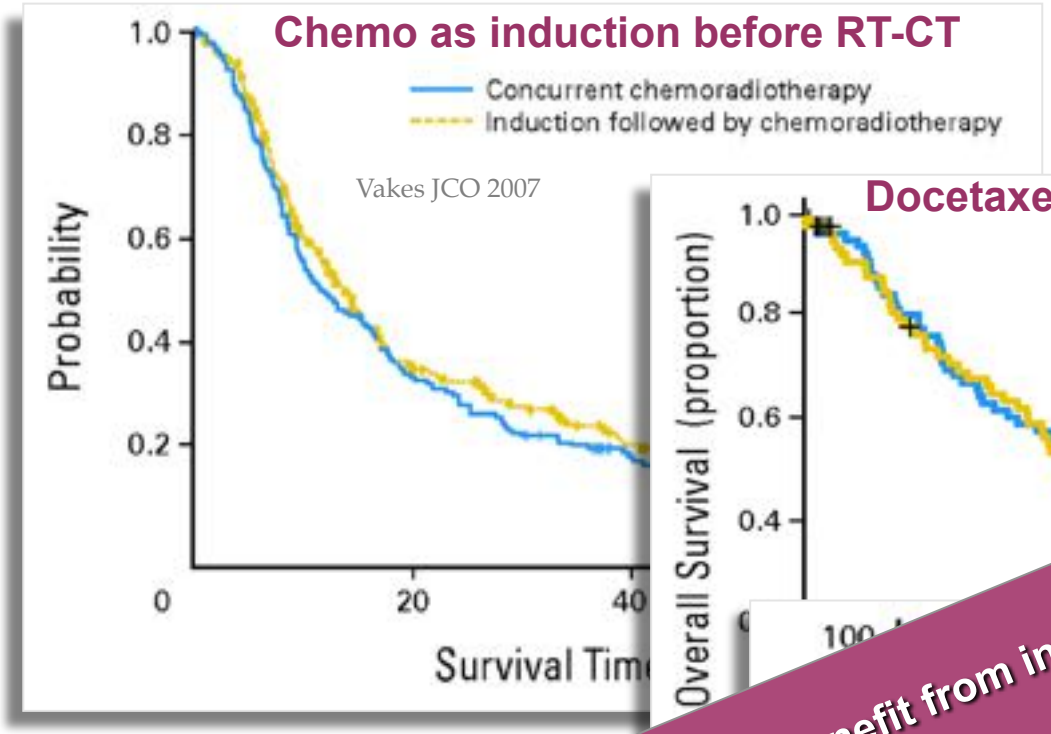




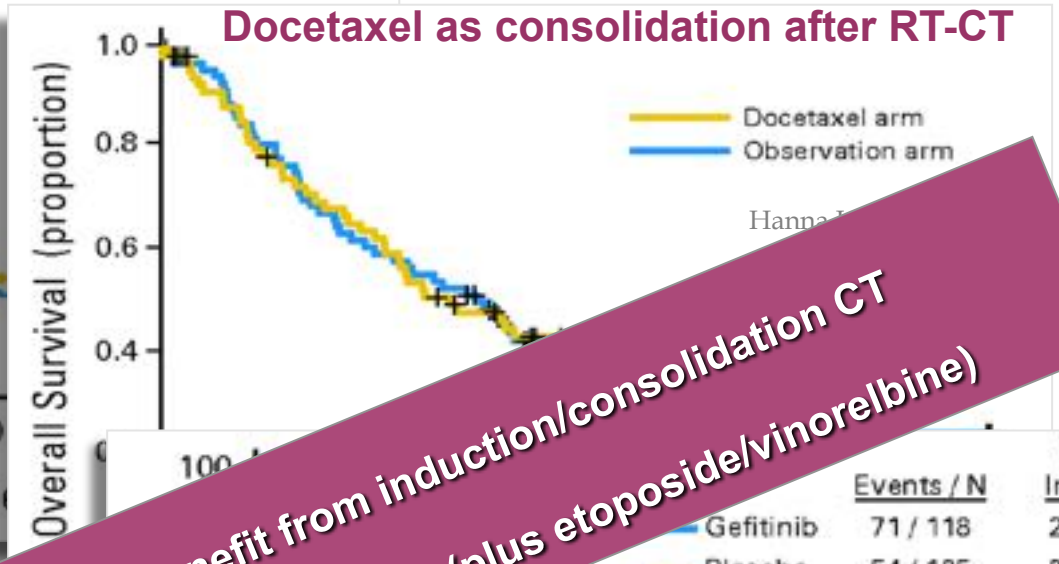
PFS

Auperin 2010

Timing for combining RT-CT



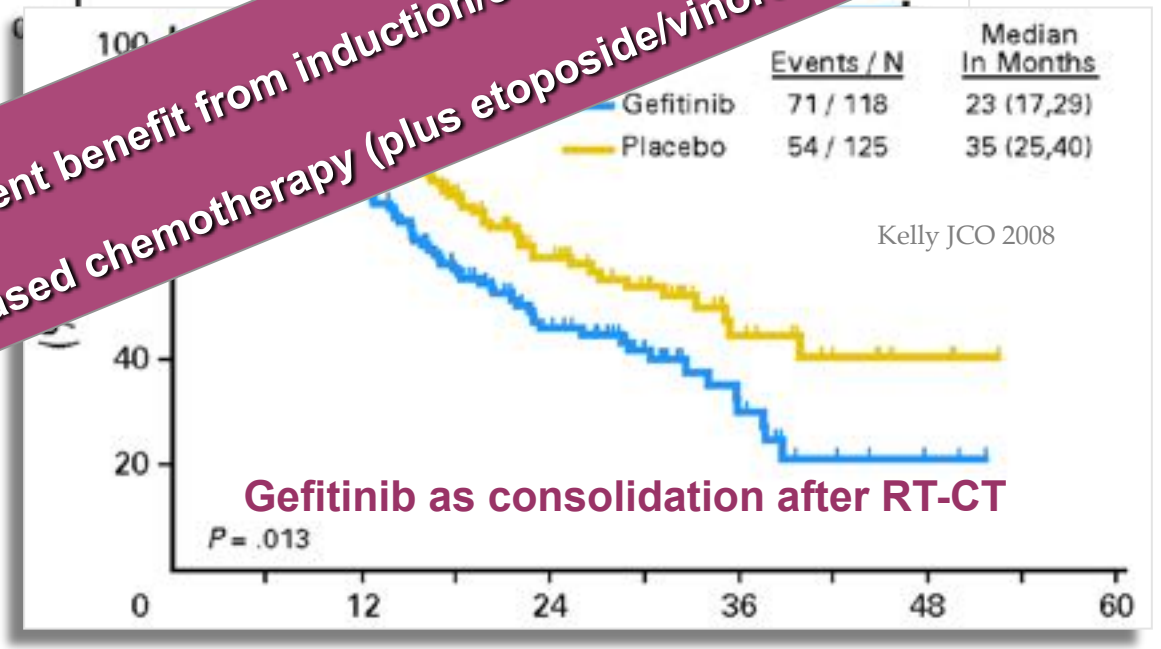
Vakes JCO 2007



Hanna J

Non apparent benefit from induction/consolidation CT

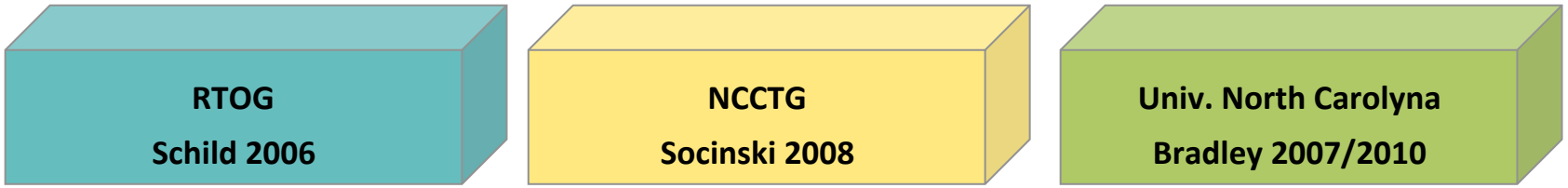
Cisplatin based chemotherapy (plus etoposide/vinorelbine)

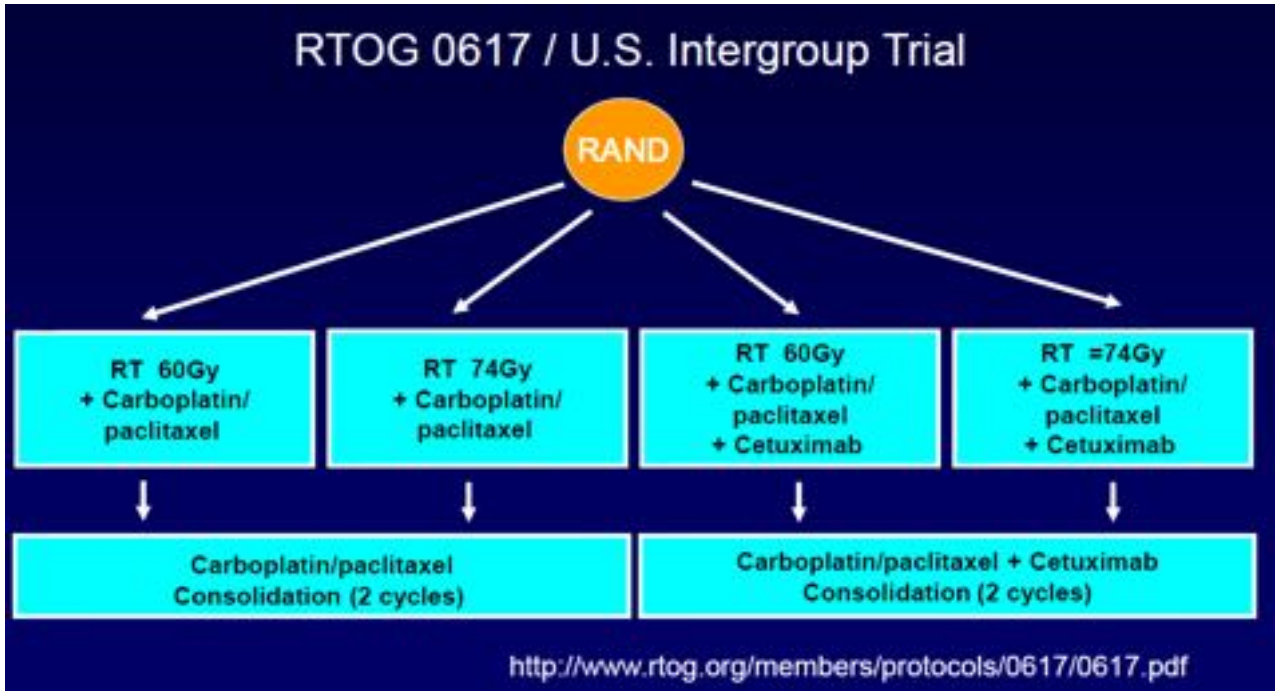


Kelly JCO 2008

What radiotherapy dose in combination with chemotherapy? Dose escalation

Safety and efficacy of using 74 Gy concurrently with chemotherapy





Bradley 2015

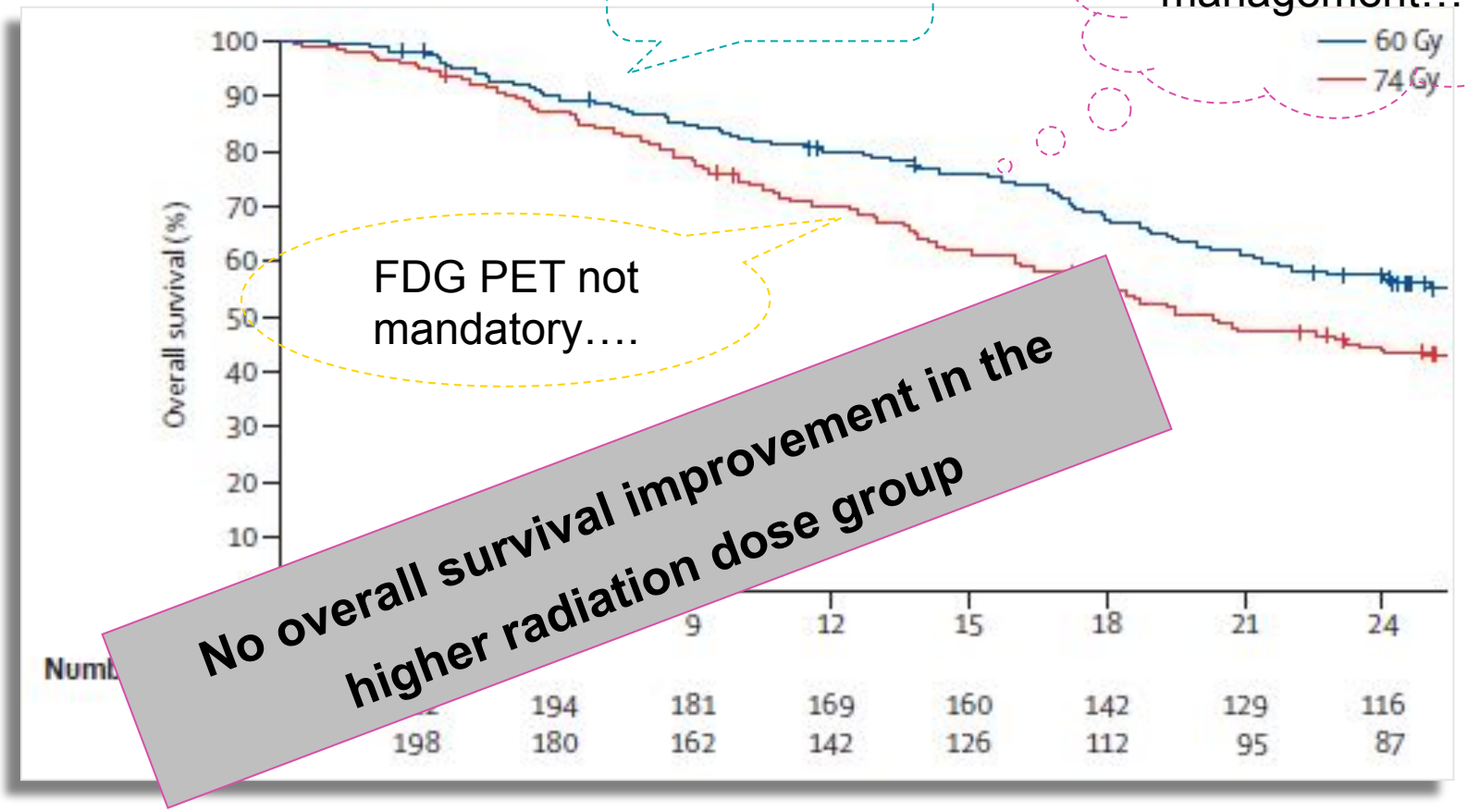
Dose escalation

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

7,5 week OTT

No motion management…

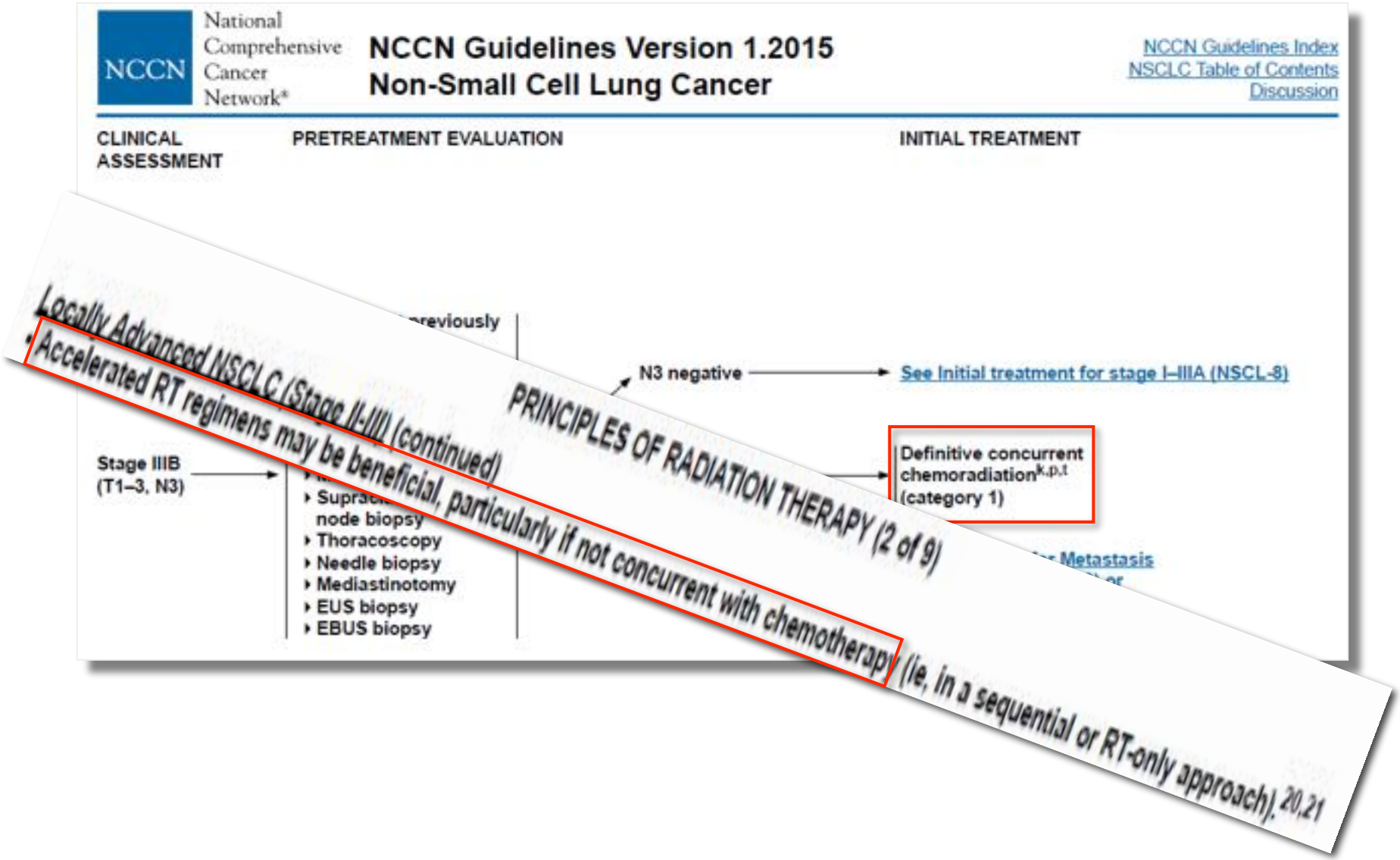
FDG PET not mandatory….



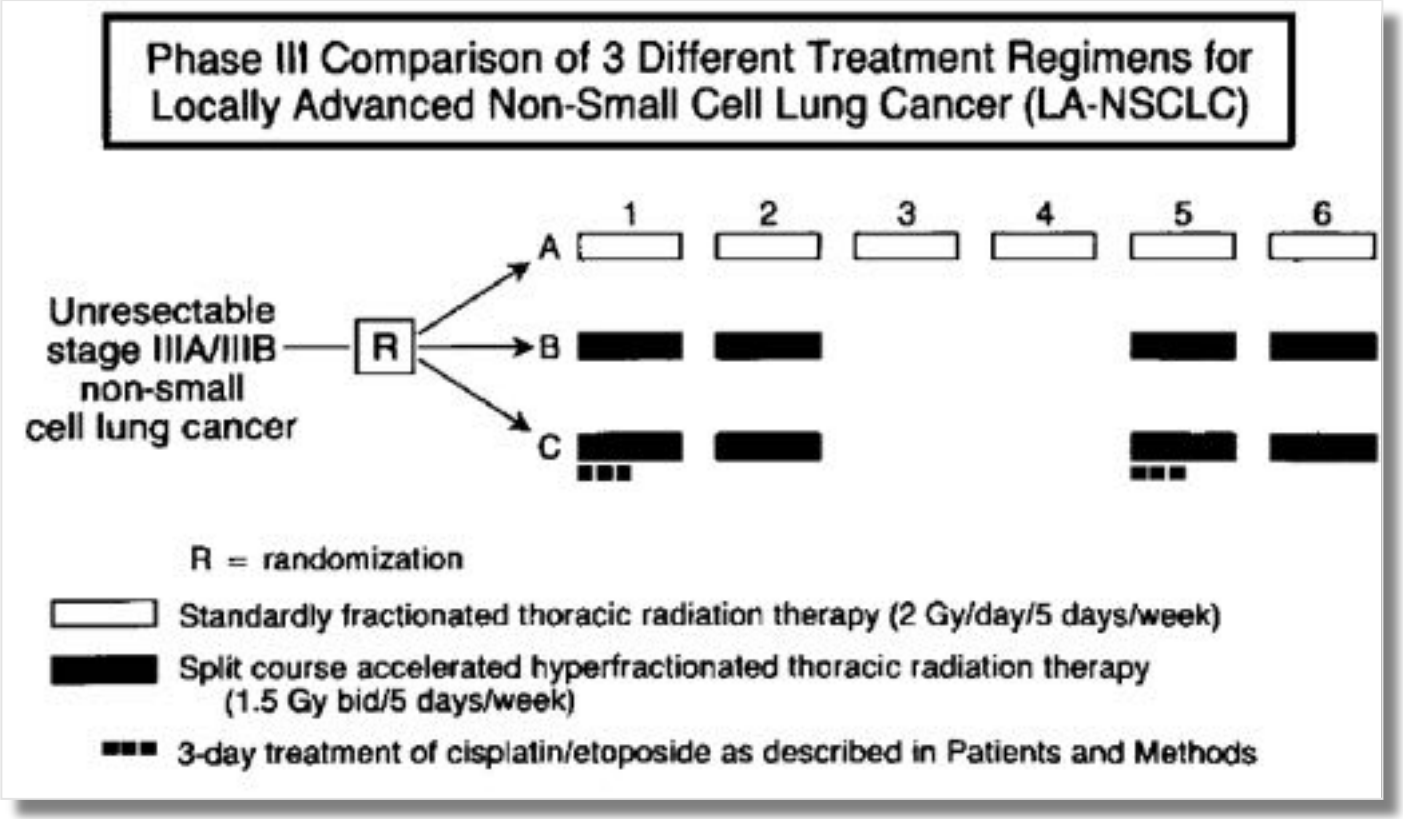
No overall survival improvement in the higher radiation dose group

Bradley 2015

What's the best option for C.?



Altered Fractionation Radiation Therapy



"Patients with stage III NSCLC treated with **accelerated HFX RT** with or without chemotherapy may have **better freedom from local progression and survival** compared with those receiving standard RT, especially non–squamous-cell carcinoma"

Bonner 1998, NCCTG

RT ALONE
Altered fractionation and and Dose-Escalation

RTOG 8311 1.2 Gy x 2/daily

(Cox 1990)

CTV doses of 60 Gy, 64.8 Gy, and 69.6 Gy, 74.4-Gy and 79.2-Gy.
The best arm received 69.6 Gy in 6.5 weeks (2-year survival rate of 29% p = .02)

EORC CHART 1.5 Gy x 2/daily

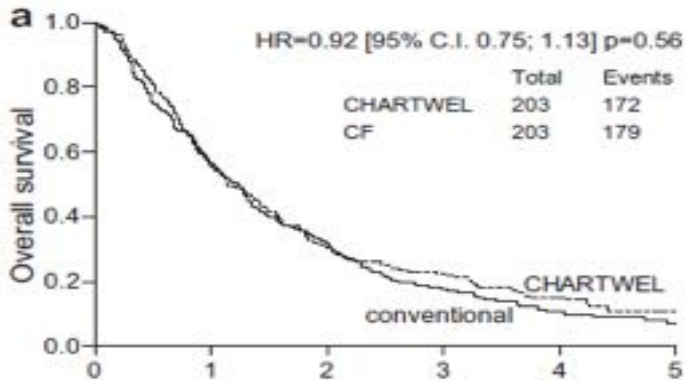
(Saunders 1999)

CTV2 = 37.5 Gy in 25 fractions
CTV1= boost 16.5 Gy in 11 fractions, for a total dose of 54 Gy

Better OS (20% vs 13% @2y and 20% vs 13% @3y) and LC (17% vs 12%) CHART cfr to standard RT
G2-3 dysphagia 49% of CHART vs 19% standard
No significant difference in late complications

> **Improvement SCC-82%** (OS @3y 21% vs 11%)

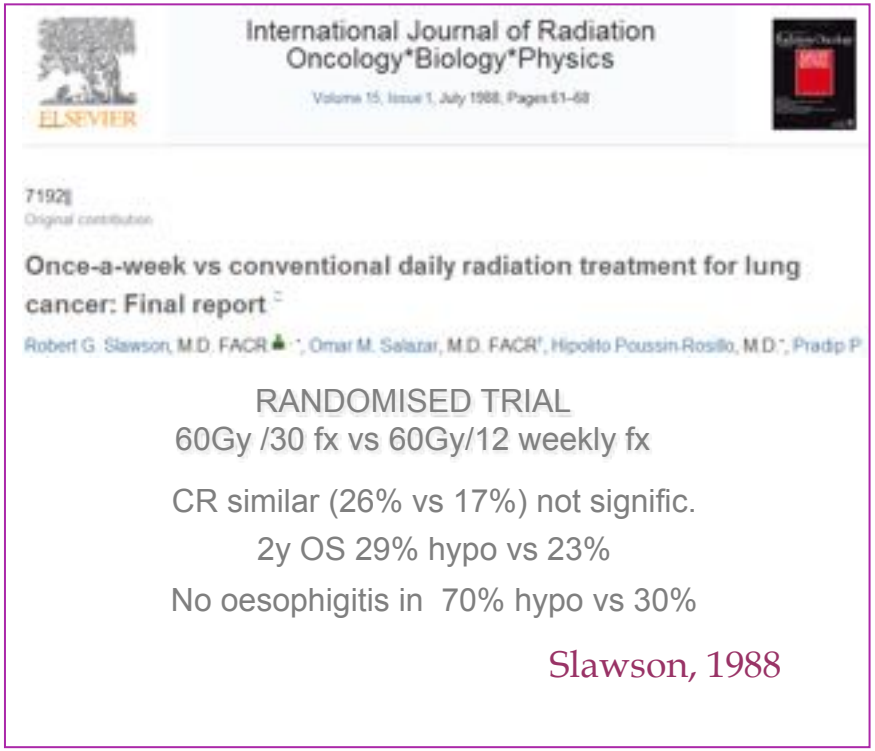
CHARTWEL 1.5 Gy x 3/die x 13 fx *vs* 66Gy 2/die



(Baumann 2011)

No OS or DFS benefit
lower fraction of squamous cell cancers (57%)
Only 27% concurrent chemo

Hypofractionation



International Journal of Radiation Oncology*Biology*Physics

Volume 15, Issue 1, July 1988, Pages 61-68

7192]

Original contribution

Once-a-week vs conventional daily radiation treatment for lung cancer: Final report

Robert G. Slawson, M.D. FACR, Omar M. Salazar, M.D. FACR, Hipolito Poussin-Rosillo, M.D., Pradip P

RANDOMISED TRIAL
60Gy /30 fx vs 60Gy/12 weekly fx

CR similar (26% vs 17%) not signific.

2y OS 29% hypo vs 23%

No oesophigitis in 70% hypo vs 30%

Slawson, 1988

88 pts **Phase I**: dose **escalation up to 94.5 Gy** in 42 fractions within **6-week**
OTT is safe for small-volume lung tumors with MLD less than or equal to 13.6 Gy or 11.3 Gy

Dose escalation trial	Number of fractions	Dose per fraction (Gy)	Overall treatment time (weeks)	D_{max} (Gy)	tBED (Gy)
University of Michigan 9204*	49	2.10	10	102.9	96
RTOG 93-11†	39	2.15	8	83.8	84
NKI-AVL	42	2.25	6	94.5	108
Dublin‡	24	3.00	5	72.0	91

Belderbos 2006

34 pts **Phase I**: upfront chemoradiation (weekly concurrent docetaxel and cisplatin) followed by 2 cycles of consolidation hypofx chemotherapy

Dose Parameter, Gy	I	II	III	IV	V
TD	60	63.6	67.2	70.8	74.4
FD	2.00	2.12	2.24	2.36	2.48
BED	64.8	69.9	75.1	80.3	85.7

Bral, 2010

HypoRT +/-"cutting edge technology" +/- protons....

Dose escalation
3 Hypofx dose levels

- ✓45 Gy(RBE) in 3-Gy(RBE)
- ✓52.5 Gy(RBE) in 3.5-Gy(RBE)
- ✓**60 Gy(RBE) in 4-Gy (RBE) 15 fx**

25 pts

Toxicity

Grade	Dermatitis	Pneumonitis	Esophagitis	Fatigue
Grade 0	18	7	15	10
Grade 1	6	13	0	6
Grade 2	1	4	9	9
Grade ≥3	0	1	1	0

Gomez 2013, phase I

Target	Current Dose-Volume Constraints for Standard Fractionated Regimens at our Institution (2-Gy Fractions to 60-74 Gy)	Dose-Volume Constraints in Current Study [BED dose assuming α/β=3 with 15-fraction regimen)
Total Lung	V_{20} <40% Mean Lung D[illegible] <20 Gy	V_{17}<40% Mean Lung Dose <17.5 Gy(RBE) [17.1 Gy(RBE)]
Liver	40%	40% <40 Gy(RBE) [38.9 Gy(RBE)]
Kidneys (both)		1/3 <18 Gy(RBE) [17.1 Gy(RBE)]
Esophagus	20% <[illegible] 50% <50 [illegible]	20% <55 Gy(RBE) [52.65 Gy(RBE)] 50% <40 Gy(RBE) [38.9 Gy(RBE)]
Heart	50% <30 Gy 40% <40 Gy	50% <25 Gy(RBE) [24.6 Gy(RBE)] 40%<32 Gy(RBE) [31.9 Gy(RBE)]
Spinal Cord	Maximum dose 45 Gy	Maximum dose 36 Gy(RBE) [35.4 Gy(RBE)]
Brachial Plexus	Maximum dose <60 Gy	Dose to <1 cm^3 must not exceed 50 Gy(RBE) [45.6 Gy(RBE)]

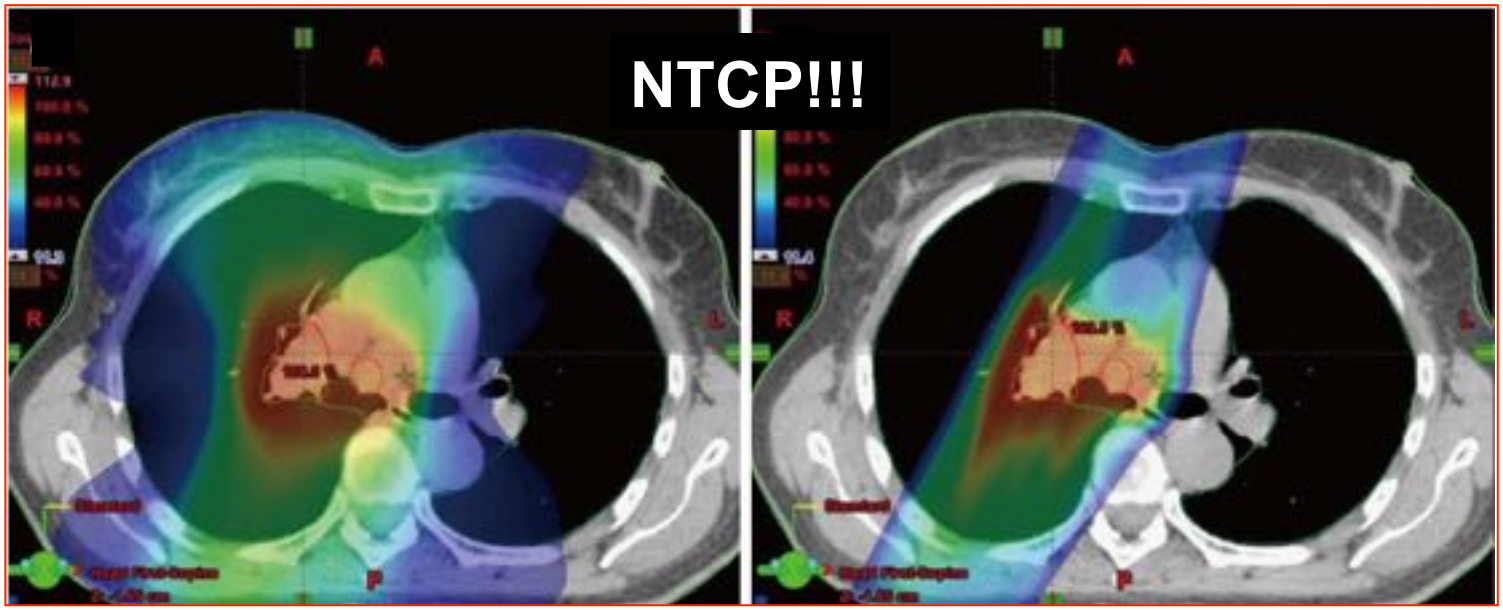
New schedules... new constraints!

Cutting edge technology + protons....

Comparison of dose–volume histograms between proton beam and X-ray conformal radiotherapy for locally advanced non-small-cell lung cancer

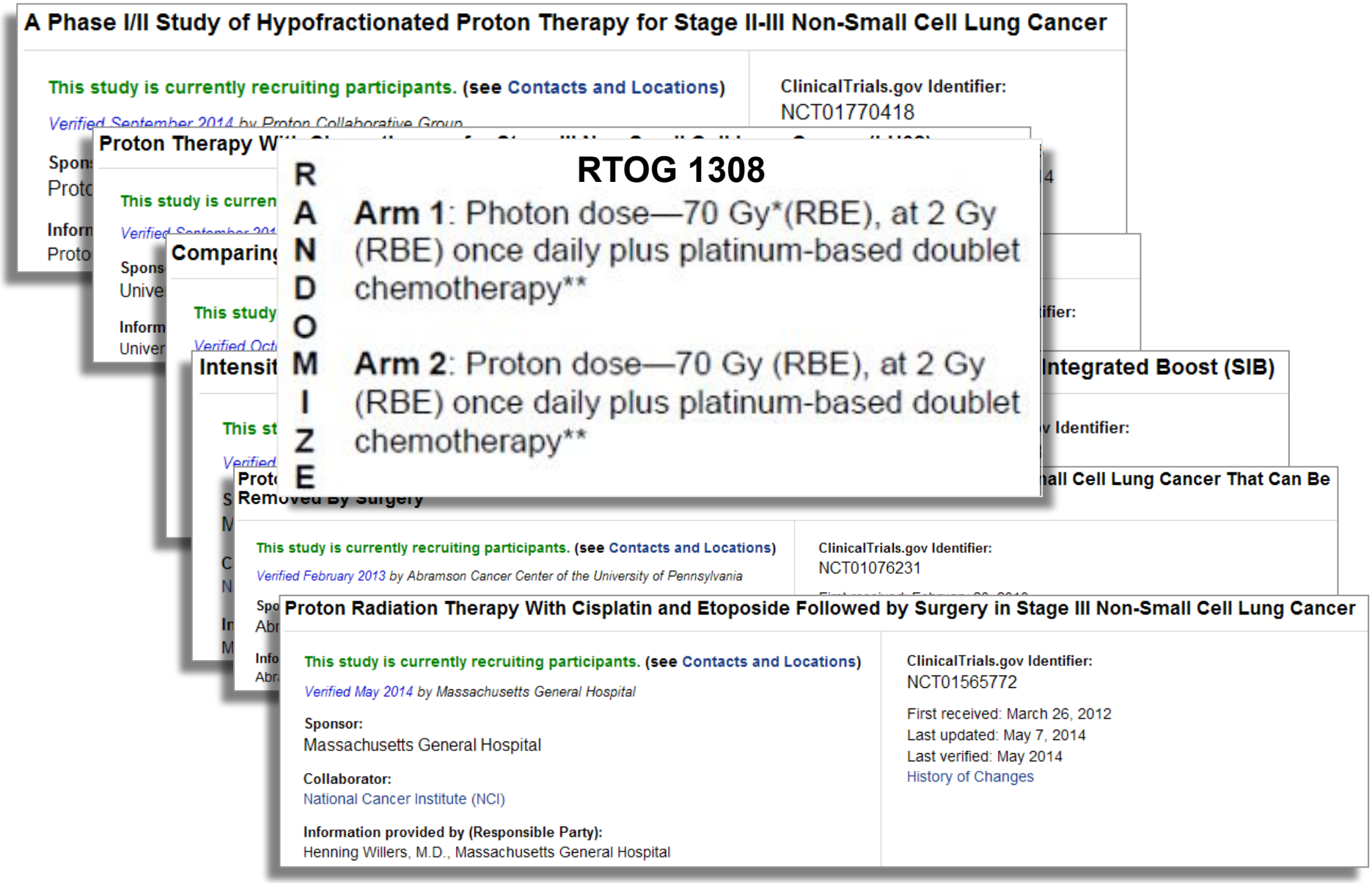
criteria: V5 ≥ 42%, V20 ≥ 25%, mean lung dose ≥ 20 Gy. The mean normal lung dose and V5 to V50 were significantly lower in PBT than in XCRT. The differences were greater with the more advanced nodal status and with the larger CTV. Furthermore, 45.7% of the X-ray plans were classified as inadequate according to the criteria, whereas 17.1% of the proton plans were considered unsuitable. The number of inadequate X-ray plans increased in cases with advanced nodal stage. This study indicated that some patients who cannot receive photon radiotherapy may be able to be treated using PBT.

Ohno, 2015



ClinicalTrials.gov
A service of the U.S. National Institutes of Health

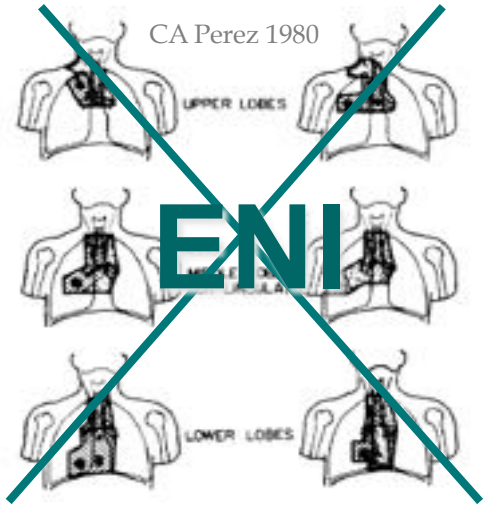
Ongoing research on Proton Therapy



EGFR TKI combined with Radiotehapy +/- *chemotherapy*

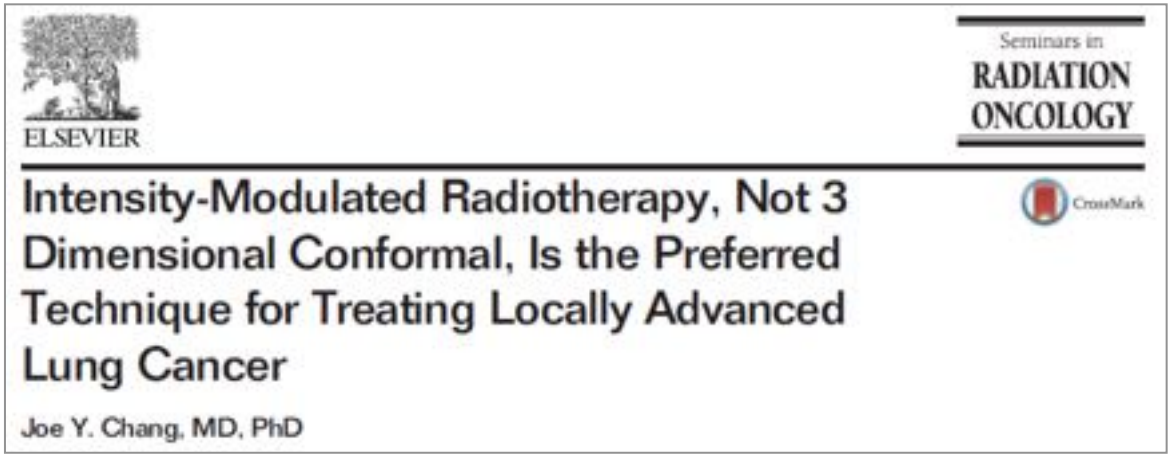
	PHASE	PZ	STAGE	DOSE RT	Chemo	Toxicity ≥ G3	mPFS (mth)	LC	mOS (mts)
Stinchcombe 2008	I	23	III	74	CT RT CT conc q7	9% Arytmia 19% Esophagytis	9	24%	16
Choong 2008	II	17 vs 17	III	66	Erlotinib + RT + CDDP&Etoposide or Carbo& Paclitaxel	3% Pneumonitis 26% Esophagytis	9	38%	11&15
Center 2010	I	16	III	70	Docetaxel+Gefitinib + RT	20% Pneumonitis 27% Esophagytis	7	46%	21
Ready 2010	II	21 PR 39 GR	III	66	CT/TKI inductio + RT/TKI +/- chemo + TKI maintenance		13.4	5%CR 48% & 76% PR 38% 1% SD 5% PD	13 19
Rothschild 2011	I	14	III	63	5 RT	1 G2 polmonite	6	21.4%	12.7
Komaki 2012	II	46	III		itaxel +Erlotinib + RT	?	14.5	80%	34
Okamoto 2011	I	9	III A/B		NO CHEMO	1 G2 Esophagytis 1 G3 Pneumonitis	14 (4.5-73)	4/4	NR
Wang 2011	II	26	III/IV	70 (42-82)	NO CHEMO	Grade 3 Esophagytis 4% Grade 3 Pneumonitis 4%	10	96%	30% 3 y
Chang 2011	II	25	IIIb-IV	40-50 Hypofx	NO CHEMO	2 G3	16	84%	62% 3 y
Niho 2012	I	23/37	III	60	NO CHEMO	1 G2 Pneumonitis 1 G3 Pneumonitis	11	73%	65% 2 y
Zhang 2013	I	45	III-IV	54-60	NO CHEMO	1 G3 (nausea)	5.9	11 PR 23 SD 11 PD	NR
Zhuang 2014	I	24	III – IV	46-66	NO CHEMO	4 G2 2 G3 3 G5	Median FU 31 (7-48)	NE	NE

Clinical Target Volumes



ISOLATED NODAL RECURRENCE from INVOLVED FILED RADIOTHERAPY

Belderbos, Int J Radiat Oncol Biol Phys 2006	PET	67	3%
De Ruysscher, Int J Radiat Oncol Biol Phys 2005	PET	44	2%
Fernandes, Radiother and Oncology 2010	PET	48	4.3%
Sulman, Radiation Oncology 2009	PET	115	1,7%
Fleckenstein, Int J Radiat Oncol Biol Phys 2011	PET	33	4%
Bradley, Int J Radiat Oncol Biol Phys 2012	PET	47	2%



Why IMRT?

Interplay effects can be minimized with **motion management techniques**

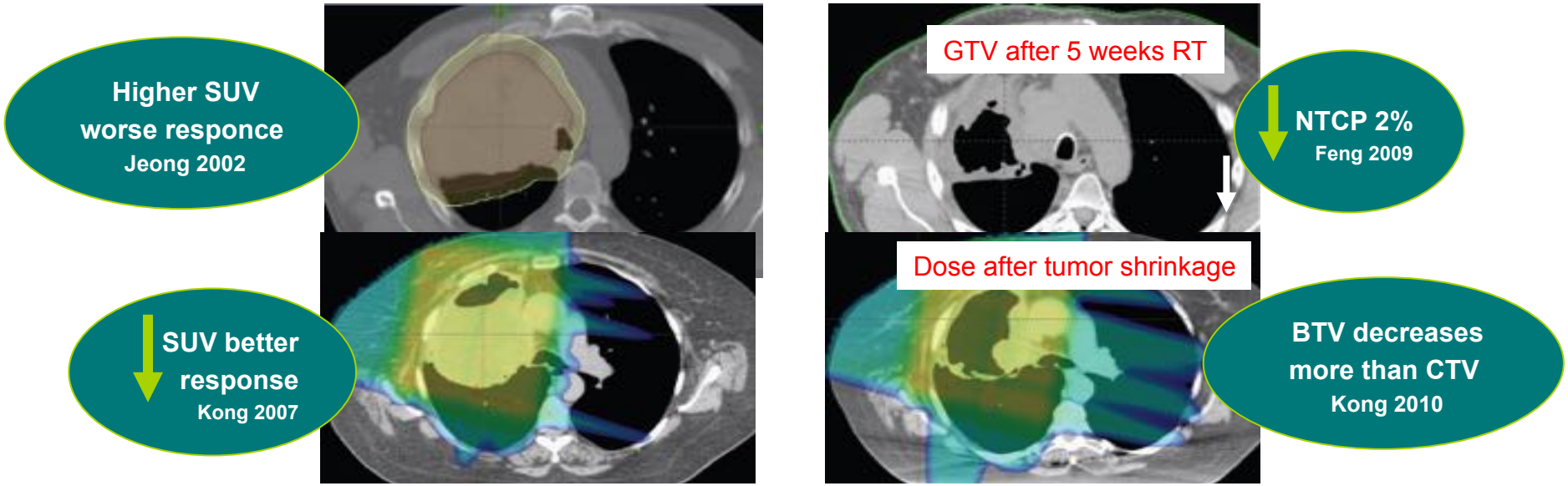
Doesn't compromise local-regional control if radical **doses are used**

Seems (?) to **improve quality of life** (less pneumonitis and esophagitis)

Dose escalation (on anatomical, biological, and molecular volumes) by **SIB** without prolonging treatment time

Chang, 2015

FDG-PET Adapted RT



RTOG 1106: randomized phase II trial of individualized adaptive radiotherapy using during-treatment FDG PET/CT and modern technology in locally advanced NSCLC

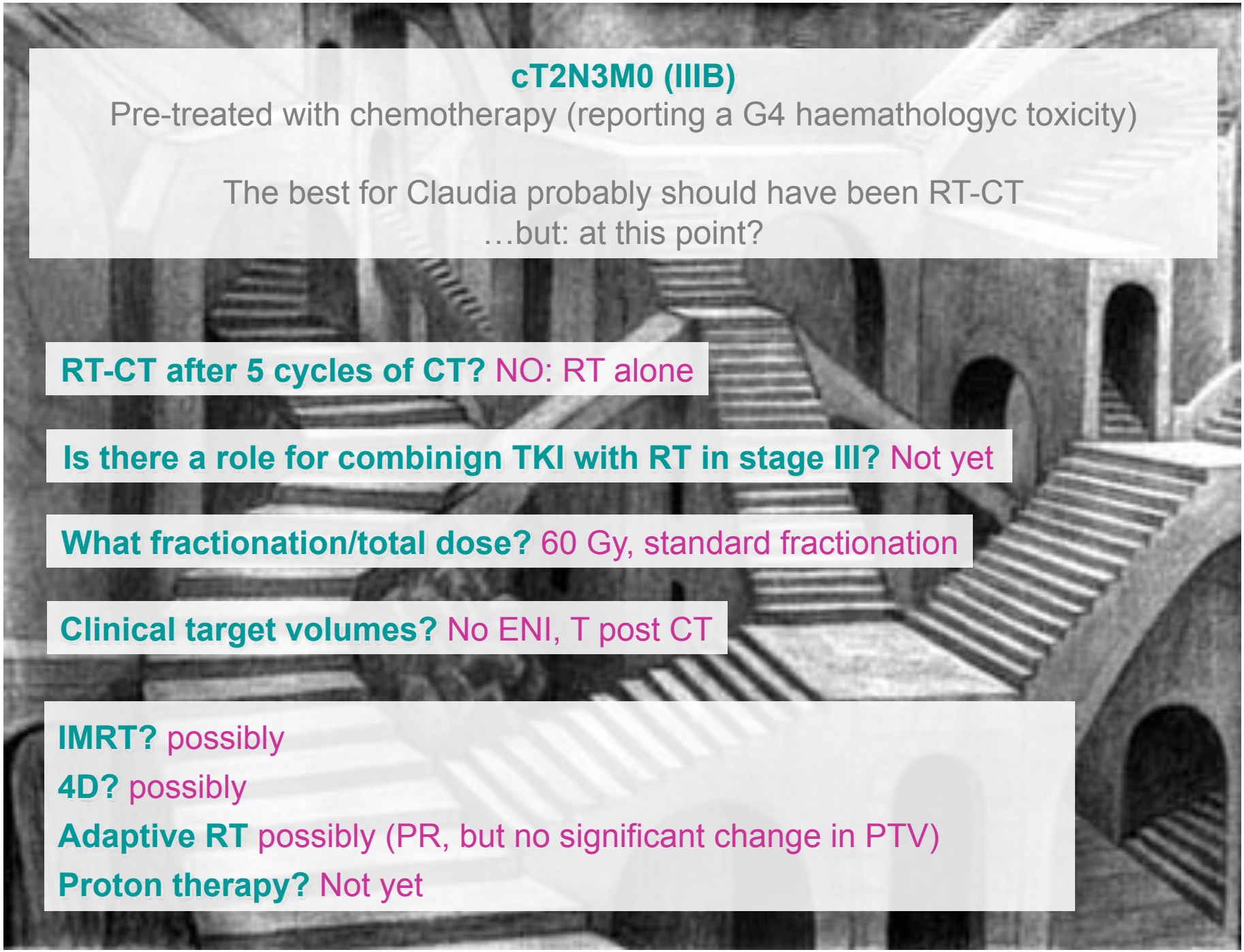
Structure Name	Description	Dose covering 95% volume
CT1PT1CTV	CT1PT1GTV+5mm	60 Gy or above
CT1PT1PTV	CT1PT1CTV+5mm	50 Gy or above
CT2PTV	PTV based on CT2GTV	70 Gy or above**
PT2PTV	PT2GTV+5mm	Up to 80.4 Gy

46.2 Gy in 2.2 Gy /die

PET/CT based boost

18/19 Fx of 2.2-3.8 Gy/die

Gomez, 2011



cT2N3M0 (IIIB)

Pre-treated with chemotherapy (reporting a G4 haemathologyc toxicity)

The best for Claudia probably should have been RT-CT
…but: at this point?

RT-CT after 5 cycles of CT? NO: RT alone

Is there a role for combinign TKI with RT in stage III? Not yet

What fractionation/total dose? 60 Gy, standard fractionation

Clinical target volumes? No ENI, T post CT

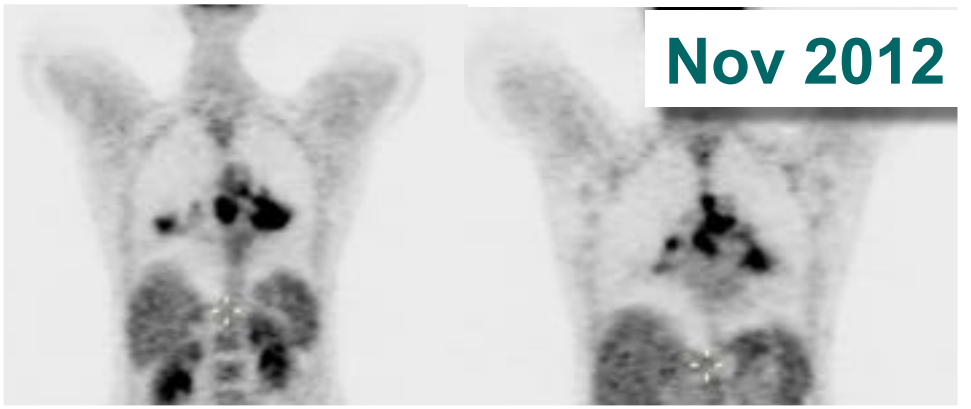
IMRT? possibly

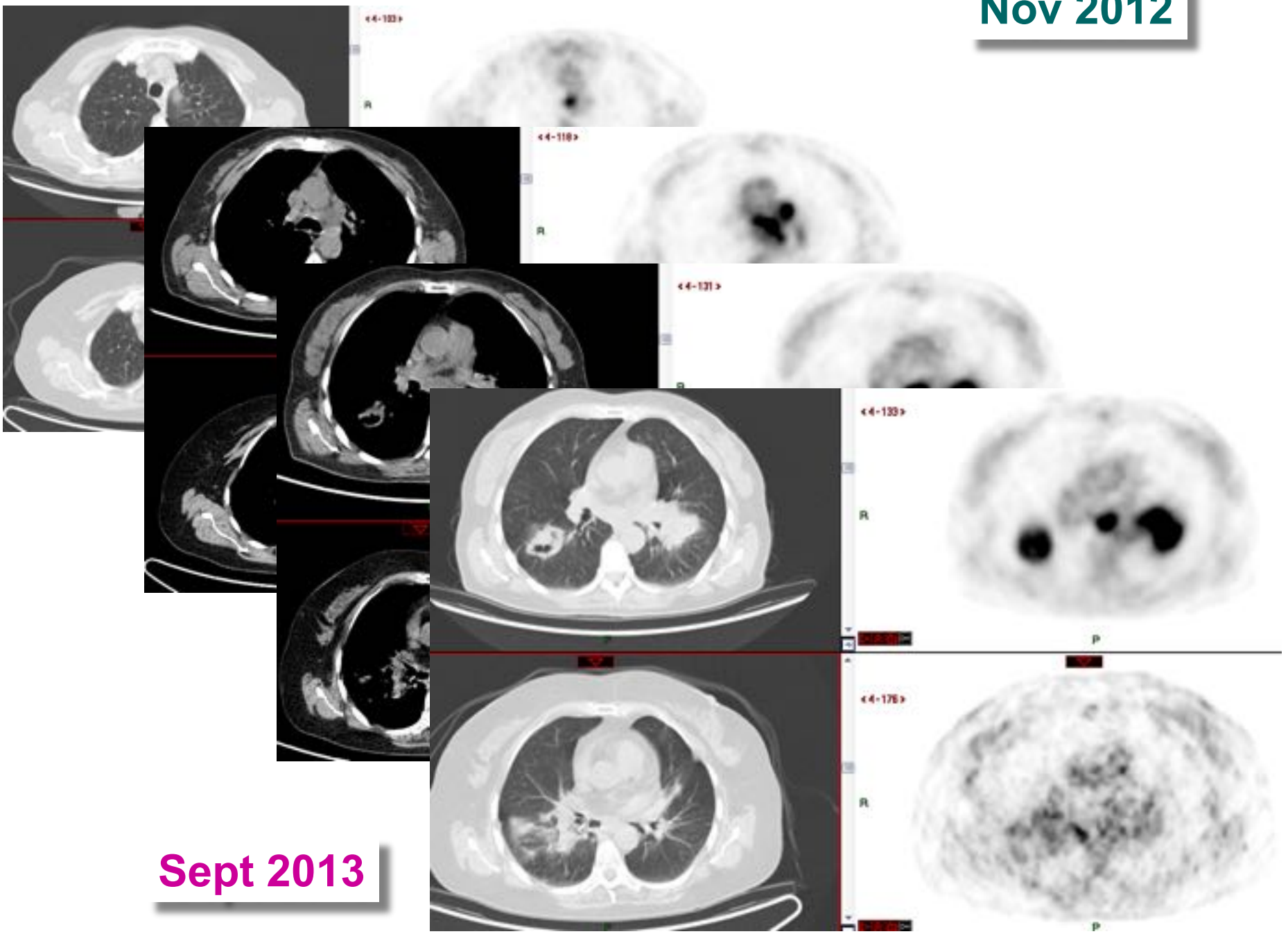
4D? possibly

Adaptive RT possibly (PR, but no significant change in PTV)

Proton therapy? Not yet

- ✓Post-CT 5 cycles
- ✓Radiotherapy alone
- ✓60 Gy
- ✓Standard fractionation 2/die
- ✓IMRT
- ✓No motion management
- ✓Acute toxicity: dysfphagya G2




Nov 2012
Sept 2013

So many questions ...
too much answers

Se in quell'istante avesse fatto in tempo a dire in modo lucido e consapevole a se stesso: "Sì, per questo attimo si può dare tutta la vita!", allora quell'istante sarebbe senz'altro valso un'intera vita.

"L'idiota" Fedor Dostoevskij