RE-IRRADIATION OF VERTEBRAL BODIES

Dorota Gabryś MD, PhD, MSc

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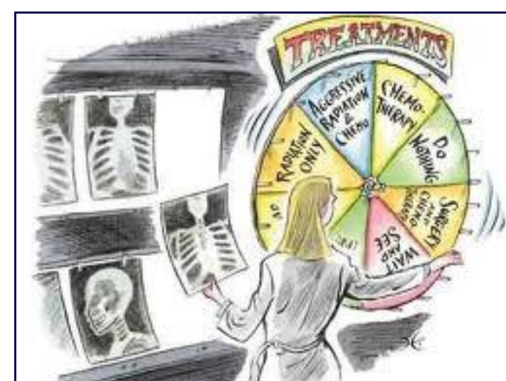
Sweden

MARIA SKLODOWSKA-CURIE MEMORIAL
CANCER CENTER AND INSTITUTE OF ONCOLOGY
GLIWICE BRANCH

Vertebral metastases

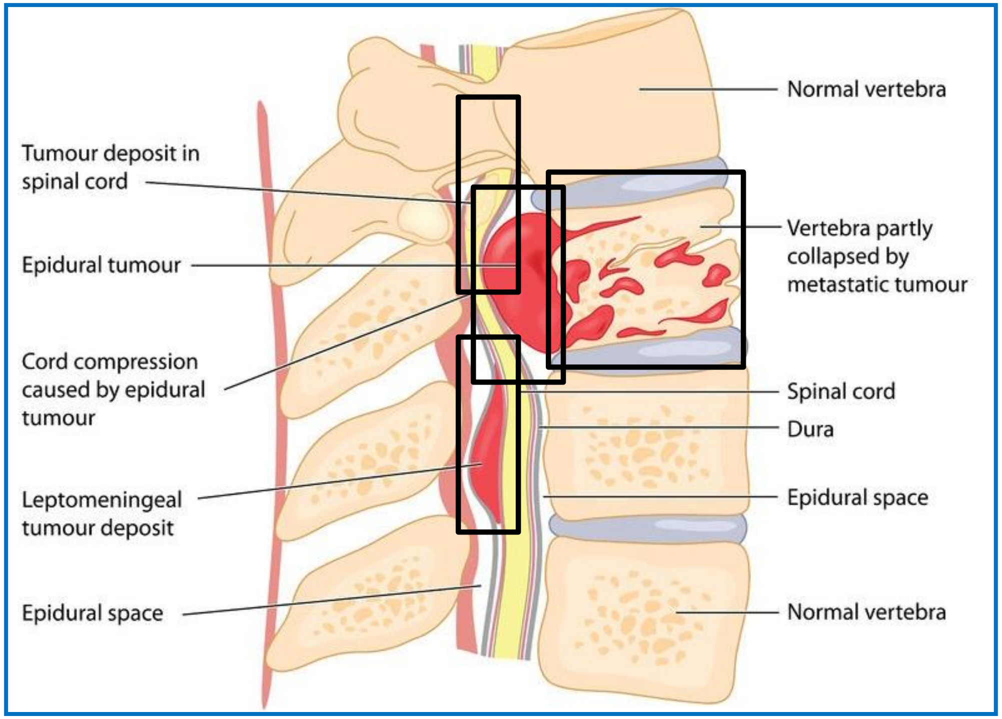
- Improvement in clincal care and therapy – patients are diagnosed and living longer
- 60–70% of patients with systemic cancer will have spinal metastasis
- 20% complete response after EBRT and partial responce 60%
- 20% after eg 8 Gy will rquire re-irradiation due to pain progression,
- Longer lenght patients survivals eg 2 yers 50-80% will have tumor progression



Tumour of vertebral bodies

- Why they are important?

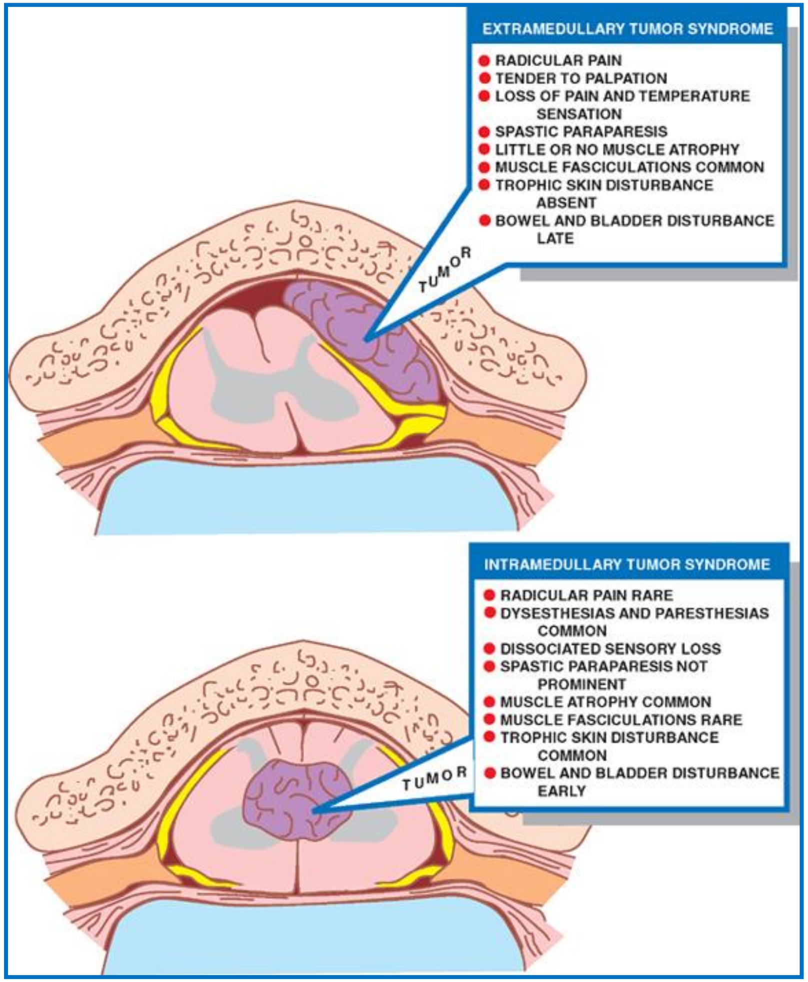
- Can involve the
  - bone
  - epidural space
  - leptomeninges
  - spinal cord



www.spineuniverse.com

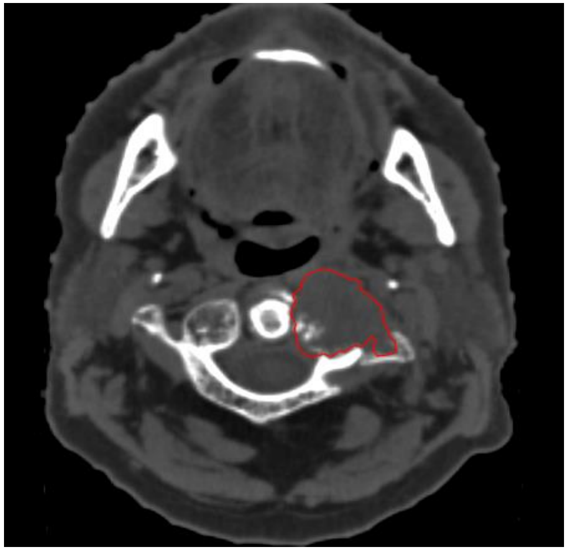
Tumour of vertebral bodies

- Pain
- Mechanical instability
- Fracture
- Radiculopathy
- Neurological dysfunction related to malignant epidural spinal cord compression



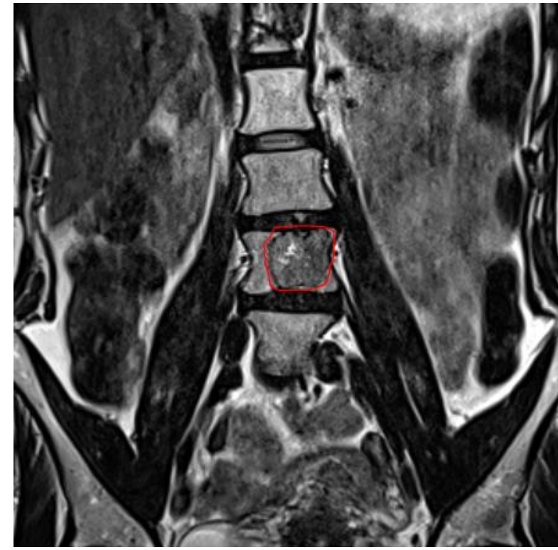
www.neupsykey.com

Imaging of vertebral metastases

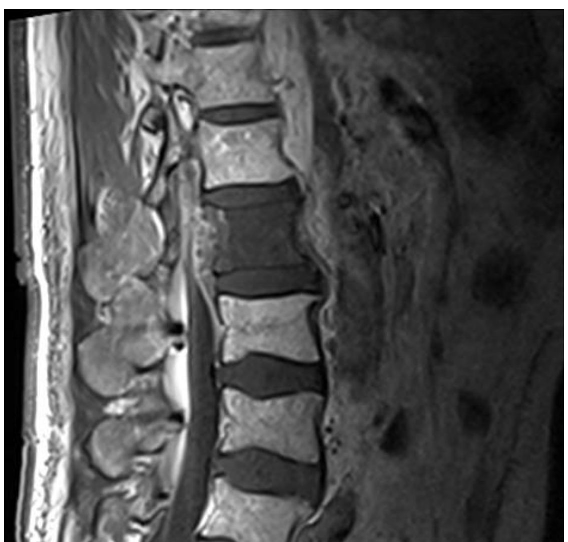


CT, Lung cancer

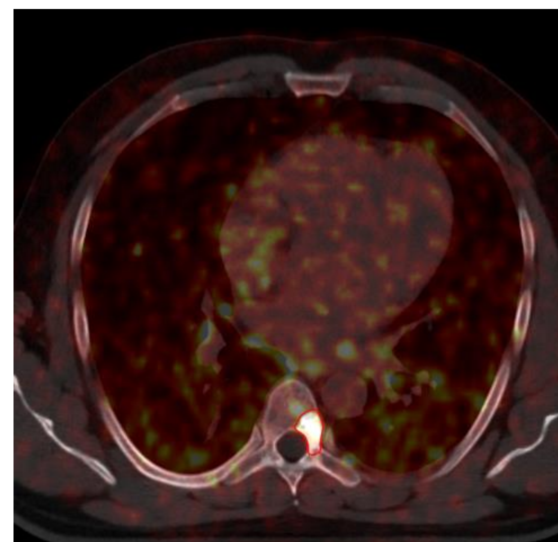
CT, Breast cancer



MR T2, Kidney cancer



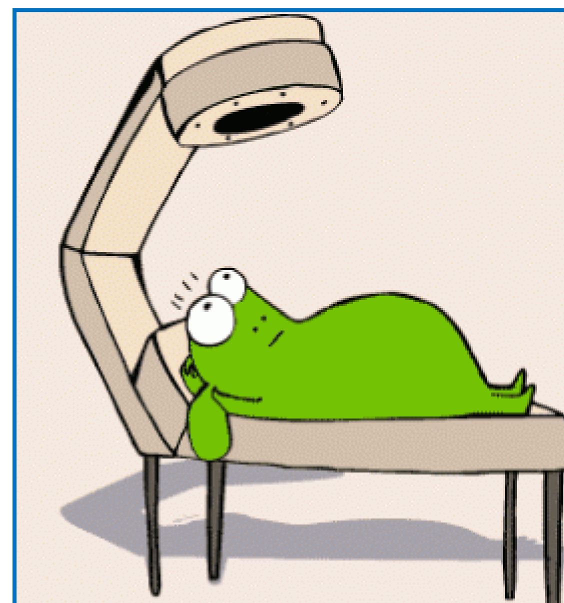
MR T1, Rectum cancer



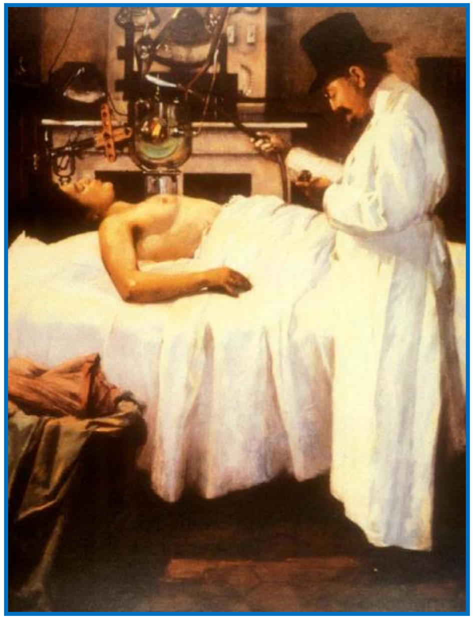
PETCT, Prostate cancer

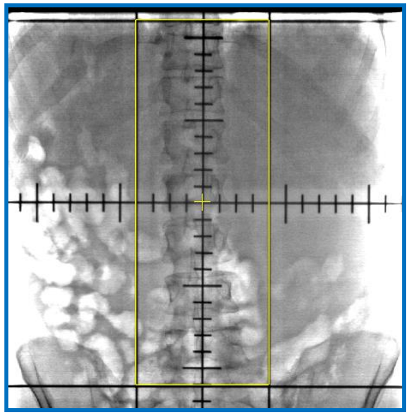
Vertebral bodies radiotherapy

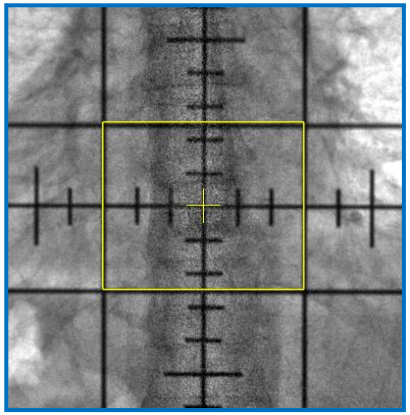
- Pain and other symptoms relief
- Preventing spine tumors growth
- As an option for surgery
- Shrinking tumors for easier removal
- Cure the patient



Technical improvements







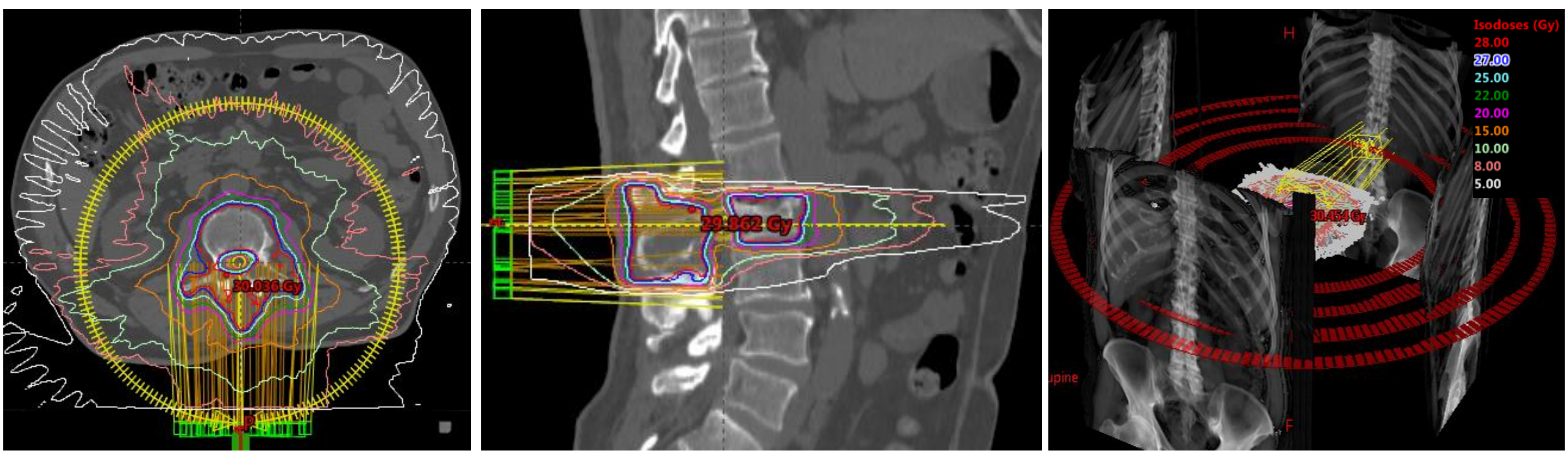
Re-irradiation of bone metastases

- 850 patients (237 spine): 8 Gy/1 fx vs 20 Gy/5 fx
- Primary RT: 6, 7, 8 Gy/1 fx, 18 Gy/4 fx, 20 Gy/5 fx, 24 Gy/6 fx, 27 Gy/8 fx, 30 Gy/10 fx
- Interval at least 4 weeks, 2 month assesement after re-irradiation
- 118 (28%) 8 Gy vs 135 (32%) 20 Gy had an overall pain response to treatment
- Pathological fractures 30 (7%) 8 Gy and 20 (5%) 20 Gy
- Spinal cord/cauda equina compressions 7 (2%) 8 Gy vs 2 (<1%) 20 Gy

Chow et al. Lancet Oncol 2014

Vertebral body radiosurgery

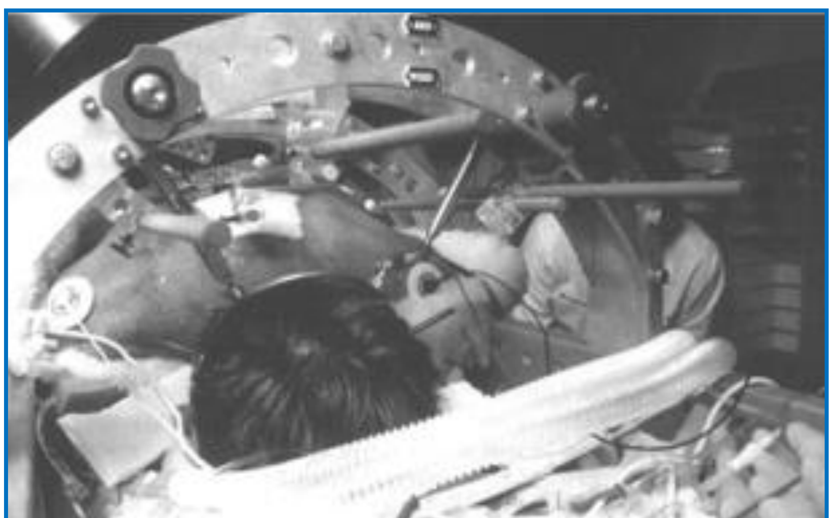
- Fewer fractions, shorter treatment, more convenients for patient
- Highier doses are potentialy more effective
- High precision – less normal tissue irradiation
- Small margins, large set up errors with inacurate positioning
- High sensivity of spinal cord to large fractions

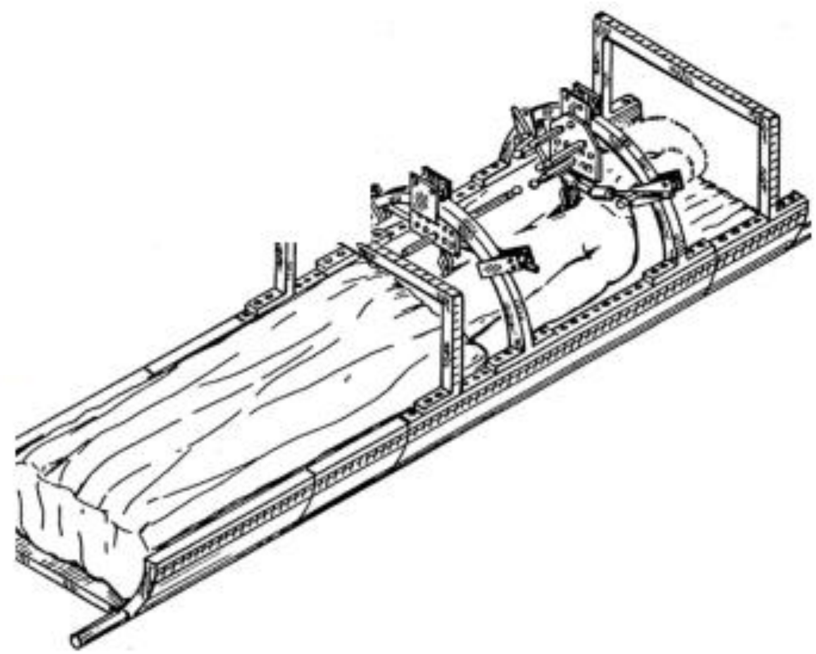


Prostate cancer patient with whole vertebral bone and lymph node metastases August 2018

1995 – First spinal radiosurgery

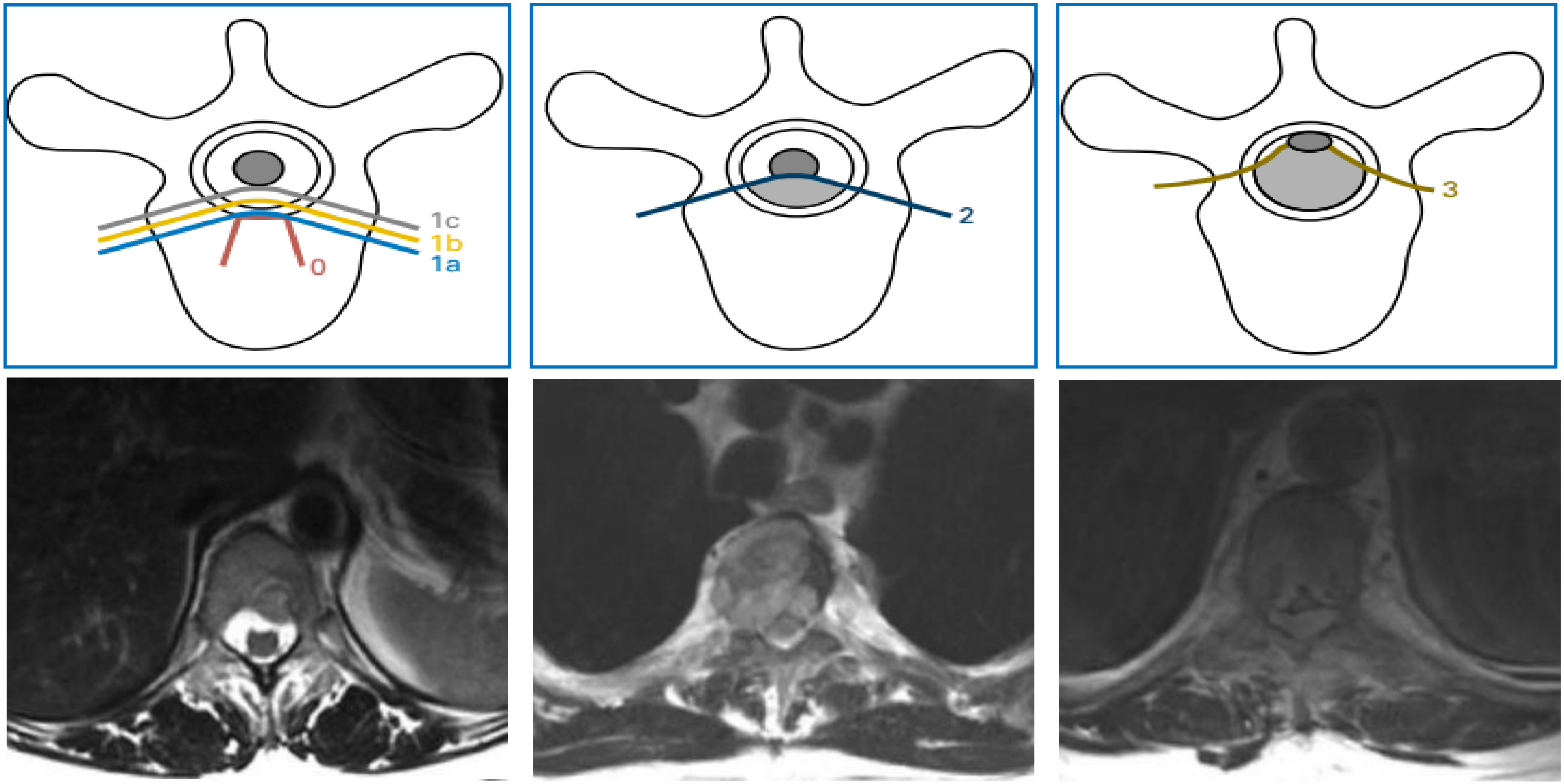
- Linac delivery with circular collimators
- System accuracy < 2mm
- 8-10 Gy with no portion of cord receiving > 3 Gy





Hamilton et al. Neurosurgery 1995

The Epidural Spinal Cord Compression (ESCC) scale



- Grade 0 Bone-only disease
- Grade 1a Epidural impingement, without deformation of thecal sac
- Grade 1b Deformation of thecal sac, without spinal cord abutment
- Grade 1c Deformation of thecal sac, with spinal cord abutment, without cord compression
- Grade 2 Spinal cord compression, with CSF visible around the cord
- Grade 3 Spinal cord compression, no CSF visible around the cord

Bilsky et al. J Neu Spine 2010
Laufer et al. Oncologist 2013

Neurologic, Oncologic, Mechanical, Systemic (NOMS) decision framework

Neurologic	Oncologic	Mechanical	Systemic	Decision
Low-grade ESCC + no myelopathy	Radiosensitive	Stable		cEBRT
	Radiosensitive	Unstable		Stabilization followed by cEBRT
	Radioresistant	Stable		SRS
	Radioresistant	Unstable		Stabilization followed by SRS
High-grade ESCC ± myelopathy	Radiosensitive	Stable		cEBRT
	Radiosensitive	Unstable		Stabilization followed by cEBRT
	Radioresistant	Stable	Able to tolerate surgery	Decompression/stabilization followed by SRS
	Radioresistant	Stable	Unable to tolerate surgery	cEBRT
	Radioresistant	Unstable	Able to tolerate surgery	Decompression/stabilization followed by SRS
	Radioresistant	Unstable	Unable to tolerate surgery	Stabilization followed by cEBRT

- Radiosensitive: seminoma, lymphoma, breast, ovarian, prostate
- Radioresitant: sarcoma, melanoma, renal, thyroid, gastrointestinal, NSCLC

Laufer et al. Oncologist 2013

International Sterotactic Radiosurgery Society practice guidelines

- Following cEBRT, retreatment with SBRT is a recomended therapeutic option in suitable patients based on multidisciplinary assesement

  level of evidence III

- Following SBRT, retreatment with SBRT is a recomended therapeutic option in suitable patients based on multidisciplinary assesement

  level of evidence III

- For patients with clinical features concerning for malignant epidural spinal compression, mechanical instability, or baseline vertebral body compression, fracture, the radiation oncologist should consult a spine surgeon before the patients undergoes SBRT

  level of evidence II

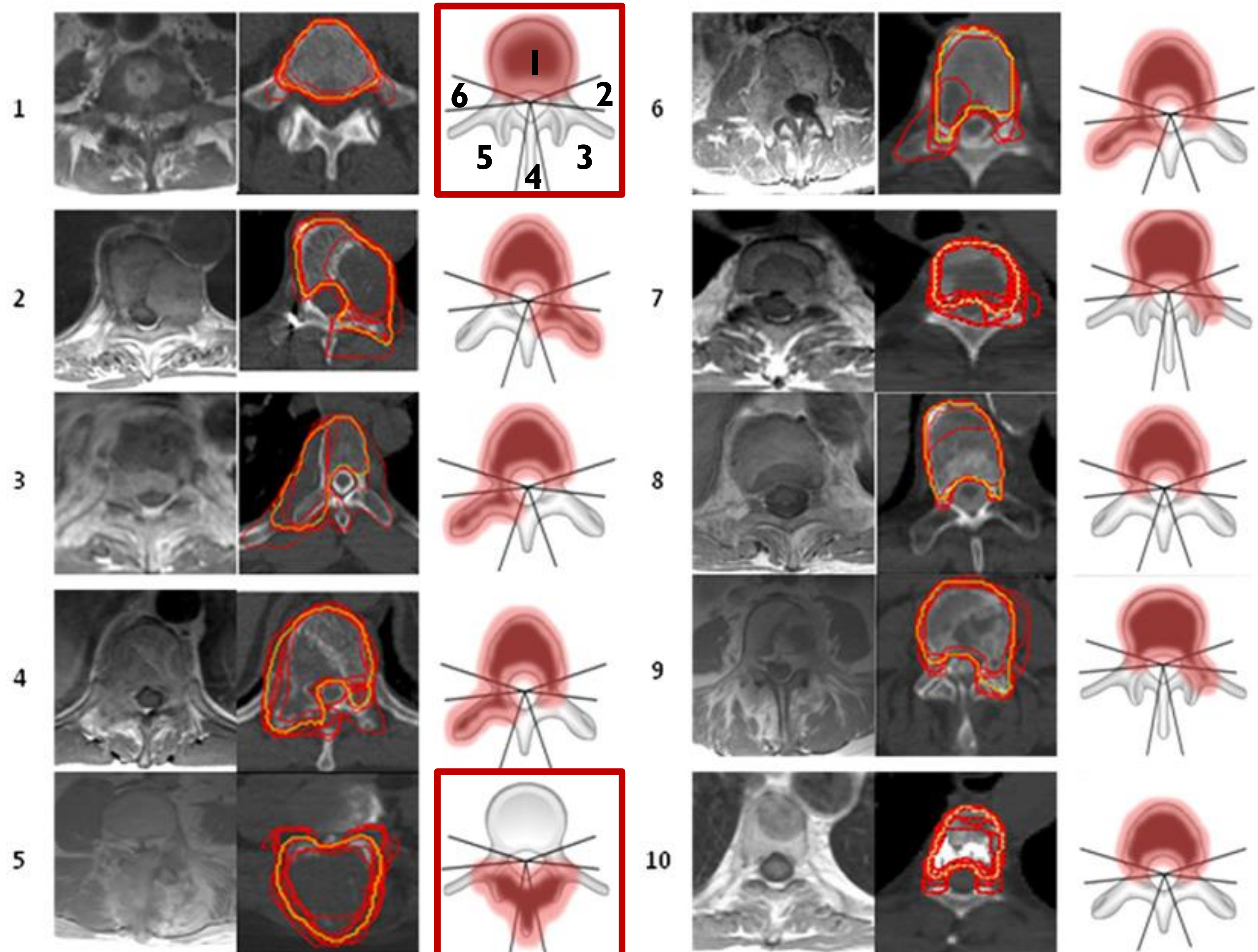
Myrehaug et al. J Neurosurg Spine 2017

Treatment Planning

- Where is the target?
- What kind of toxicity we have?
- What was the primary total dose and dose per fraction?
- What kind of toxicity we expect?
- What was the time between irradiations?
- What we can achieve?

- ….Do it carefully

Volume delineation in spinal radiosurgery



Red indicates contours and orange indicates consensus

Cox et al. IJROBP 2012

Volume delineation in spinal radiosurgery

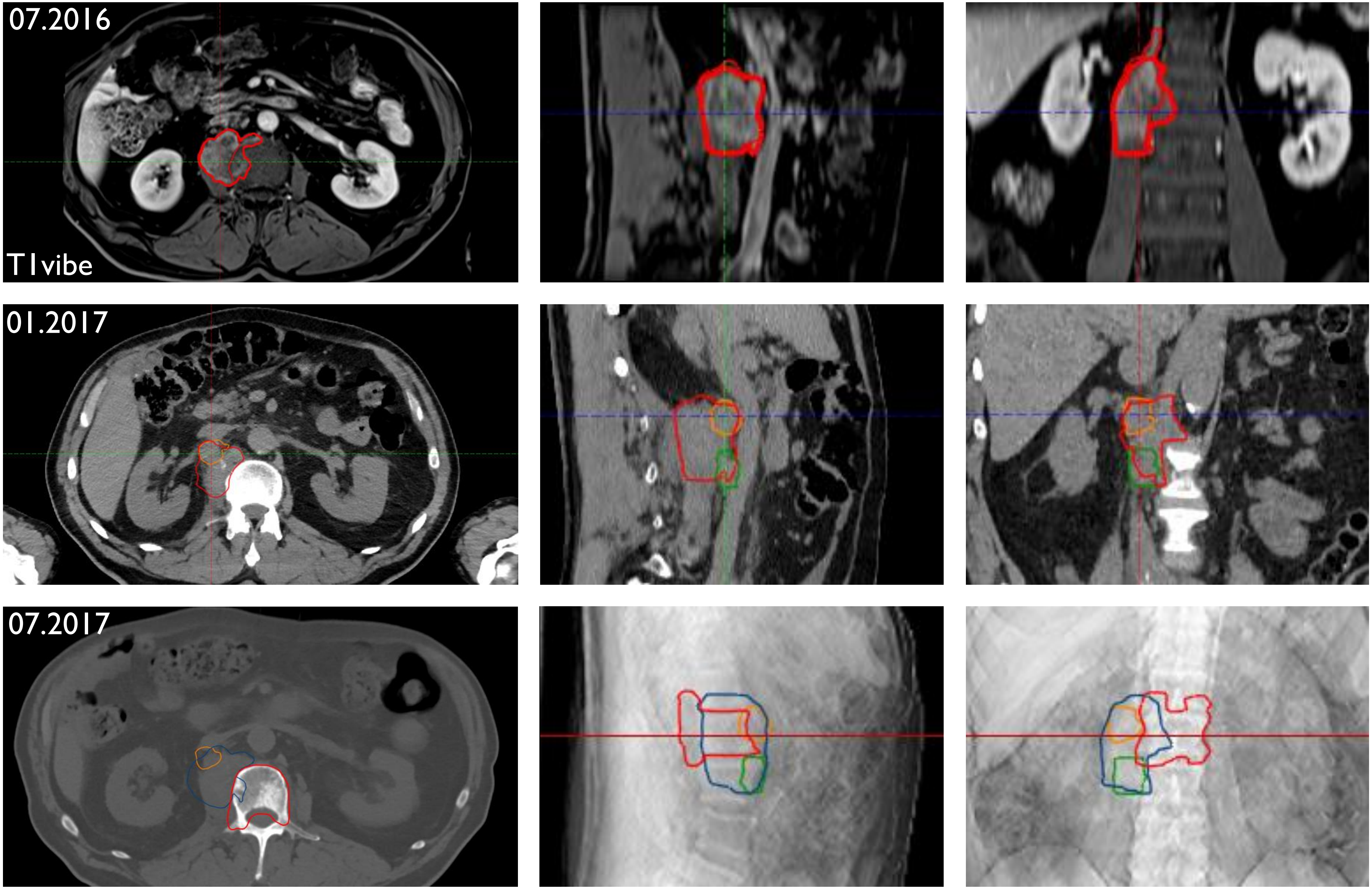
Summary of contouring guidelines for GTV, CTV, and PTV in spinal stereotactic radiosurgery

Target volume	Guidelines
GTV	• Contour gross tumor using all available imaging • Include epidural and paraspinal components of tumor
CTV	• Include abnormal marrow signal suspicious for microscopic invasion • Include bony CTV expansion to account for subclinical spread • Should contain GTV • Circumferential CTVs encircling the cord should be avoided except in rare instances where the vertebral body, bilateral pedicles/lamina, and spinous process are all involved or when there is extensive metastatic disease along the circumference of the epidural space without spinal cord compression
PTV	• Uniform expansion around CTV • CTV to PTV margin $\leq$3 mm • Modified at dural margin and adjacent critical structures to allow spacing at discretion of the treating physician unless GTV compromised • Never overlaps with cord • Should contain entire GTV and CTV

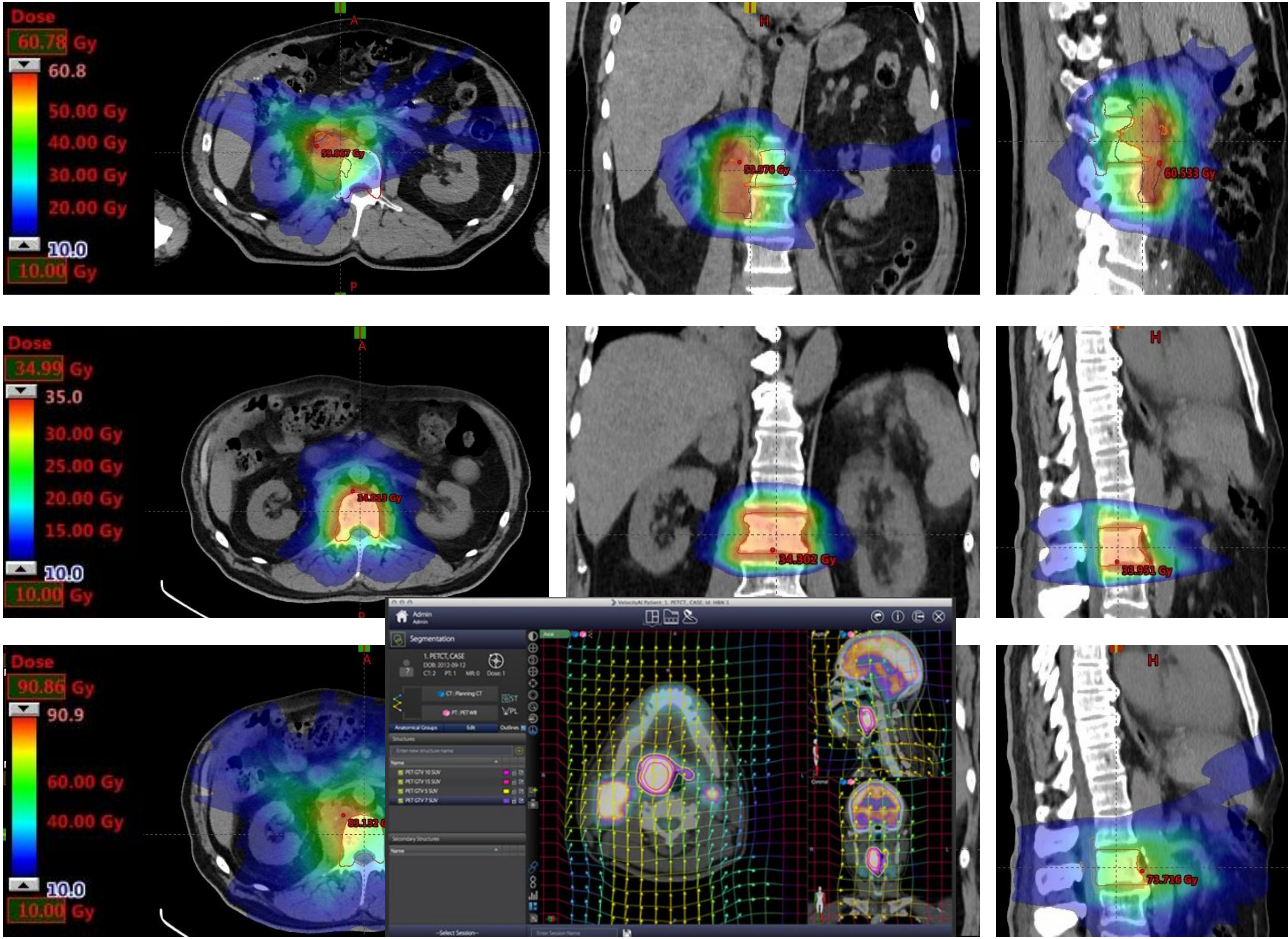
Abbreviations: CTV = clinical target volume; GTV = gross tumor volume; PTV = planning target volume.

Cox et al. IJROBP 2012

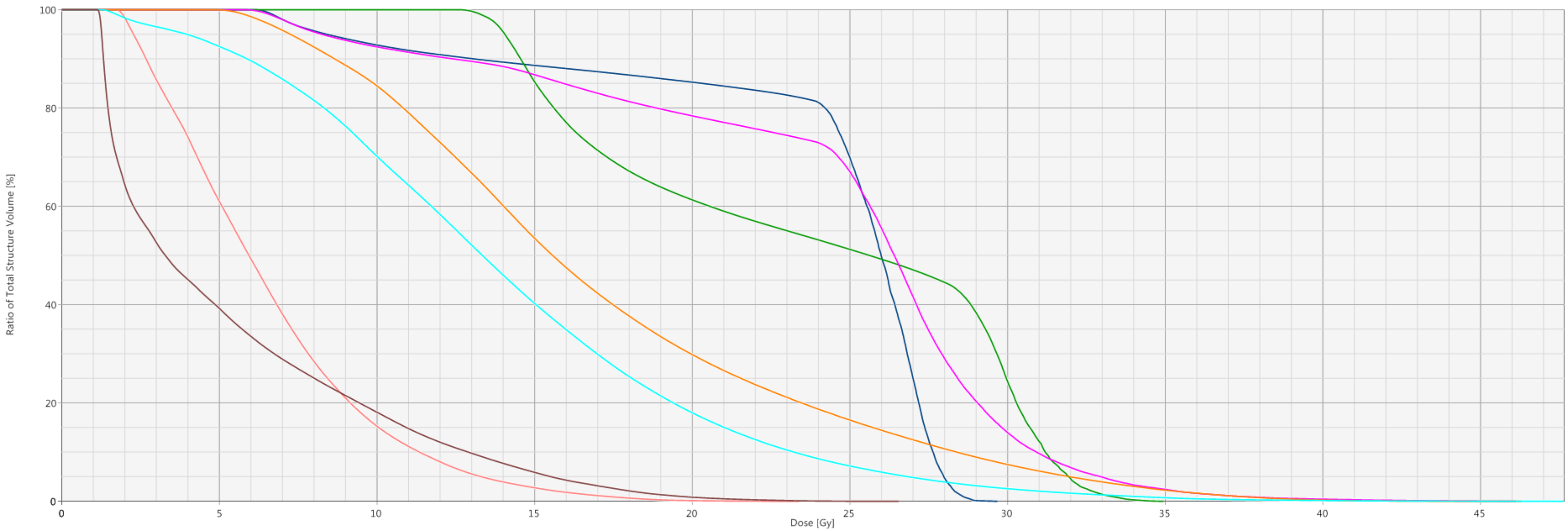
Volume delineation



What about the dose?


Dose
60.78 Gy
60.8
50.00 Gy
40.00 Gy
30.00 Gy
20.00 Gy
10.0
10.00 Gy
A
P
H
59.976 Gy
60.533 Gy
Dose
34.99 Gy
35.0
30.00 Gy
25.00 Gy
20.00 Gy
15.00 Gy
10.0
10.00 Gy
34.302 Gy
33.951 Gy
Dose
90.86 Gy
90.9
60.00 Gy
40.00 Gy
10.0
10.00 Gy
73.716 Gy
Admin
Segmentation
1. PETCT, CASE

Combined dose to the normal tissue



Show DVH	Structure	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [Gy]	Max Dose [Gy]	Mean Dose [Gy]
☑	SpinalCord	3.6	100.0	99.9	6.188	29.684	23.964
☑	CaudaEquina	2.5	100.0	100.8	12.678	34.979	23.689
☑	Kidney_L	274.7	100.0	100.0	1.748	23.393	6.565
☑	Kidney_R	224.1	100.0	100.1	4.777	46.331	17.190
☑	Bowel.	2909.5	100.0	100.0	1.222	47.656	14.094
☑	Liver.	2327.5	100.0	100.0	1.134	26.586	5.392
☑	ThecalSac	20.3	100.0	99.8	5.724	46.125	24.436

Spinal cord max	7.6	5.6	18.1

Re-irradiation of vertebral bodies

Reference	Contoured spinal cord structure	Median initial dose	Retreatment SBRT total dose/fraction
Ahmed 2012	Spinal cord	30 Gy/10 fractions	24 Gy/3 (median)
Boyce-Fappiano 2017	NR	30 Gy/10 fractions	16 Gy/1
Chang 2012	Thecal sac	39 Gy (mean)	20.6 Gy/1 (median)
Choi 2010	NR	40 Gy/20 fractions	20 Gy/2 (median)
Damast 2011	NR	30 Gy/10 fractions	20 Gy/5 or 30 Gy/5
Garg 2012	Spinal cord	30 Gy/10 fractions	30 Gy/5 or 27 Gy/3
Hashim 2016	Spinal cord + spinal canal	30 Gy/10 fractions	16.6/1 or 24 Gy/3 (median)
Mahadevan 2011	Thecal sac	30 Gy/10 fractions	25—30 Gy/5 or 24 Gy/3
Sahgal 2009	Spinal cord + 1.5 mm PRV or thecal sac	36 Gy/14 fractions	24 Gy/2
Thibault 2014	Spinal cord + 1.5 mm PRV or thecal sac	30 Gy/10 fractions	24 Gy/2
Thibault 2015			
Sahgal 2012	Spinal cord + 1.5 mm PRV or thecal sac	24 Gy/2 or 24 Gy/2 + 30 Gy/10 fractions	30 Gy/4 (median)
Recommendations		20 Gy/5, 30 Gy/10, 37.5 Gy/15	
		40 Gy/20 or 45 Gy/25	
		50 Gy/25	

Myrehaug et al. Clinical Oncology 2017

Response to re-irradiation

	Study type	Targets treated	Local control	Overall survival	Pain response	VCF
Ahmed 2012	Prospective	22	1 year, 83%	1 year, 28%	NR	5%
Boyce-Fappiano 2017	Retrospective	237	1 year, 71%	NR	81%	9.3%
Chang 2012	Retrospective	54	1 year, 81%	Median, 11 months	81%	22%
Choi 2010	Retrospective	51	1 year, 73%	1 year, 68%	65%	NR
Damast 2011	Retrospective	92	1 year, 66%	Median, 13.6 months	77%	9.8%
Garg 2012	Prospective Phase I/II	63	1 year, 68%	1 year, 76%	Improvement at 6 months	NR
Hashimi 2016	Multi-institutional pooled analysis	247	1 year, 83%	1 year, 48%	74.3%	4.5%
Mahadevan 2011	Retrospective	81	1 year, 93%	Median, 11 months	79%	NR
Sahgal 2009	Retrospective	37	1 year, 82%	Median, 21 months	NR	NR
Thibault 2014	Retrospective	11	1 year, 83%	NR	NR	0
Thibault 2015	Retrospective	56	1 year, 81%	Median, 10 months	NR	NR

NR, not reported; VCF, vertebral compression fracture.

• Pooled analysis included both single and muhedian dose/fractionation is provided for both treatment options.

Myrehaug et al. Clinical Oncology 2017

No RM 1 st: EQD2 39.8 $Gy_{2/2}$ (29.0–64.5 Gy), 15 mts (5–85)

2nd: 24 Gy (10–30 Gy) in 3 (1–5) fractions

RM 1 st: EQD2 38 $Gy_{2/2}$ (18.3–52.5 Gy2), 18 mts (11–81)

2nd: 20 $Gy_{2/2}$ (12-32) in 1-3 fractions

Shagal et al. 2012

Adverse effects

- Acute pain – self-resolving; dexamethasone reduce the risk of pain flare from 53% to 26% after cEBRT

Chow et al. Lancet Oncol 2015

- It is effective both as a rescue for pain flare and as prophylactic treatment with 4 or 8 mg orally per day started on day 1 of SBRT and for 4 days after

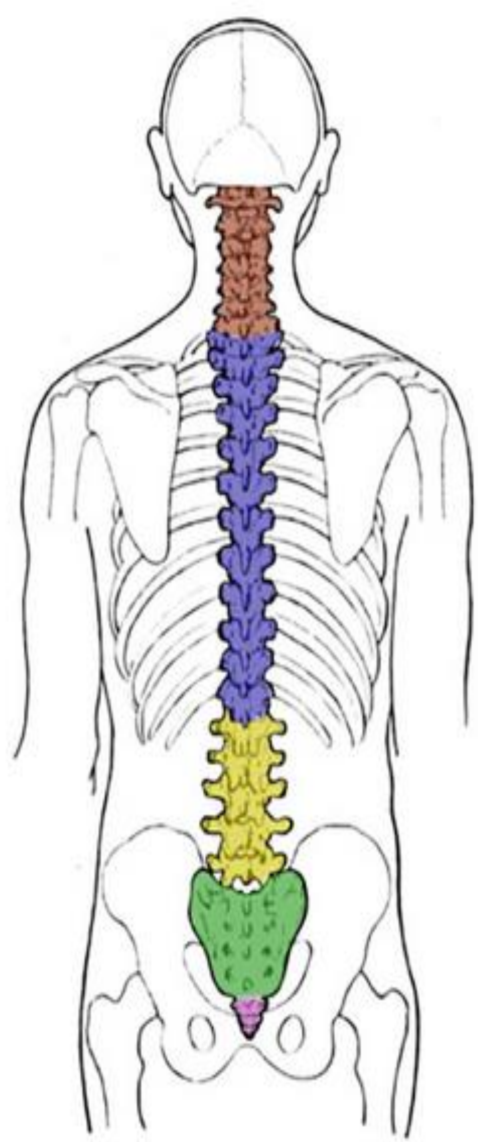
Khan Support Care Cancer 2015

- Early VCF - an intense inflammatory reaction and tissue necrosis that causes destabilisation of the bony architecture, resulting in mechanical compromise
- Late VCF phase of radiation necrosis and fibrosis may result in continued changes in the strength of the bone that renders it weaker and unable to sustain the loading forces

Myrehaug et al. Clinical Oncology 2017

Critical organs

- Spinal cord
- Cauda equina
- Large vessels
- Brain
- Larynx
- Thyroid
- Oesophagus
- Stomach
- Trachea
- Lung
- Heart
- Liver
- Kidney
- Small and large bowel
- Blader
- Rectum



Follow up

Study	Follow up shedule
Choi 2010 Thibault 2014 Garg 2011 Navarria 2012	MRI every 2-3 months
Damast 2011	MRI every 3-4 months
Ahmed 2012	MRI at 2 months then every 6 months±PET
Chang 2012	MRI/PET at 3,6,&12 months
Mahadevan 2011	CT 1 month, otherwise not defined
Hashimi 2016	MRI/PET not specified
Sahgal 2012	Clinically 1 month & every 3-6 months

Dose constrains for spinal cord

Structure	Single-Fraction SRS	Hypofractionated SRS (3 fxn)	Hypofractionated SRS (5 fxn)
Spinal cord	D_{max} = 14 Gy or 12 Gy max circumferential dose (myelogram defined cord MSKCC) D_{max} = 13 Gy QUANTEC (myelopathy < 1%) D_{max} = 14 Gy RTOG 0915 $V_{7\ Gy} < 1.2\ cm^3$ D_{max} = 10 Gy RTOG 0631 And $V_{10} < 0.35\ cm^3$ And $V_{14} < 0.03\ cm^3$ D_{max} = 12.4 Gy (Sahgal myelopathy < 5%)	D_{max} = 21 Gy total (myelogram defined cord) D_{max} = 20.3 Gy (Sahgal myelopathy < 5%)	D_{max} = 25 Gy total (myelogram defined cord) D_{max} = 25.3 Gy (Sahgal myelopathy < 5%)

Katsoulakis et al. Sem in RO 2017

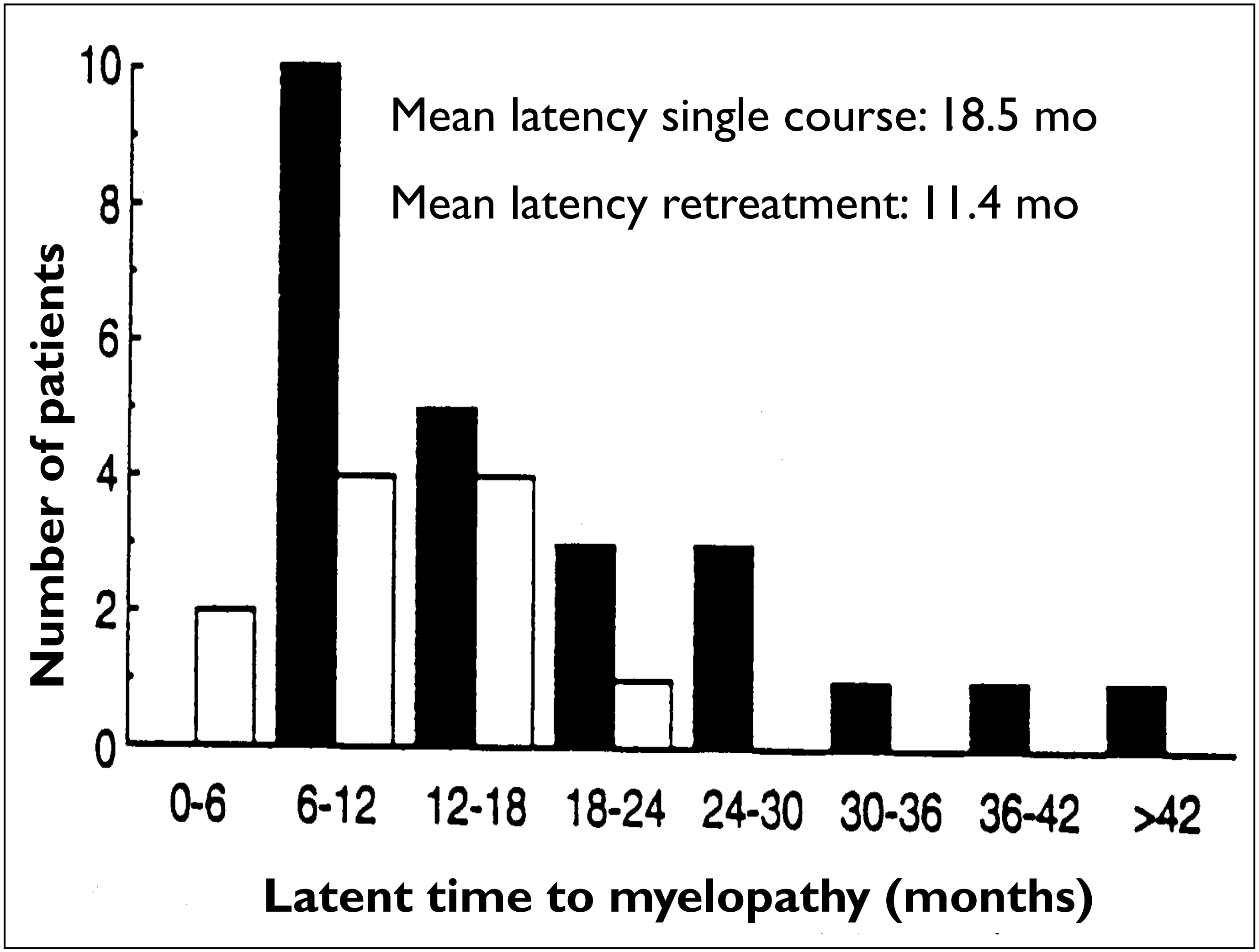
Re-irradiation of vertebral bodies

Reference	Contoured spinal cord structure	Median initial dose	Retreatment SBRT total dose/fraction	Retreatment spinal cord dose	Cumulative cord/thecal sac EQD2	Reported myelopathy
Ahmed 2012	Spinal cord	30 Gy/10 fractions	24 Gy/3 (median)	Dmax 17 Gy (median)	70.1	1%
Boyce-Fappiano 2017	NR	30 Gy/10 fractions	16 Gy/1	10 Gy to 10% of spinal cord, Dmax 14 Gy	93.5	0.6%
Chang 2012	Thecal sac	39 Gy (mean)	20.6 Gy/1 (median)	Dmax 12 Gy (median)	83.4	0%
Choi 2010	NR	40 Gy/20 fractions	20 Gy/2 (median)	Dmax 19.3 Gy (median)	96.2	2%
Damast 2011	NR	30 Gy/10 fractions	20 Gy/5 or 30 Gy/5	14 Gy Dmax spinal cord 16 Gy Dmax cauda equina	58.3	0%
Garg 2011	Spinal cord	30 Gy/10 fractions	30 Gy/5 or 27 Gy/3	10 Gy (mean) 9 Gy (mean)	47.5 48.7	0%
Hashimi 2016	Spinal cord + spinal canal	30 Gy/10 fractions	16.6/1 or 24 Gy/3 (median)	NR	65.6 (1 fraction) 47.8 (3 fractions)	0%
Mahadevan 2011	Thecal sac	30 Gy/10 fractions	25–30 Gy/5 or 24 Gy/3	Dmax 30 Gy (5 fractions) or 24 Gy (3 fractions)	97.5	0%
Sahgal 2009	Spinal cord + 1.5 mm PRV or thecal sac	36 Gy/14 fractions	24 Gy/2	12.2 Gy Dmax spinal cord	65.8	0%
	Spinal cord + 1.5 mm PRV or thecal sac	30 Gy/10 fractions	24 Gy/2	12.2 Gy	75.5	0%
Thibault 2014 **Thibault 2015**	Spinal cord + 1.5 mm PRV or thecal sac	24 Gy/2 or 24 Gy/2 + 30 Gy/10 fractions	30 Gy/4 (median)	12.2 Gy Dmax spinal cord PRV or thecal sac	54.6 80.4	0%
Sahgal 2012 Recommendations		20 Gy/5, 30 Gy/10, 37.5 Gy/15		1 fraction: Dmax 9 Gy 2 fraction: Dmax 12.2 Gy 3 fraction: Dmax 14.5 Gy 4 fraction: Dmax 16.2 Gy 5 fraction: Dmax 18 Gy		
		40 Gy/20 or 45 Gy/25		1 fraction: Dmax N/A 2 fraction: Dmax 12.2 Gy 3 fraction: Dmax 14.5 Gy 4 fraction: Dmax 16.2 Gy 5 fraction: Dmax 18 Gy		
		50 Gy/25		1 fraction: Dmax N/A 2 fraction: Dmax 11 Gy 3 fraction: Dmax 12.5 Gy 4 fraction: Dmax 14 Gy 5 fraction: Dmax 15.5 Gy		

EQD2, equivalent dose to 2 Gy/day fraction size; NR, not reported; Dmax, maximum point dose: V10, volume receiving 10 Gy radiation; SBRT, stereotactic body radiotherapy; PRV planning organ-at-risk volume.

S. Myrehaug et al. Clinical Oncology 2017

Late effects – spinal cord



35 pts

retreatment
EQD2 74 Gy

single course RT
EQD2 60.5 Gy

Wong et al. 1994

Late effects – spinal cord clinical

Study	Cumulative EQD2 median
Jackson 1987	65 Gy (58.5-65.5)
Baumann 1996	60.7 Gy (58.5-63)
Magrini 1990	57.8 Gy (47.8-67.8)
Wright 2006	47.5 Gy (11-56.5)
Navarria 2012	51.25 Gy (27.9-57.6)
Wong 1994	71.5 Gy (67-81.5)
Kawashiro 2016	59.1 Gy (47.5-82.3)

No myelopathy for cumulative EQD2 < 67,5 Gy_2 if neither course exceeds 45 Gy_2

Spinal cord dose-volume effect

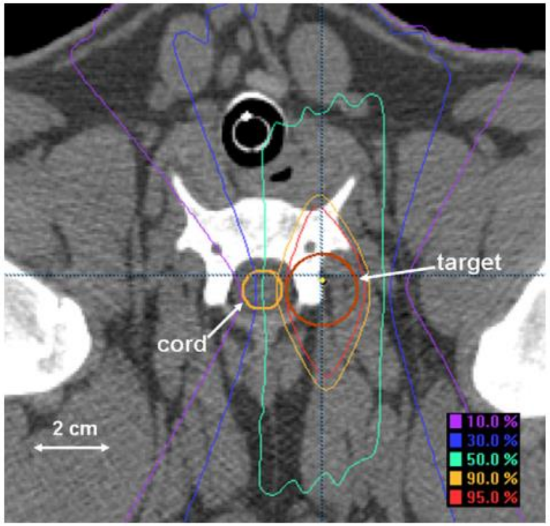
- Dmax 50.2 to 57.1 Gy
- 4 pts 0.5 cm^3 vol. 50.4–53.6 Gy
- 2 pts 1.0 cm^3 vol. 52.8–51.2 Gy

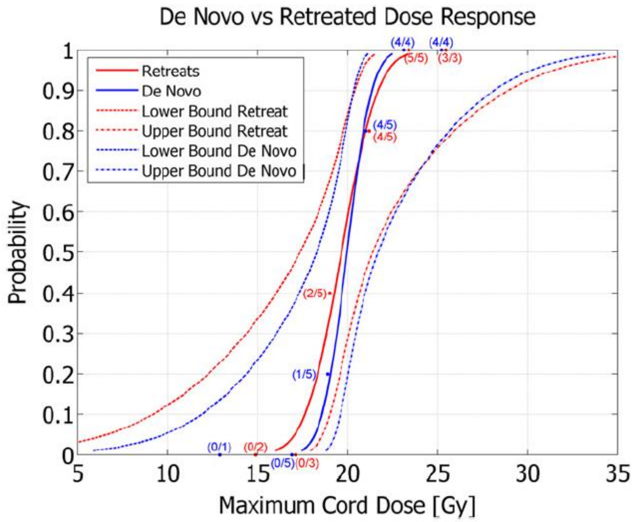
Zschaeck et al. Strahlenther Oncol 2017

- 0.5 cm^3 vol 45.5 Gy (40.7-53.3)

Kawashiro Journal of Radiation Research 2016

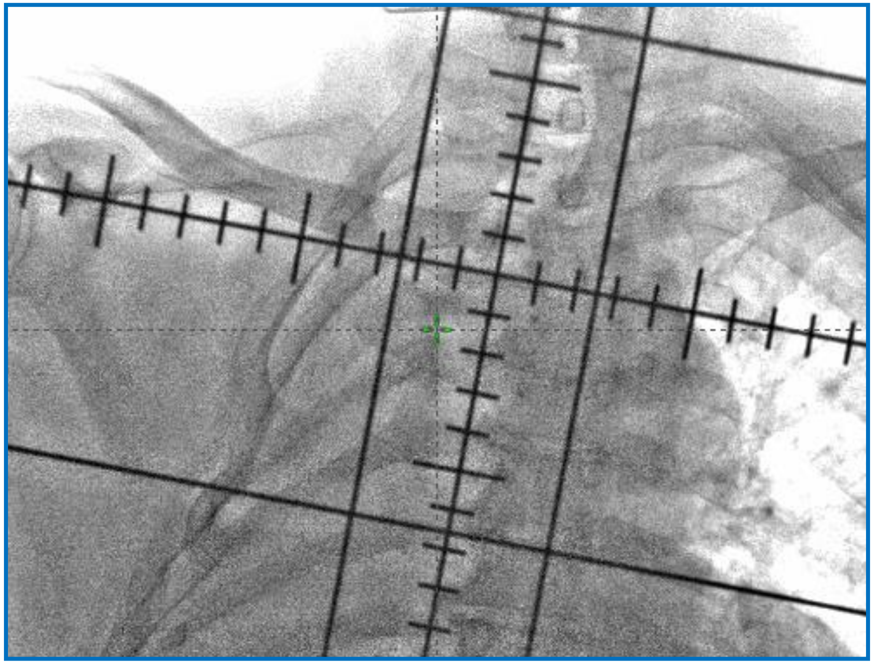
No neurological symptoms





Medin et al. IJROBP 2012

I RT – clinical example

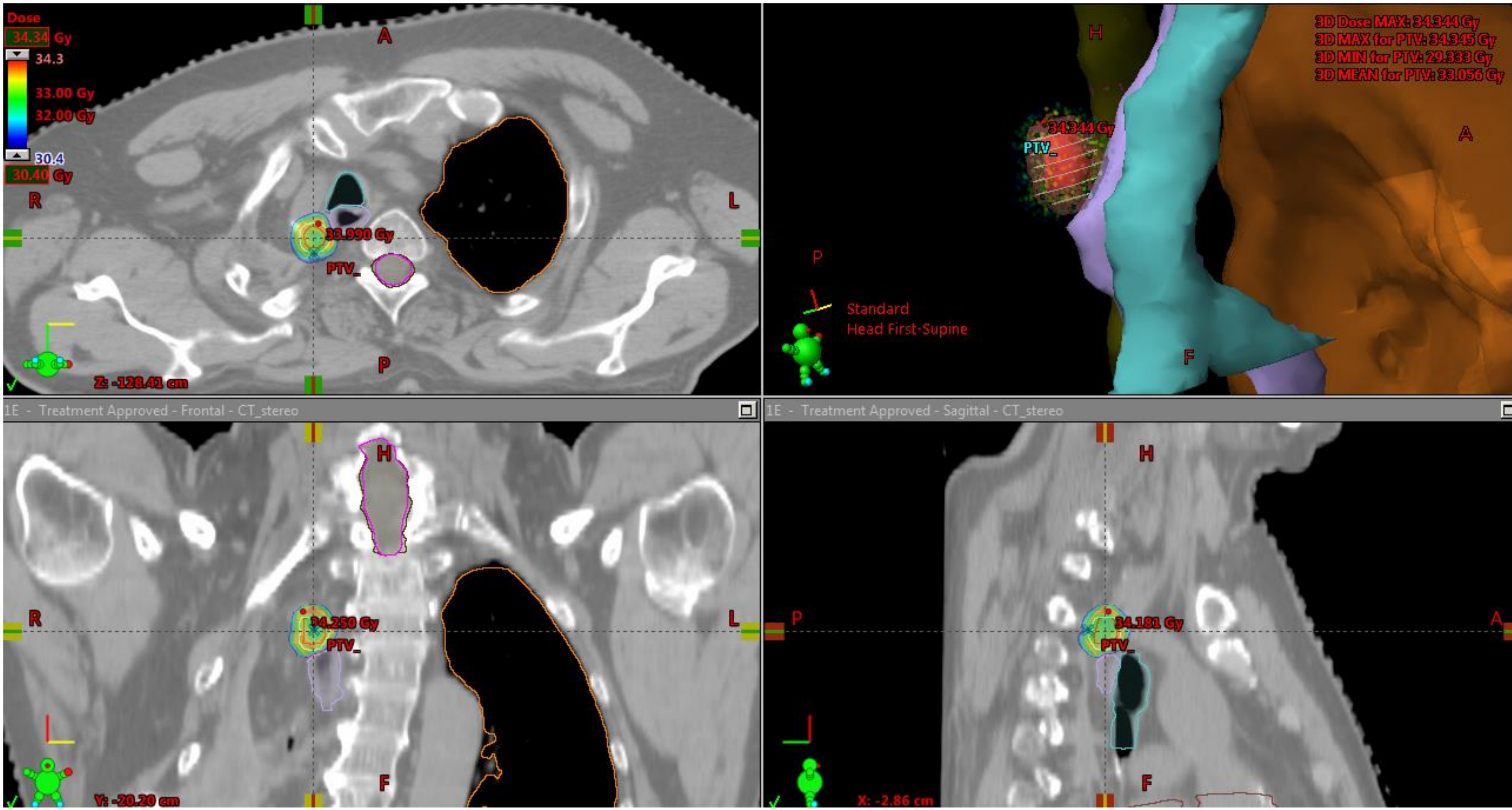


- December 2013
- Paliative radiotherapy
- 2 AP-PA fields
- total dose: 30 Gy
- df: 3 Gy

$$EQD_2 = D \left(\frac{d + \alpha/\beta}{2 + \alpha/\beta} \right) = 30 \left(\frac{3.0 + 2}{2.0 + 2} \right) = 37,5$$

2 RT – clinical example

June 2014 Gated radiotherapy, Total dose: 32 Gy df: 8 Gy



2 RT – clinical example

- D max spinal cord 7.97 Gy
- Recalculated dose to 2 Gy?

$$\mathbf{EQD_2 = D}\left(\frac{d + \alpha/\beta}{2 + \alpha/\beta}\right) = \mathbf{7.97}\left(\frac{2.0 + 2}{2.0 + 2}\right) = \mathbf{7.97}$$

I Rt + 2 RT 37.5 + 7.97 = 45.47

3 RT – clinical example

Lost from follow up return in October 2016 with tumour progression

Question:

How calculate the dose to the spinal cord?

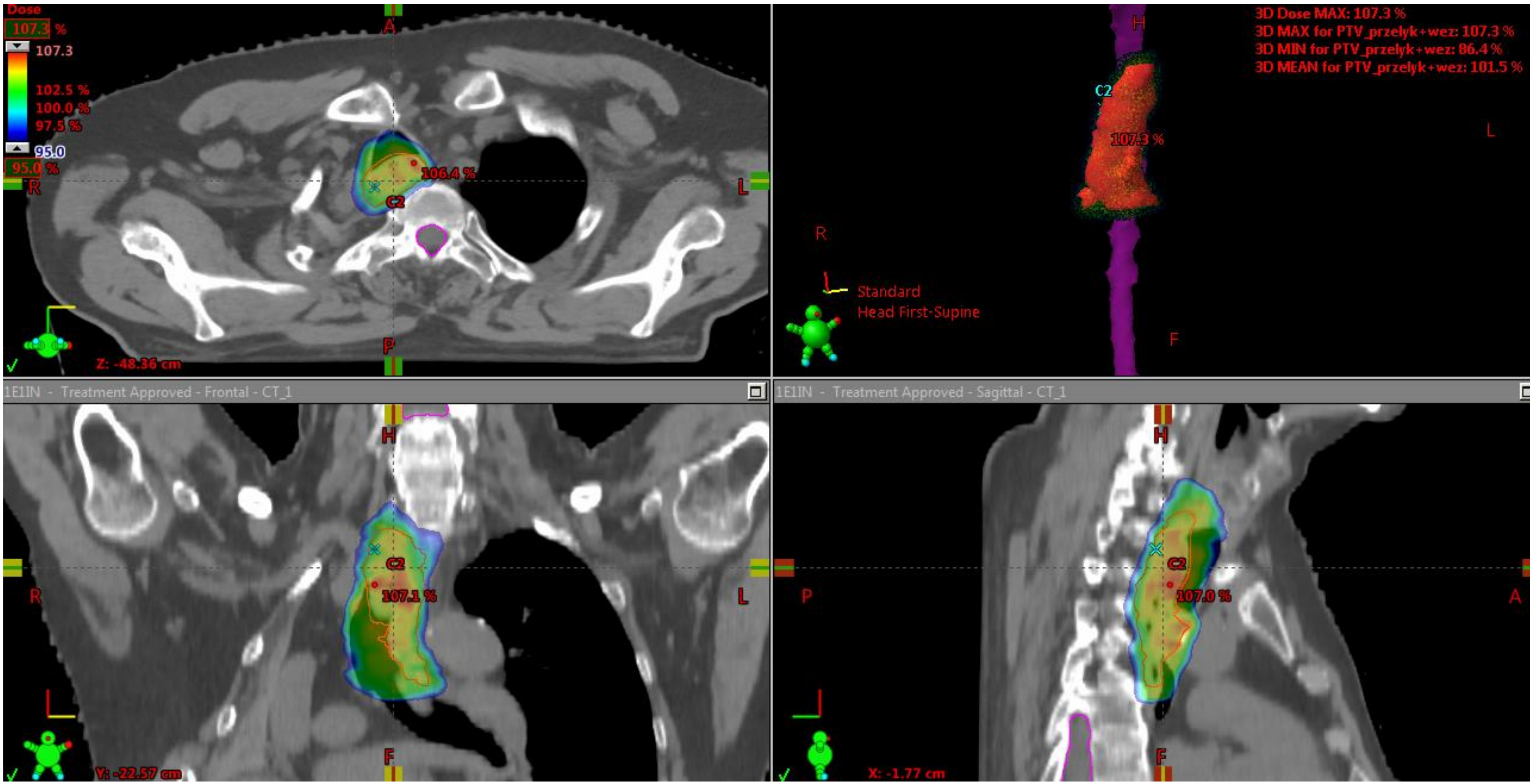
1 Rt + 2 Rt + 3 RT 37.5 + 7.97 + 4.53 = 50 Gy₂

$$EQD_2 = D \left(\frac{d + \alpha/\beta}{2 + \alpha/\beta} \right) = 7 \left(\frac{0.47 + 2}{2.0 + 2} \right) = 4.31$$

1 Rt + 2 Rt + 3 RT 37.5 + 7.97 + 4.31 = 49.78 Gy_2

3 RT – clinical example

- Plliative radiotherapy total dose: 30 Gy, df: 2 Gy
- Spinal cord **6.2 Gy** in 15 fx (**3.7 Gy$_2$**)



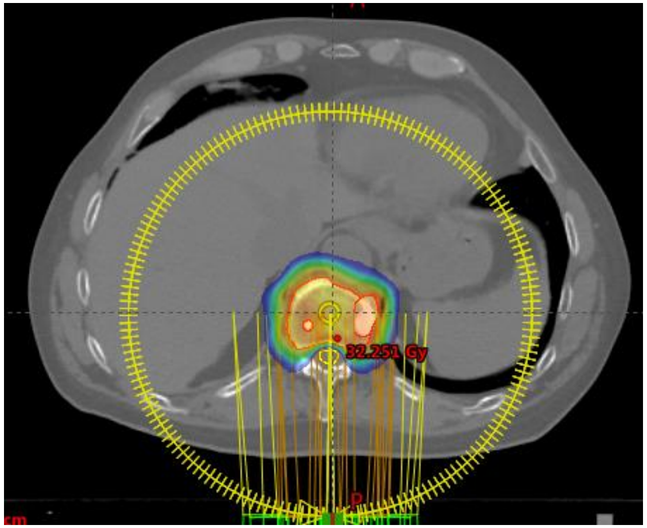
Clinical example

- Inoperable
- Did not quelified to systemic treatment
- August 2017 Gastrostomy
- October 2017 Palliative brachytherapy

  Total dose: 18 Gy, df: 6 Gy
- August 2018 stable disease on CT, pain controlled with drugs, gastrostomy

Conclusion

- Re-irradiation of vertebral bodies is feasible
- Have to be performed with extreme accuracy and precision
- Dose constrains are not confirmed in a large trials



Thank you