Reirradiazione

La radioterapia stereotassica ablativa: torace

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Background

- Stage III NSCLC
  - isolated locoregional recurrence in 25% of pts
  - mostly unresectable; low RR with 2nd line CT

    Auperin A et al, J Clin Oncol 2010; Curran W et al, J Natl Canc Inst 2011
- Second primary lung cancer
  - up to 10% risk within 5 y of tx in early stage
  - up to 20% risk within 5 y post pneumonectomy

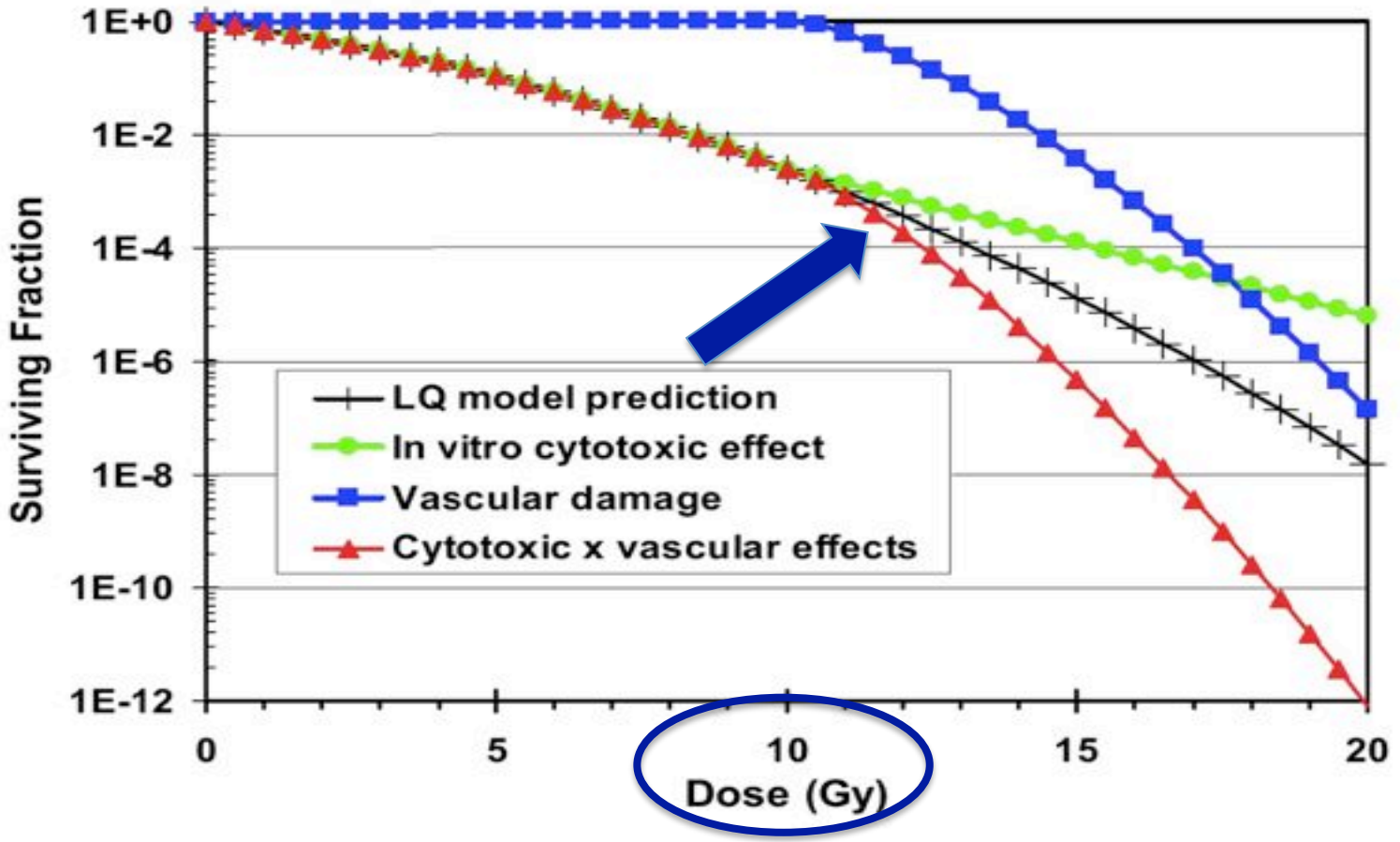
    Senthi S. et al, Lancet Oncol 2012; Senthi S. et al, J Thorac Dis 2013
- Pulmonary oligo-metastatic disease
  - 2nd/3rd rounds of SABR delivered in selected pts

    Ashworth A et al, Lung Cancer 2013

The challenge of thoracic re-irradiation

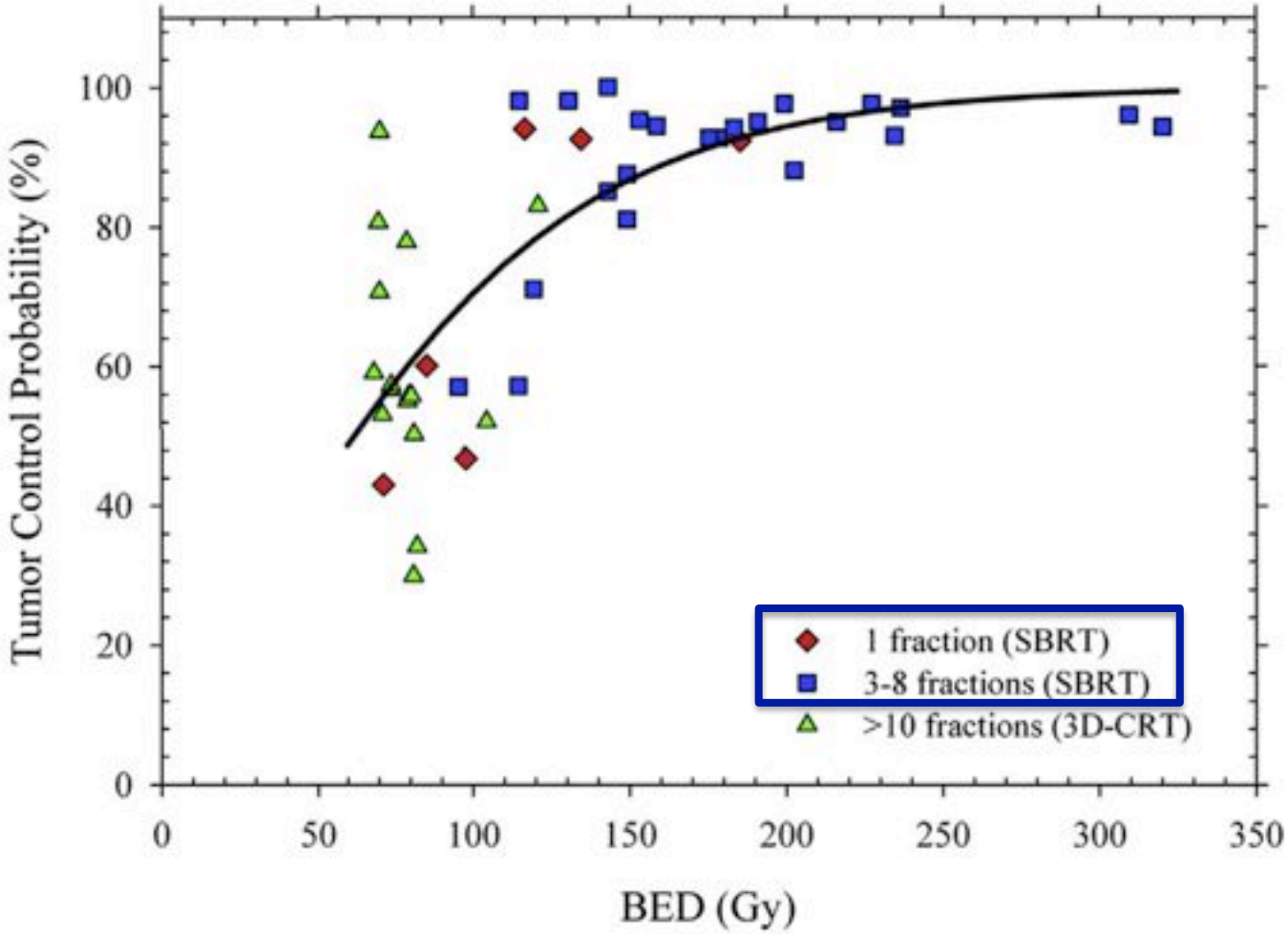
- High-dose re-irradiation is feasible
  - improved treatment planning & delivery techniques
  - conventionally fractionated and stereotactic series have been published
- This is not palliative care!
  - If $EQD_2 \geq 45$ Gy are given

SABR: a bigger hammer



Kirkpatrick JP et al, Semin Radiat Oncol 2008

Dose Escalation, Not "New Biology," Can Account for the Efficacy of Stereotactic Body Radiation Therapy With Non-Small Cell Lung Cancer



Metha N et al, Practical Radiat Oncol 2012
Brown JM et al, Int J Radiat Oncol Biol Phys 2013

Outline

- Stereotactic re-irradiation in NSCLC
  - **is it safe?**
  - **is it effective?**
- Considerations for clinical practice
- Future directions

SABR series: a lot of caveats!

- Limited evidence available
  - retrospective; small no. of patients; selection bias; short follow-up, & more
- Technical heterogeneity
  - size & location of targets, fx schemes, prescription isodose, PTV margins, & more
- Dose conversion from SABR to 2-Gy equivalents: reliable?

Author	N	Med FU	≥ G3 Toxicity (%)
Peulen 2011 Karolinska	29	12 mo.	G3 pneumonitis: 20% G4-G5 13% (all central): - 1 pt G4 tracheal fistula - 3 pts G5 bleeding
Liu 2012 MDACC	72	16 mo.	G3 pneumonitis: 19% - 1 pt G5 pneumonitis
Trakul 2012 Stanford	15	15 mo.	None
Meijneke 2013 Rotterdam	20	12 mo.	None
Reynold 2013 MSKCC	39	12 mo.	G3 pneumonitis: 5% G4 skin: 2.5%
Kilburn 2014 Wake Forest	33	17 mo.	G3 pneumonitis: 3% - 1 pt G5 aorto-esoph. fistula
Trovo' 2014 Aviano	17	18 mo.	G3 pneumonitis: 23% - 1 pt G5 pneumonitis - 1 pt G5 bleeding

15 mo. median ≥G3 toxicity: 7.5%

Dosimetric predictors of toxicity

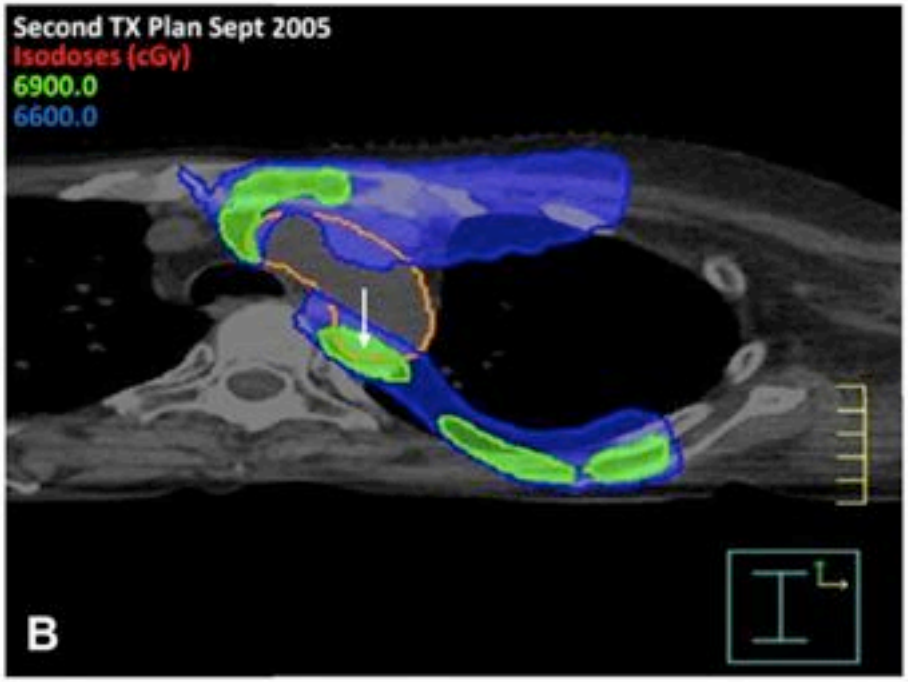
- ≥ G3 pneumonitis when
  - ECOG PS = 2-3 (pre SABR)
  - $FEV_1 \leq 65\%$ (pre SABR)
  - V20 ≥ 30% in the composite plan

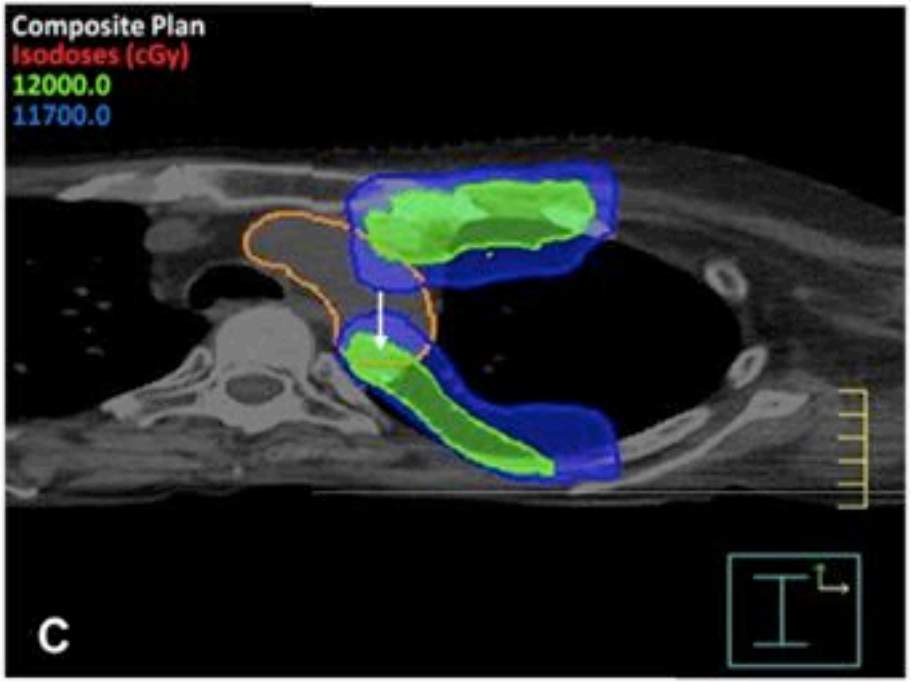
Liu H et al, Int J Radiat Oncol Biol Phys 2012

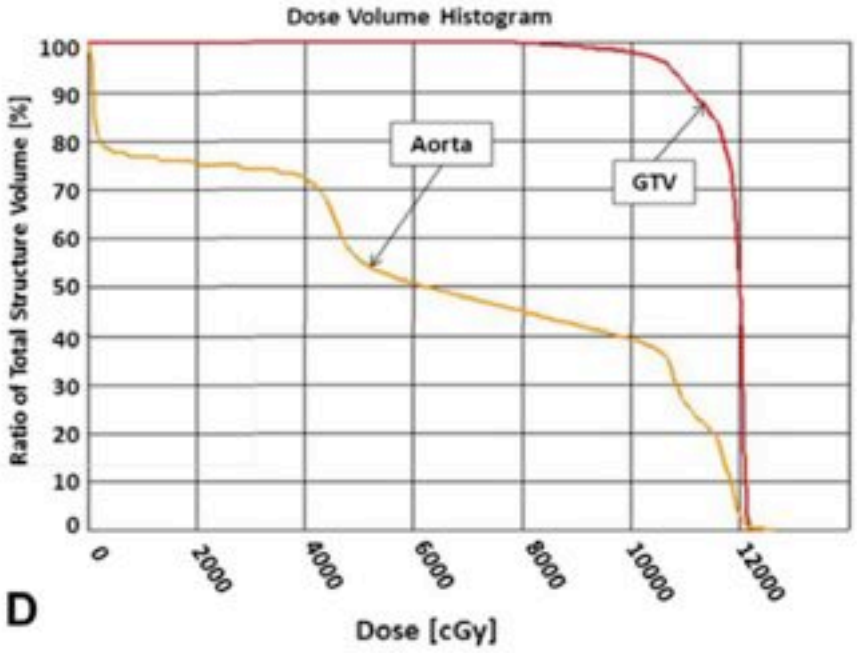
- 25% risk of G5 bleeding when
  - composite dose ≥ 120 Gy to 1 cc of the aorta

Evans JD et al, Radiother Oncol 2013


First TX Plan Jan 2004
Isodoses (cGy)
5040.0
3960.0
A


Second TX Plan Sept 2005
Isodoses (cGy)
6900.0
6600.0
B

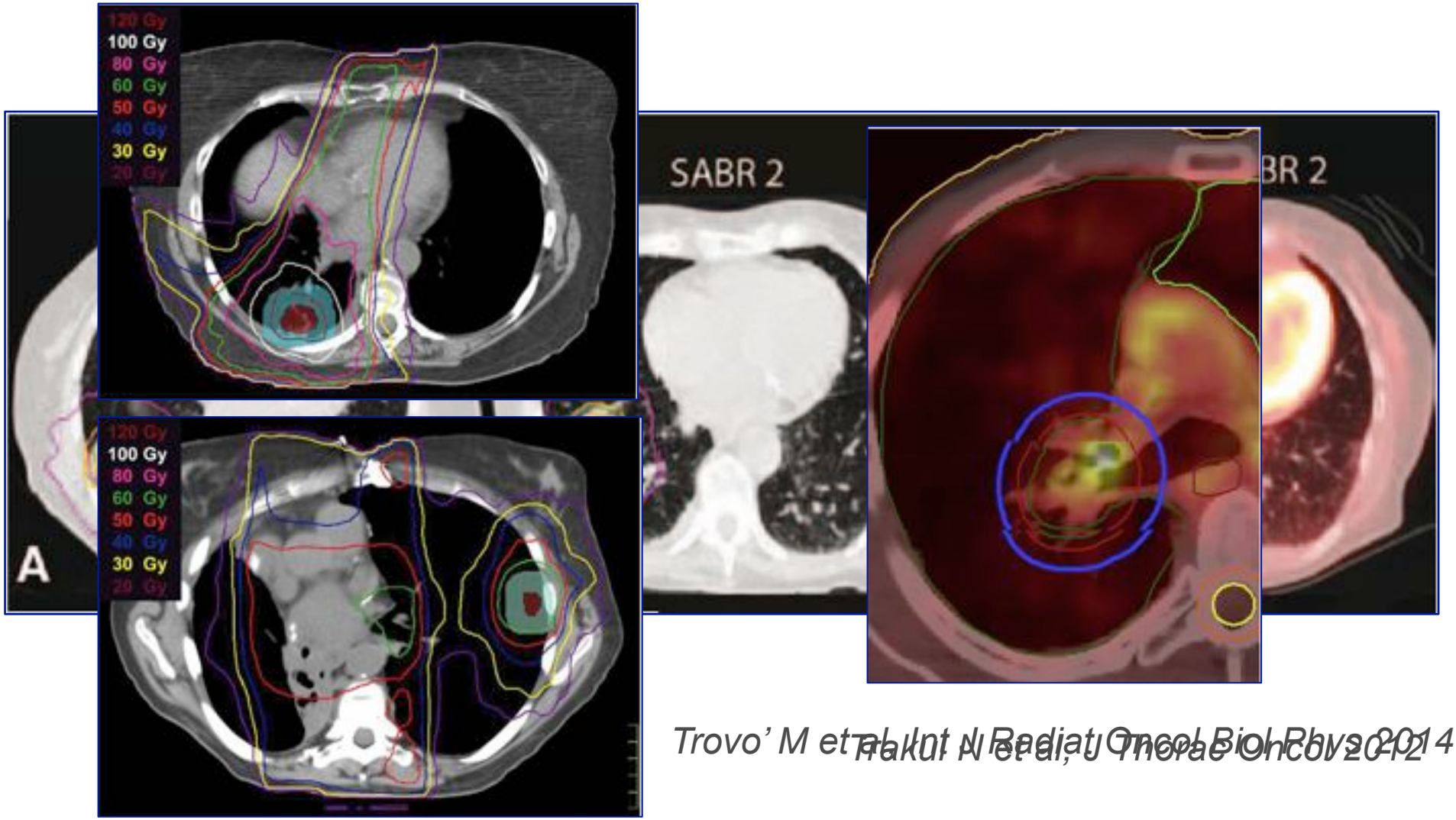

Composite Plan
Isodoses (cGy)
12000.0
11700.0
C


Dose Volume Histogram
Ratio of Total Structure Volume [%]
100
90
80
70
60
50
40
30
20
10
0
Aorta
GTV
0
2000
4000
6000
8000
10000
12000
Dose [cGy]
D

Is it safe?

- **Large uncertainty** about the tolerance of OAR's to high-dose retreatment
- **Possibly safe** when conservative constraints are used
- **Repair capacity** of late responding tissues?
- Influence of **comorbidites**? chemotherapy?

What about efficacy?



Trovo' M et al, Int J Radiat Oncol Biol Phys 2014

Takur N et al, J Thorac Oncol 2012

Kelly P et al, Int J Radiat Oncol Biol Phys 2010

Author	N	Interval	Local control (1 year)	Med OS	Med PFS
Peulen 2011 Karolinska	29	14 mo.	52% *(@ 5 mo.)*	19 mo.	NS
Liu 2012 MDACC	72	21 mo.	95%	26 mo.	12 mo.
Trakul 2012 Stanford	15	16 mo.	65%	NS	NS
Meijneke 2013 Rotterdam	20	17 mo.	75%	15 mo.	10 mo.
Reyngold 2013 MSKCC	39	37 mo.	77%	22 mo	13 mo.
Kilburn 2014 Wake Forest	33	18 mo	67%	21 mo	16 mo.
Trovo' 2014 Aviano	17	18 mo	86%	19 mo.	NS
		18 mo.	**75%**	**20 mo.**	**12,5 mo.**

Is it effective?

- **Encouraging data regarding local control**
  - lower with conventionally fx retreatment (≤55%)
  - no data on QoL & symptoms control
- **OS: unclear benefit**
  - long interval between primary RT and ReRT
  - most pts receive sequential CT
- **PFS: possible benefit**
  - median PFS: 12.5 months
  - deferral of CT: true endpoint!

Considerations for clinical practice

1) Patients' selection

- PS 0 – 1
- cM0 at whole body scan, FDG-PET
- biopsy confirmation whenever possible
- time interval from first RT $\geq$ 9 mo.

2) Dose prescription

- choice of dose/fx according to size & location
- max diameter 4 cm?
- peripheral vs central; recurrence vs 2nd primary?

Considerations for clinical practice

3) Account accurately for the primary treatment
   - in-field vs out-of-field lesion?
   - convert to 2-Gy equivalents
   - assess degree of PTV and dosimetric overlap
   - rigid & deformable registration for cumulative doses

4) Be cautious!
   - try to keep OAR's below constraints of primary tx
   - see what others have published
   - **inform the patient about the lack of evidence!**

Future directions

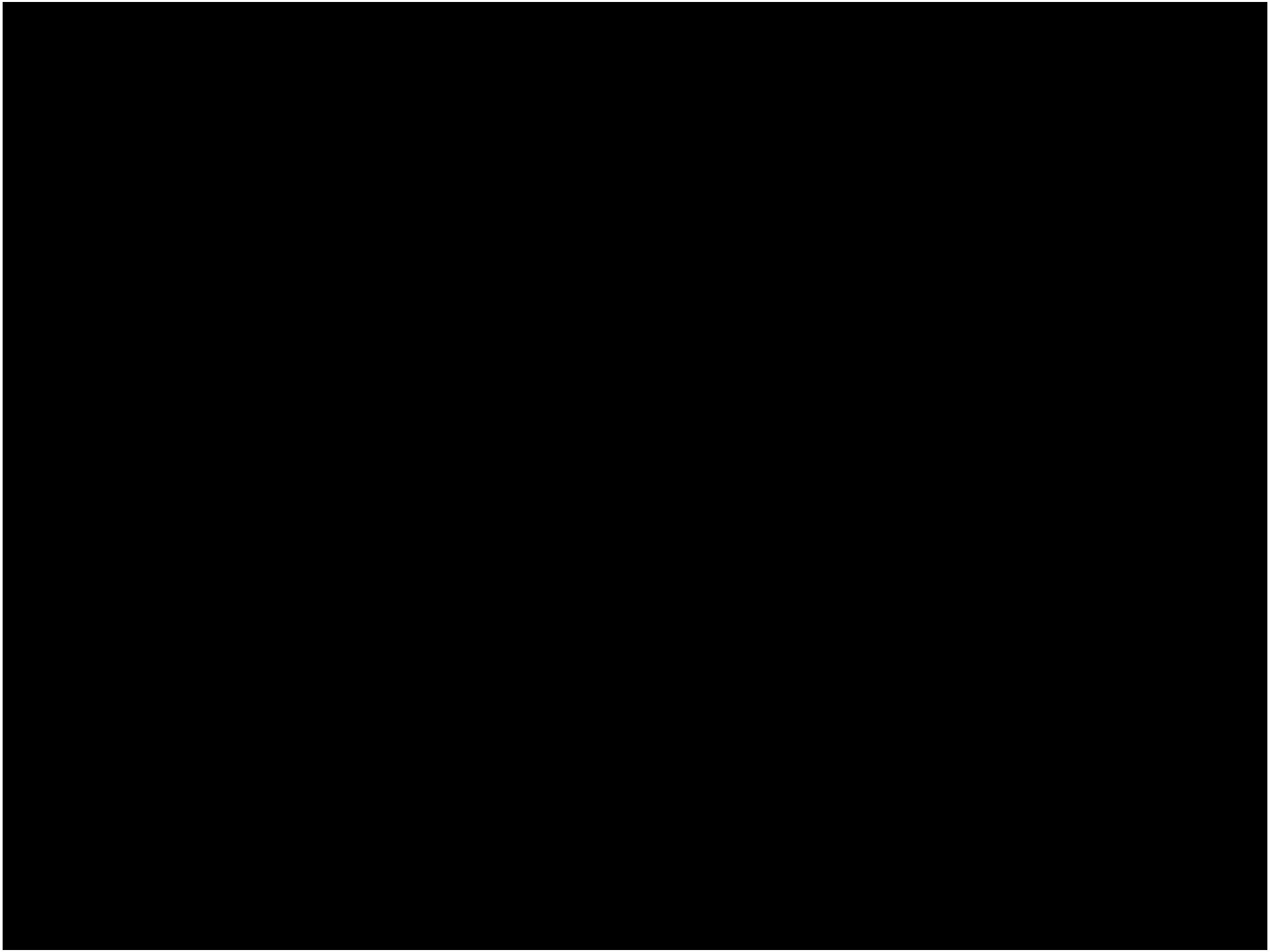
- Clear need of prospective data
- Main endpoints should be:
  - correlate cumulative DVH parameters to acute & late toxicities
  - evaluate dose-response relationship for OAR's and targets in the re-irradiation setting
  - in progress: dutch phase II trial (RETHO protocol)

- Proton beam therapy
  - potential therapeutic option (MDACC series)

McAvoy S et al, Radiother Oncol 2013

Summary

- **Selected patients may benefit from high-dose thoracic re-irradiation**
- **Overall toxicity seems acceptable – but higher risk for central tumors**
- **Highly individualized risk – benefit decision**
- **Reliable normal tissue tolerance parameters remain to be defined prospectively**



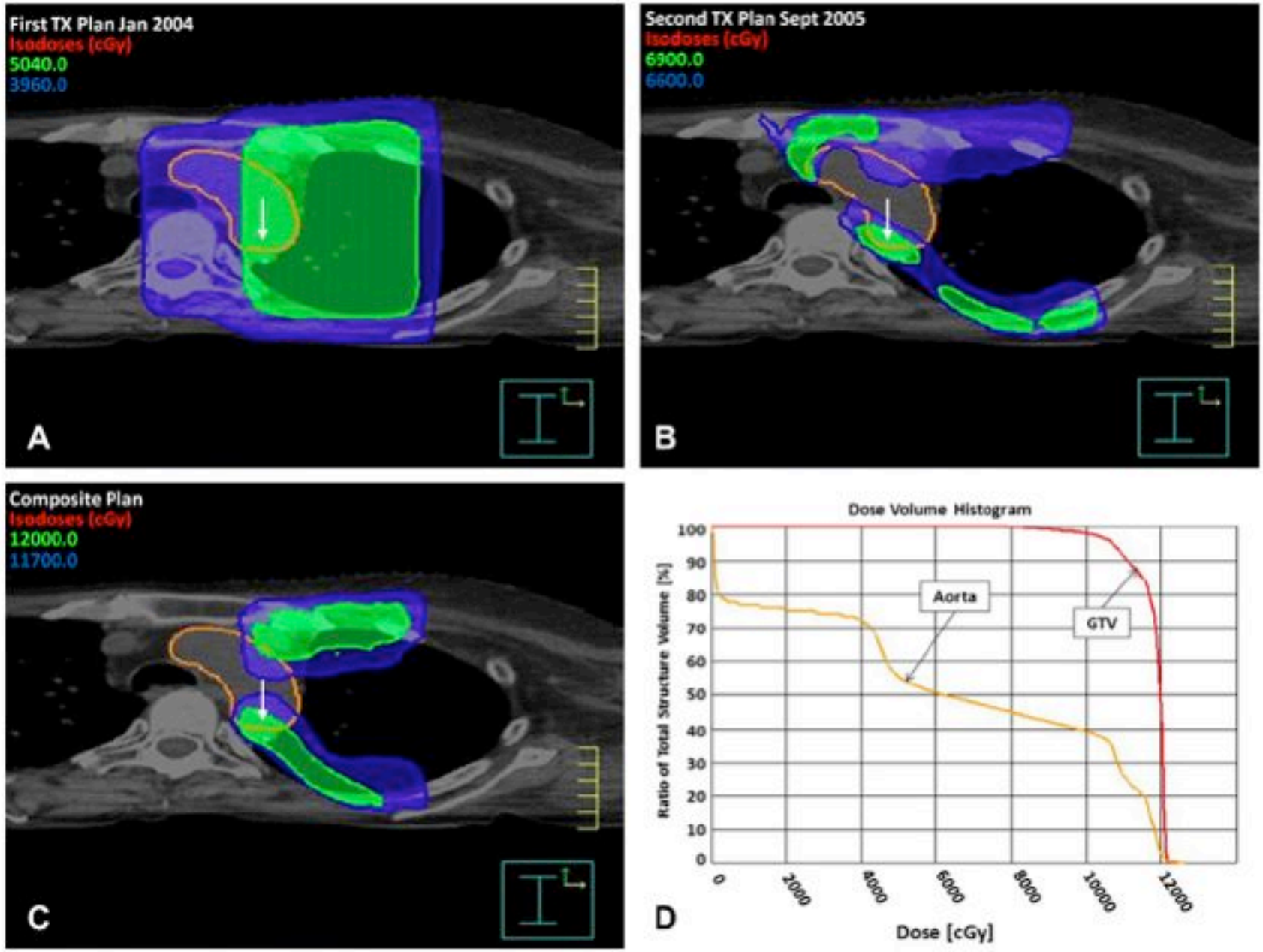
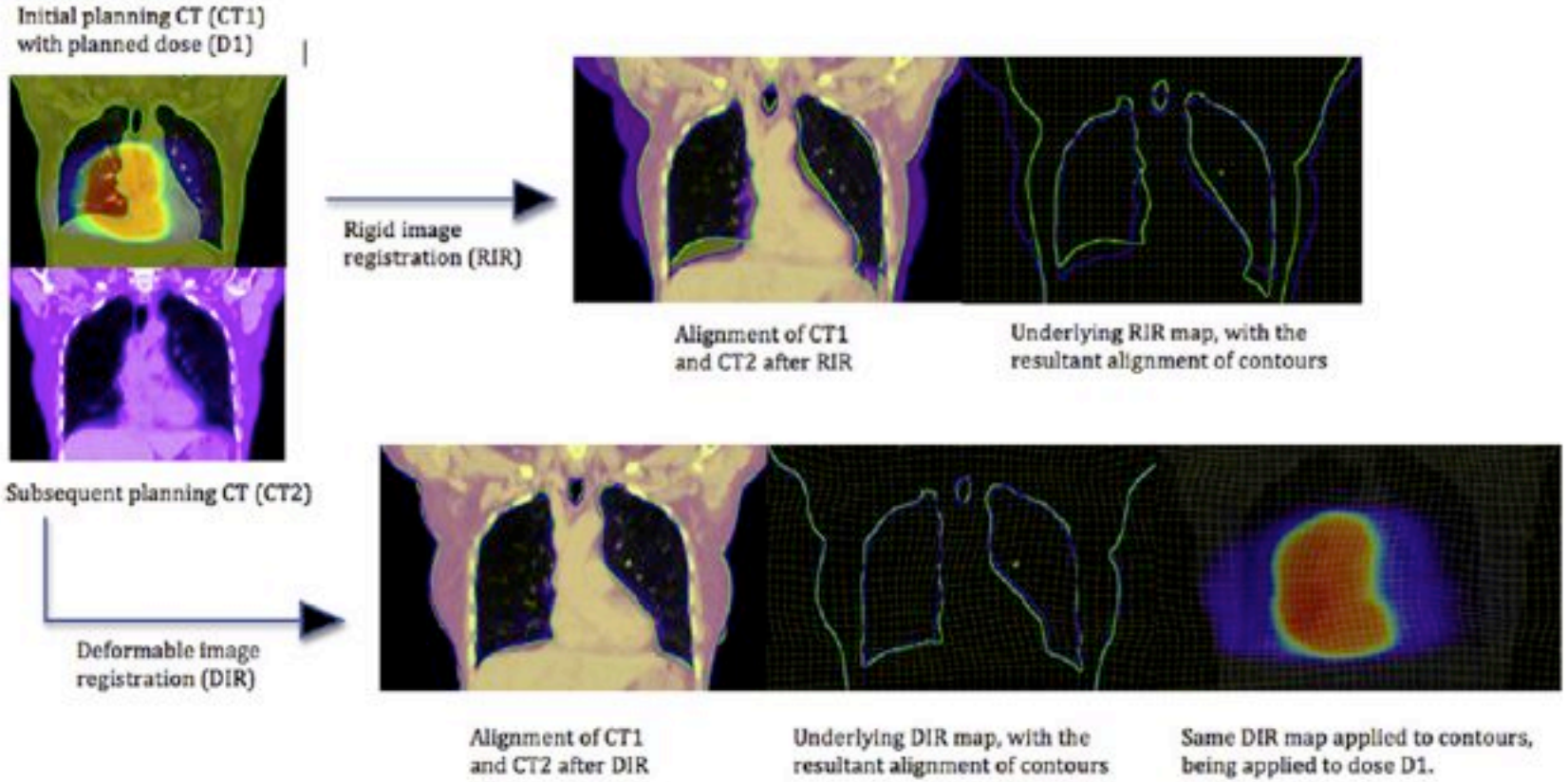


Fig. 2. Axial views of thoracic treatment plans for a woman who died of radiation-induced aortic damage. The aorta is contoured in yellow. (A) The initial plan involved treatment to 50.4 Gy (green isodose line; blue isodose line is 39.6 Gy). (B) The second plan involved treatment to 66.0 Gy (blue isodose line; green isodose line is 69.0 Gy). (C) The composite plan illustrates a green hot spot in the aorta (arrow) that received 120.0 Gy. (D) Dose volume histogram for the composite plan. GTV, gross tumor volume.



gid (RIR) and deformable (DIR) image registration and the resulting registration maps being applied to manual clinician contours and planned radiotherapy doses.

Comment & clinical practice

- registration

Author	N	Dose/fx	PTV (cc)	Med FU	≥ G3 Toxicity
Kelly 2010 MDACC	36	50 Gy/4fx	Med size 1.7 cm	15 mo.	G3 pneumonitis: 28% G3 esophagitis: 8%
Peulen 2011 Karolinska	29	# doses (15x2, 8x5)	Med 76 cc	12 mo.	G3 pneumonitis: 20% G4-G5 13% (all central): - 1 pt G4 tracheal fistula - 3 pts G5 bleeding
Liu 2012 MDACC	72	50 Gy/4fx	Med 46 cc	16 mo.	G3 pneumonitis: 19% - 1 pt G5 pneumonitis
Trakul 2012 Stanford	15	# doses (20x1, 8x5)	Med 31 cc	15 mo.	None
Meijneke 2013 Rotterdam	20	# doses (10-12x5)	Med 69,5 cc	12 mo.	None
Reynold 2013 MSKCC	39	# doses (12x4)	Med 67 cc	12 mo.	G3 pneumonitis: 5% G4 skin: 2.5%
Kilburn 14 Wake Forest	33	# doses (5 x 10, 20x1)	Average 2.5 cm	17 mo.	G3 pneumonitis: 3% - 1 pt G5 aorto-es. fistula
Trovo' 2014 Aviano	17	30 Gy/5-6 fx	NS	18 mo.	G3 pneumonitis: 23% - 1 pt G5 pneumonitis - 1 pt G5 bleeding

Author	N	Interval	Med FU	Location	Local control	Med OS	Med TTP
Kelly 2010	36	22 mo.	15 mo.	30% in field 70% out of field	92% 2 year	2-y 59%	2-y PFS 26%
Peulen 2011	29	14 mo.	12 mo.	65% perip 35% central	52%	19 mo.	NS
Liu 2012	72	21 mo.	16 mo.	94% oerip 6% central	95%	2-y 74%	2-y PFS 41%
Trakul 2012	15	16 mo.	15 mo.	65% perip 35% central	65% 1 year	1-y 80%	1-y PFS 58%
Meijneke 2013	20	17 mo.	12 mo.	NS	75%	15 mo. 2-y 33%	1-y DFS 50%
Reyngold 13	39	37 mo.	12 mo.	NS	77% 1 year 64% 2 year	22 mo	13 mo.
Kilburn 2014	33	18 mo	17 mo.	48% perip 52% central	67% 2 year	21 mo	16 mo.
Trovo	17	18 mo	18 mo.	100% central	86% 1 year	19 mo. 2 y 29%	NS