Metastatic disease of the spine. Radiosurgery treatment

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Nothing to disclose

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Spinal metastases a relevant problem

5-50% of cancer patients

WHO expects an increase of the total number of metastatic patients in the next years

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Spinal metastases
Symptoms

- Pain (90%)
- Motor impairment (35-75%)
- Vertebral fractures
- Paralysis

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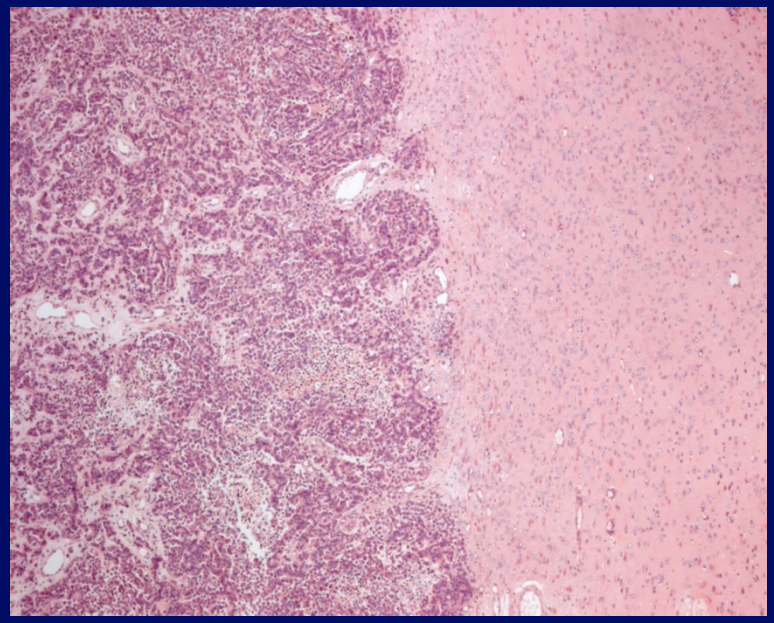
Spinal metastases goals

- Early detection
- Appropriate treatment



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Spinal metastases therapy

- Conventional external beam radiotherapy
- Decompression and stabilisation
- Minimally invasive surgery (vertebroplasty and kyphoplasty,)
- Others (bisphosphonates, systemic radioisotopes, chemotherapy)
- Radiosurgery

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Radiosurgery for Spine metastases
Why?

Conventional 3D EBRT lacks the precision to deliver ideal dose to the tumour because of the proximity of radiosensitive structures.

This often limits the treatment dose to a level far below the optimal therapeutic dose, resulting in less than optimal clinical response.

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Local recurrence rate after surgery and conventional radiotherapy

- 6 months → 57,9 %
- 1 year → 69,3 %
- 4 years → 96 %

Klekamp J, Samii H Acta Neurochir (Wien) 140:957–967, 1998

Radiosurgery for Spine metastases
Why?

Comparing different treatment schedules, the most recent EBRT experiences indicate that the **higher** is the total dose , the **longer** is the **local control.**

The pain relief rate is similar

•Bone Pain TrialWorking Party. Radiother Oncol 1999;52(2):111–21
•Rades D et al. J Clin Oncol 2005;23(15):3366–75.
•Chow E et al. J Clin Oncol 2007;25(11):1423–36.

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Radiosurgery for Spine metastases & the relative radio-resistance

Some recent studies suggest that
a single fraction, high dose treatment,
as in the intracranial disease,
could overtake the problem of the relative radio-resistant tumours response.

Gerszten et al. Spine 2007
Yamada et al. Int J Radiat Oncol Biol Phys 2008
Wowra et al. Spine 2008

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Radiosurgery

"Radiosurgery is a technique which utilizes multiple narrow radiation beams directed stereotactically to produce radiobiological effects within a carefully defined, "small " volume" Larson, 1994

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Radiosurgery for Spine metastases

Rationale

- → Higher confomality to target
- → → smaller target volumes and smaller spinal cord exposure
- → Higher doses to tumour and lower dose to the spinal cord
- → higher tumor growth control and lower radiation myelophaty risk

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-Targeting Accuracy

1 mm accuracy

using

CT with 1.25 mm slice thickness

MRI 2 mm slice thickness T1 ce

Image Guided Radiotherapy

(Chang 2003-07, Gerszten 07-010, Sheehan 08, de Salles 04, Benzil 04, Ryu 04)

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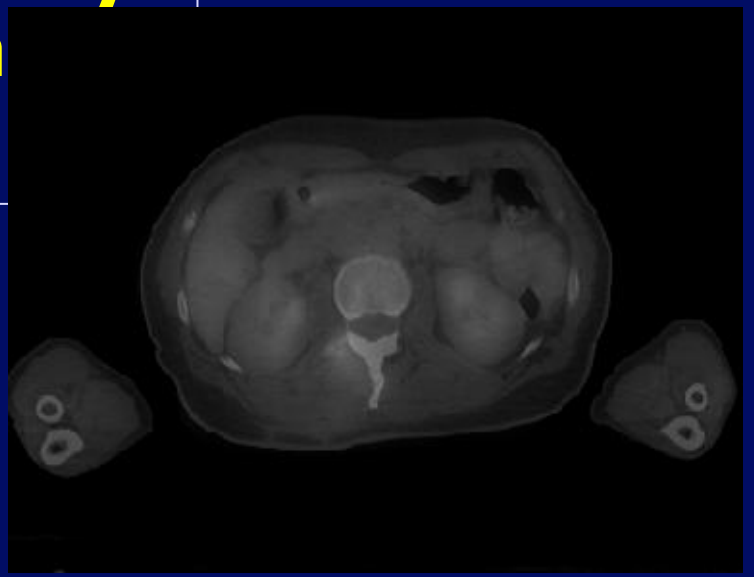
solutions

Image fusion

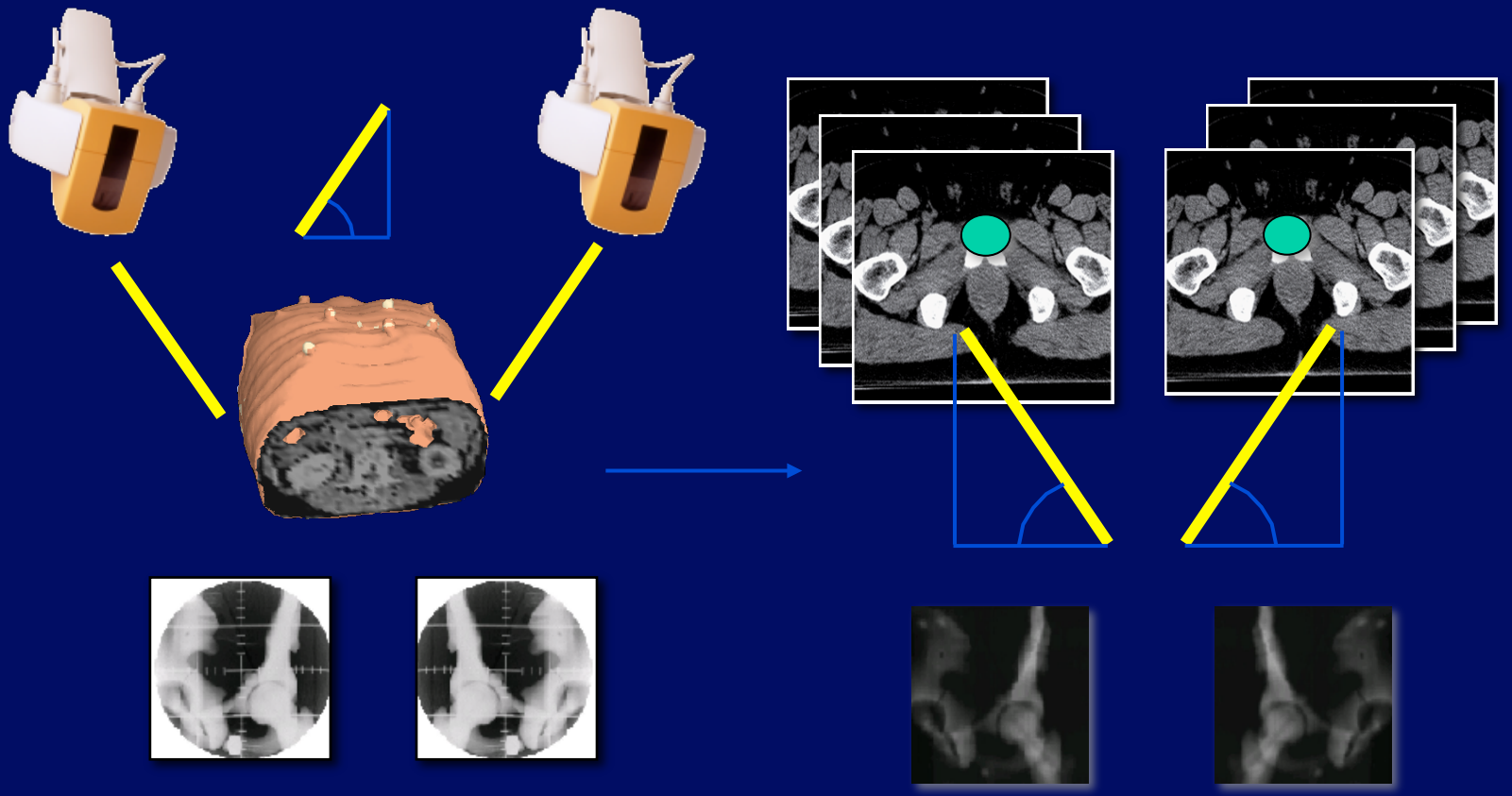
- MRI
- Sequences determined from pathology
- T1 seq. enhanced frequently used
- But it requires in depth study in multidisciplinary tea
- Integration with PET



solutions

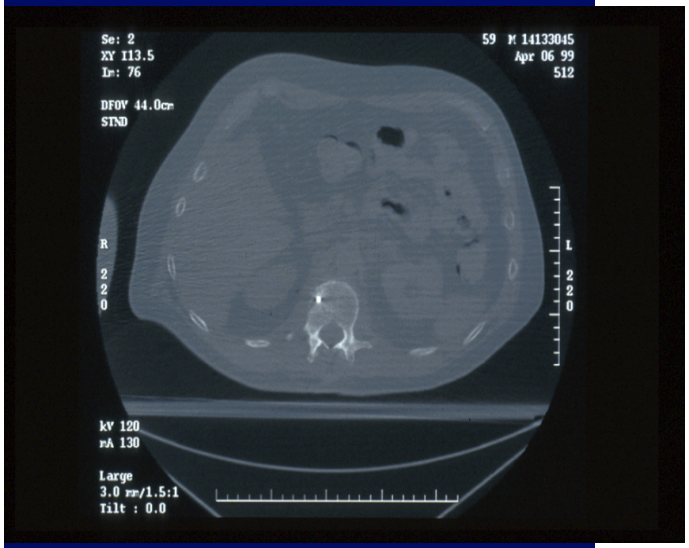
Correct repositioning

DRR and X-Ray Acquisition & Comparison



Challenges of Spinal Tumor Treatments

- The spine moves during treatment
  - Vertebrae can move independent of one another
  - Rigid transformation is not valid in most cases
- Adjacent structures necessitate sub-millimeter precision and accuracy



RTOG 0631

Quality assurance and protocol compliance criteria

In order to achieve the highest standard of spine SRS, four core methods of quality assurance were adopted with institutional credentialing of image-guided radiation therapy (IGRT) and intensity-modulated radiation therapy (IMRT), spine phantom irradiation, rapid review of the cases, and central dosimetric analysis.

Image-guidance criteria: To check the alignment of coordinate systems between imaging system and delivery system, data of pre-treatment, post-shift imaging (if applicable), and post-treatment images, including a completed IGRT spreadsheet of the shifts, were obtained by the Image-Guided Therapy Center (ITC). Setup images were compared to corresponding reference images to identify potential deviation. Optimal (per protocol) IGRT had to demonstrate a < 2 mm difference between simulation/planning and treatment, and at the end of treatment. A difference of 2-3 mm was considered acceptable (minor variation). A difference > 3 mm was considered unacceptable (major deviation).

Int J Radiat Oncol Biol Phys. Author manuscript; available in PMC 2013 July 15.

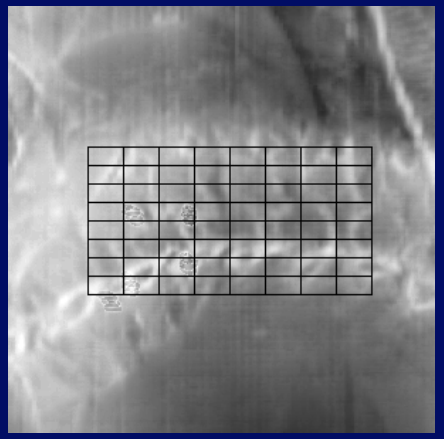
Spine Tracking System

- Non-invasively registers non-rigid and bony anatomy landmarks for radiosurgical targeting accuracy
  - Fiducials or frames not required
  - Automatically tracks, detects, and corrects for movement
  - throughout the treatment
- Unlimited spinal reach
  - Cervical, thoracic, lumbar and sacral
- Proven sub-millimeter targeting accuracy:
  - Overall targeting error of 0.52 +/- 0.22 mm* **
- Nearly 100% eligibility for all spine cases

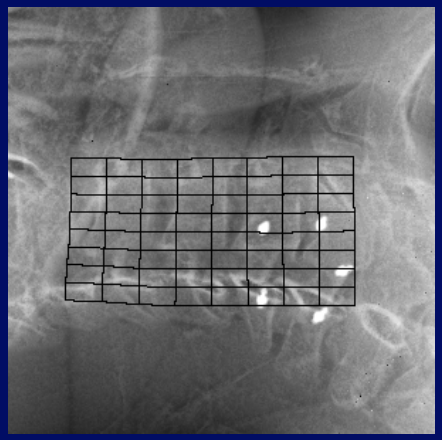
* As measured in end-to-end testing. Reference: Muacevic, A., Staehler, M., Drexler, C., Wowra, B., Reiser, M. and Tonn, J. Technical description, phantom accuracy and clinical feasibility for fiducial-free frameless real-time image-guided spinal radiosurgery. J Neurosurgery Spine.
** Xsight accuracy specification of .95 mm.

How it Works…

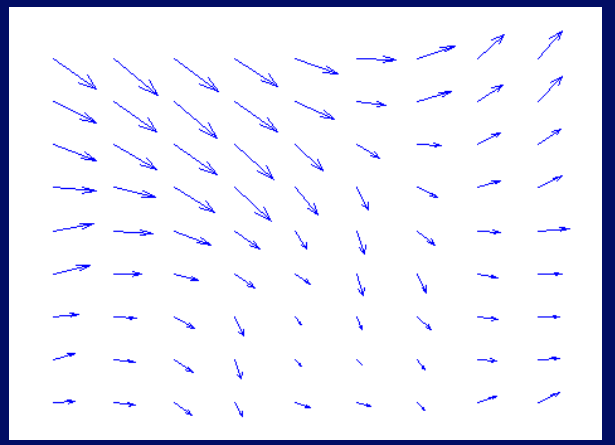
Image A

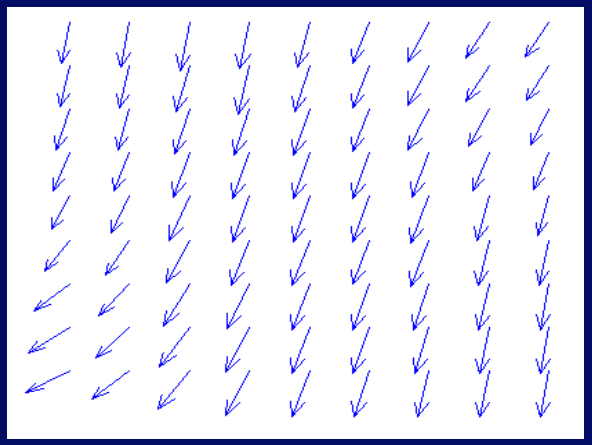


Live kV image



Displacement Field





Treatment plan optimisation

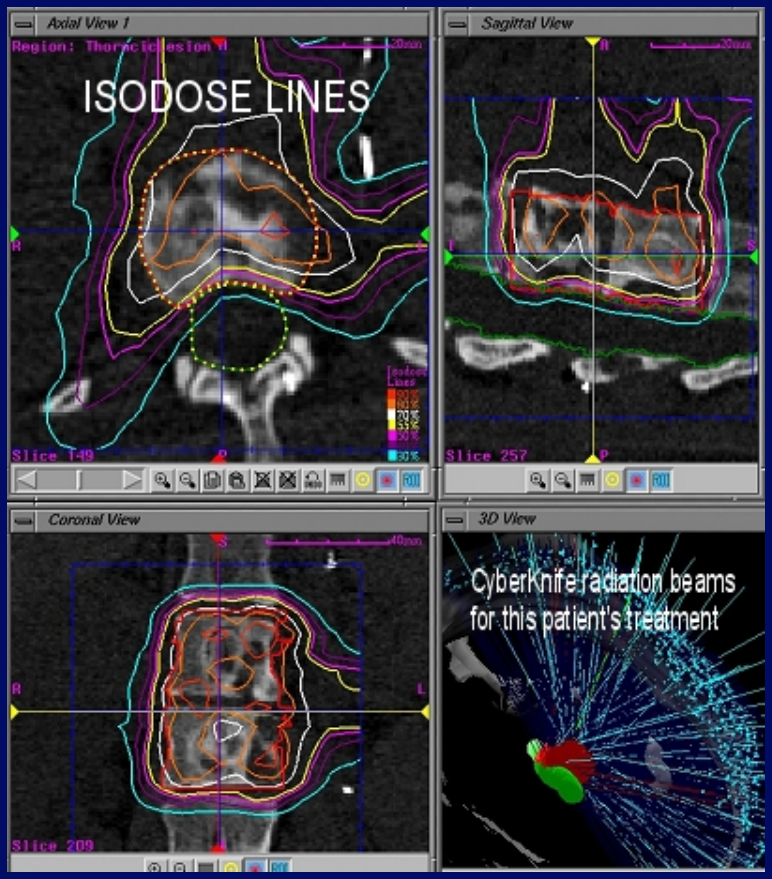
Homogeneity Index

Max dose /
prescription dose
= 1.48

Acceptable < 2

Conformity Index

Inverse planning
technique



International Spine Radiosurgery Consortium Consensus Guidelines for Target Volume Definition in Spinal Stereotactic Radiosurgery

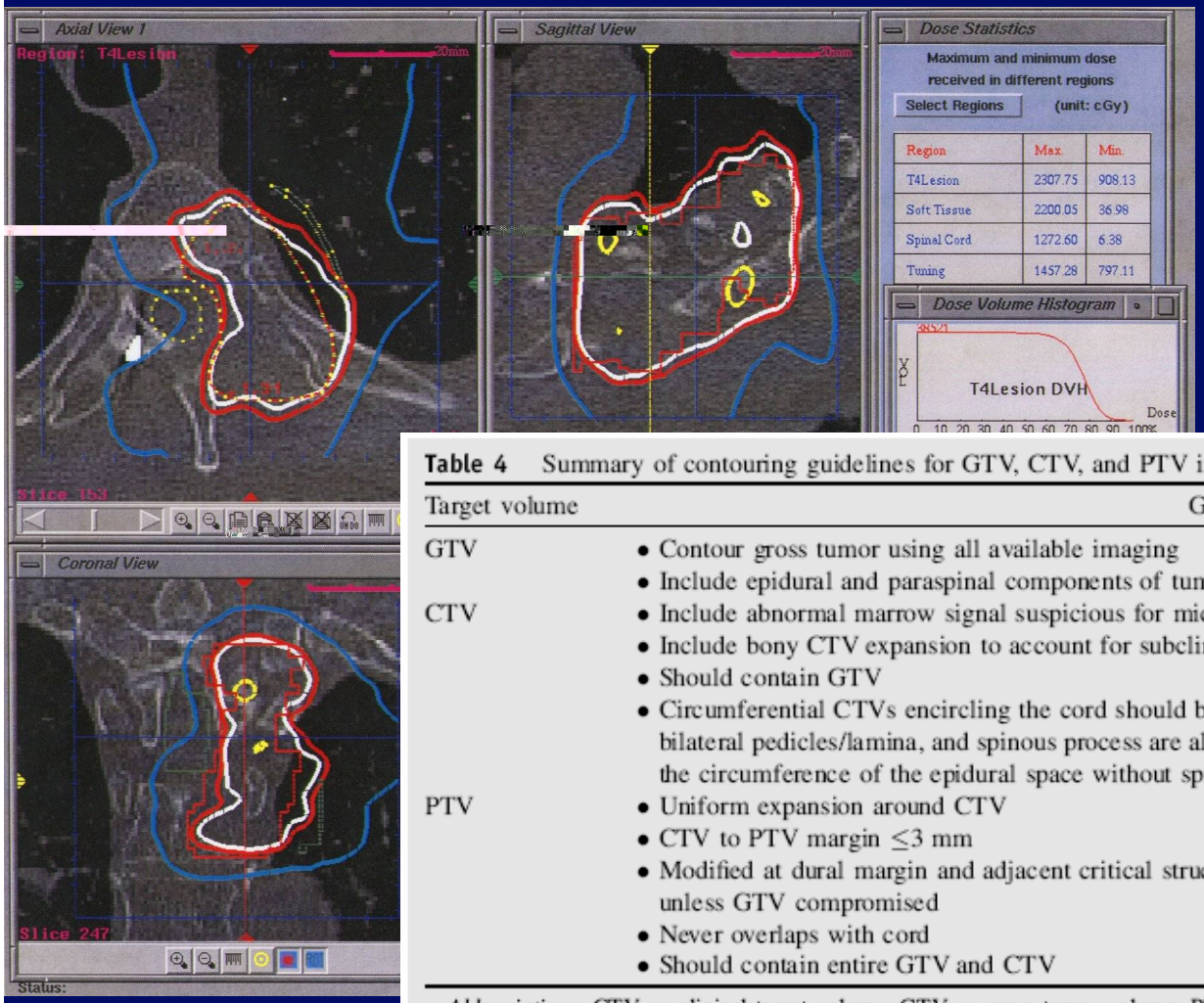


Table 4 Summary of contouring guidelines for GTV, CTV, and PTV in spinal stereotactic radiosurgery

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.

radiosurgery

- Single fraction
- Multisession radiosurgery (up to 5)
- Dose fraction ?

Radiosurgery in spine metastasis: indications for clinical trials

ASTRO guidelines 2011

- Spinal or para spinal metastasis
- No more than 2 consecutive or 3 non contiguous segments
- Following gross total or subtotal resection
- Surgery refused
- Oligometastatic or bone only metastatic disease
- Previous EBRT
- KPS >50

Boost after conventional XRT pre operative management

Radiosurgery for spinal metastases
A lot of positive experiences

TABLE 2: Literature review of the current evidence, including only studies reporting on spinal metastases*

Authors & Year	Total No. Tumors/ No. Pts	No. Tumors w/ Retx/No. Pts	No. Postop Pts	FU in Mos (range)	Local Control/ Criteria†	Tumor Dose/No. Frx/Rx Isodose	Pain Response (pain assessment tool)
postop SBRT							
Moulding et al., 2010	21/21	0	21	median 10.3	17 of 21 (81%) w/ 1-yr local control 90.5%/ imaging	median 24 Gy/1/100%	NS
Rock et al., 2006	18/18	1/1	18	median 7 (4–36)	17 of 18 (94%)/imaging &/or clinical	4 of 18: EBRT 25 Gy/10 frx + SBRT boost; median 6 Gy/1/90%; 14 of 18: SBRT only; median 14 Gy/ 1/90%	6 of 18 w/ CR (NS)
Gerszten et al., 2005[17]	26/26	7/7	26	median 16 (11–24)	24 of 26 (92%)/imaging & pain	mean 18 Gy/1/80%	improved in 24 of 26 (VAS)
total	65/65	8/8	65		58 of 65 (89%)		

From: Stereotactic body radiotherapy for spinal metastases: current status, with a focus on its application in the postoperative patient.
Sahgal et al. J Neurosurg Spine. 2011 Feb;14(2):151-66.

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A lot of positive experiences

SBRT for tumors w/ no prior radiation							
Yamada et al., 2008	103 /93	0/ 0	0	median 15 (2–45)	90% at 15 mos, ~93 of 103/ imaging	median 24 Gy/1/100%	NS
Ryu et al., 2004	61/49	0/ 0	N S	median 6.4 (6–24)	57 of 61 (93%)/imaging & pain	10–16 Gy/1/90%	85% comb CR/PR rate (VAS)
Ryu et al., 2003	10/10	0/ 0	N S	mean 6 (3–12)	10 of 10 (100%)/imaging & pain	EBRT 25 Gy/10 frx + SBRT boost; 6–8 Gy/1/90%	5 of 9 w/ CR, 4 of 9 w/ PR (NS)‡
Sahgal et al., 2009[45]	23/14	0/ 0	5	median 9 (1–26)	18 of 23 (78%)/imaging &/or pain§	median 24 Gy/3/67%	NS
total	197/ 166	0/ 0			178 of 197 (90%)		

From: Stereotactic body radiotherapy for spinal metastases: current status, with a focus on its application in the postoperative patient.
Sahgal et al. J Neurosurg Spine. 2011 Feb;14(2):151-66.

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studies w/ a mixture of SBRT indications							
Nguyen et al., 2010	55/ 48		15	median 13.1 (3.3–54.5)	43 of 55 (78%; 1-yr FFP 82%)/imaging	30 Gy/5 frx; 24 Gy/3; 24 Gy/1; Rx isodose such that CTV covered by 80%–90%	52% w/ lasting response; pain free at 12 mos (BPI)
Tsai et al., 2009	127/ 69		0	median 10 (3–21)	96.8% at 10 mos, 123 of 127 (97%)/imaging	mean 15.5 Gy/2/80%	61 of 69 w/ improved pain (VAS)
Nelson et al., 2008	33/ 32		0	median 7 (3–21)	29 of 33 (88%)/imaging &/or pain	median 18 Gy/3/NS	13 of 32 w/ CR & 17 of 32 w/ PR at 1 mo (questionnaire)
Chang et al., 2007	74/ 63		29	median 21.3 (1–50)	57 of 74 (77%; 1-yr FFP 84%)/imaging	30 Gy/5 frx (32 of 63); or 27 Gy/3 frx (31 of 63); Rx isodose such that 80%–90% target coverage	narcotic use declined from 60% to 36% at 6 mos (BPI)
Gibbs et al., 2007	102/ 74		0	mean 9 (0–33)	NS	14–25 Gy/1–5/61%–89%	84% of symptomatic pts w/ resolution or benefit (VAS)
Gerszten et al., 2007	500/ 393		9/500 tumors	median 21 (3–53)	440 of 500 (88%)/ imaging	mean 20 Gy/1/80% (7 of 500 w/ comb EBRT + SBRT boost)	290 of 336 w/ improvement (VAS)
Yamada et al., 2005	21/ 21		0	median 7 (1–24)	19 of 21 (90%; actuarial 81%)/imaging	median 20 Gy/5 frx	NS for pts w/ metastases only (0–10 self-assessed pain scale)
total	912/ 700				710 of 809 (88%)		

From: Stereotactic body radiotherapy for spinal metastases: current status, with a focus on its application in the postoperative patient.
Sahgal et al. J Neurosurg Spine. 2011 Feb;14(2):151-66.

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Radiosurgery for spinal metastases
A lot of positive experiences

SBRT for tumors w/ prior radiation							
Mahan et al., 2005	8/8	8/8	0	mean 15.2	8 of 8 (100%)/NS	median 30 Gy/15/NS	6 of 8 w/ CR, 2 of 8 w/ PR (NS)
Milker-Zabel et al., 2003	19/ 18	19/ 18	0	median 12 (4–33)	18 of 19 (95%)/imaging	median 39.6 Gy/2 (aim was 90% coverage)	13 of 16 (NS)
Hamilton et al., 1995	5/5	5/5	0	median 6 (1–12)	5 of 5 (100%)/imaging &/or clinical	median 10 Gy/1/80%	NS
Sahgal et al., 2009[45]	37/ 25	37/ 25	0	median 7 (1–48)	34 of 37 (92%)/imaging &/or pain	median 24 Gy/3/60%	NS
total	69/ 56	69/ 56	0		65 of 69 (94%)		

From: Stereotactic body radiotherapy for spinal metastases: current status, with a focus on its application in the postoperative patient.
Sahgal et al. J Neurosurg Spine. 2011 Feb;14(2):151-66.

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Meta analysis

Pooled results of spinal radiosurgery series.

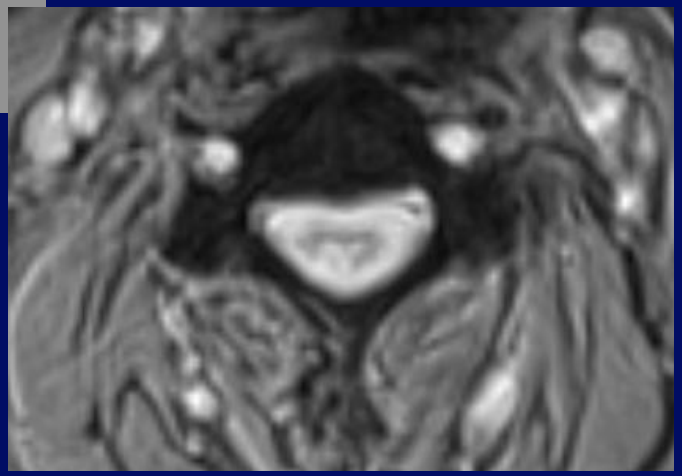
Description	Values
Total patients	1388
Total lesions	1775
Patients with previous RT	888
Mean F/U time (months)	15
Pain improvement rate (n=902)	79%
Local control rate (n=1169)	90%
Myelopathy rate (n=1388)	0.4%

Abbreviations: RT, radiation therapy; F/U, followup.

Int J surg oncol 2011

Radiosurgery for Spine metastases
Open questions

- Tumor missing in planning
- Spinal cord dose tolerance



Target missing
others experiences

- Ryu et al.2004 → no failures in adjacent untreated vertebrae
- Chang et al. 2007 → 1 case of failures in adjacent untreated vertebrae
- Gerszten et al. 2007 → no failures in adjacent untreated vertebrae

Int J Radiat Oncol Biol Phys. 2010 Nov 11.

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toxicity

Acute reactions associated with irradiation of the spine are usually not severe

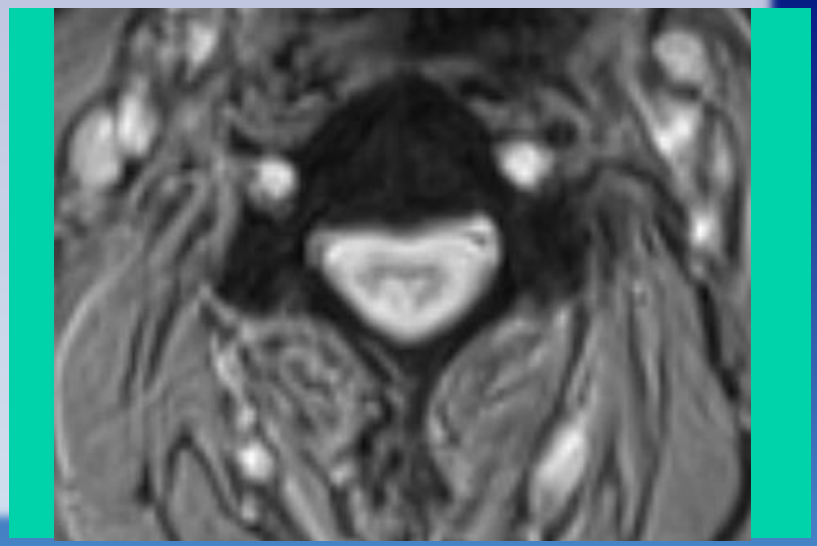
Subacute effects are related to transient demyelinisation (radiation injury to oligodendrocytes or through alteration of capillary permeability)

toxicity

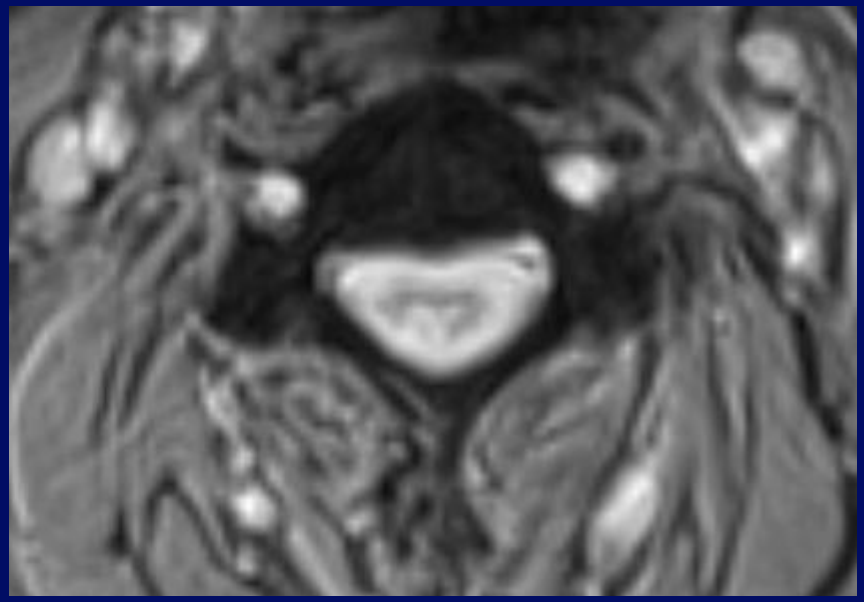
true myelopaty occurs within several months or up to many years after RT

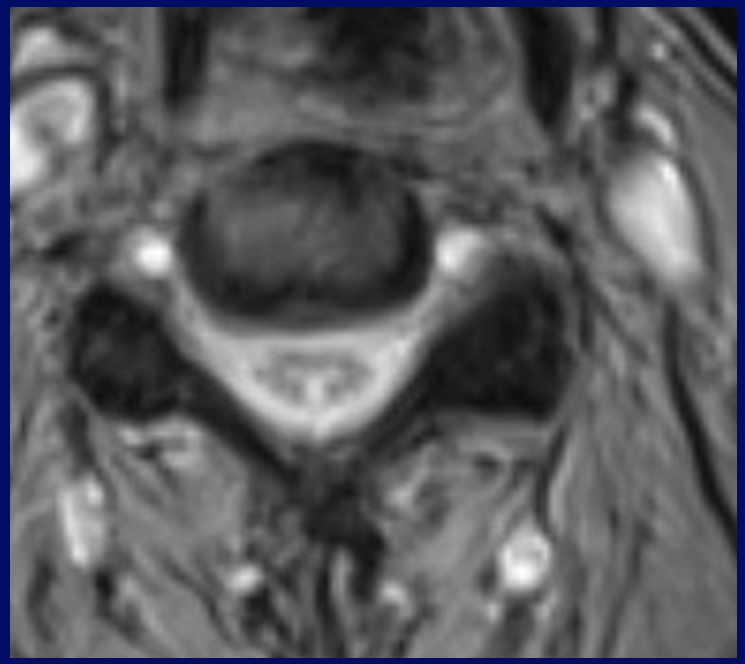
There is evidence that capillary endothelial damage causes late effects in the spinal cord rather than a direct effect on the parenchimal cells in animals model

toxicity



At radiological point of view MRI may show cord swelling,decreased intensity on T1 weighted and increased intensity on T2 images indicative of oedema





Radiation tolerance of the spinal cord
is a dose limiting factor
in the treatment of many malignancies.
The risk on injury increases
with incresing of total dose and dose/fr

the conventional TD that would result
in a 5% incidence of myelopathy is
between 57 and 61 Gy:
because of the morbidity, spinal cord
doses are be supposed to be minimized

tolerance

A time/dose relation for radiation induced spinal cord injury suggests that

- Doses of 20 Gy in 5 fractions,
- 30 Gy in 10 fractions,
- 50 Gy in 20 fractions

were safe

Experiments on animal model have shown that

- Spinal cord has a possibility to recover sub-occultal damage but
  - short interval between fractions (time)
  - and high dose

  are unfavourable elements

SRS dose and corresponding total RT dose to produce a similar radiobiological effect for late (α/β 2) and early responding (α/β10) tissues

SRS dose	CRT dose (Gy)	
	α/β 2	α/β 10
10	30	16.7
20	110	50
30	240	110

Larson 93

A regional difference in radiosensitivity was observed by irradiating the cord: the lateral white matter was more sensitive than the central part of white matter

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It is not known whether
the sensory tracts
may be more tolerant
to RX than motor tract

Cauda equina and spinal nerves do have really a higher radiation tolerance?

TOLERANCE

estimates of tolerance of spinal cord
to single doses
may be derived from modelling or
extrapolation of clinical data
to be in the range
of 10 Gy

clinical data: dose

A report of palliative hypofractionated EBRT for lung cancer found

no myelopaty after single dose of 8.5 Gy to toracic spinal cord

(Cross , IJROBP 03)

clinical data: dose

- RTOG 97-14 randomized trial
- Painful osseous metastatic site
- 8 Gy single shot vs 30 Gy in 10 fractions
- No difference in pain control after 3 months
- No spinal cord toxicity

clinical data : dose

Phase III randomized multicentric trial:

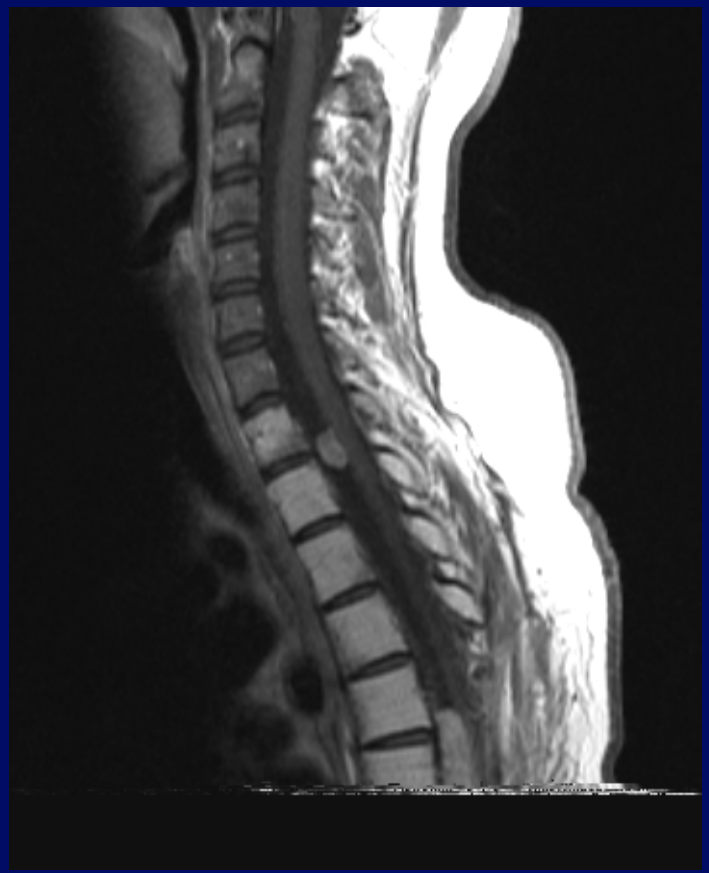
Short course vs split course EBRT in metastatic spinal cord compression

16 Gy, 2 fractions in one week

→ **No spinal cord toxicity (mean follow up 33 months)**

(Maranzano IJROBP 05)

Not only the dose level but also the existence of a volume effect should be taken into account...



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clinical data : volume

- Radiosurgery treatment
- Gertzen 04 : 115 pt with metastatic spine lesions
- Mean SRS dose 14 Gy
- Mean 0.2 cm3 spinal cord volume receving more than 8 Gy
- No toxicity but too short follow up (median 18 months)

clinical data : volume

102 spinal metastasis treated with SRS or SRT:
three patients developed treatment-related severe myelopathy;
one patient was initially asymptomatic. All three
patients were female with lesions of the thoracic spine.
Two of these patients had received prior irradiation to doses
of 50.4 and 39.6 Gy in 1.8 Gy fractions, at 70 and 81 months,
respectively, prior to radiosurgery.

Logistic regression failed to identify predictors of complication among analyzed factors including age, gender, primary site, anatomic location, anatomic level, previous treatment, total dose, dose per fraction, maximum dose,maximum spinal cord dose, and tumor volume.

Gibbs 2007

clinical data : volume

- Partial volume tolerance of spinal cord and complications of single dose SRS
  - (Ryu, Cancer 07)

    - **8-18 Gy ; 230 treated metastatic lesions**
    - **Reference isodose 90%**
    - **Average fall off from 90 to 50% 5 mm**

50 % of the cord volume received a mean dose of 5 Gy

- Partial volume tolerance of spinal cord and complications of single dose SRS
  - (Ryu, Cancer 07)

The maximum point dose to the spinal cord was 13± 2 Gy

Dose constraint has been 10 Gy to 10% of the partial spinal cord volume

Only 1 late toxicity in pt with large metastatic mass to skull-base- C1 vertebra

Open question
Spinal cord dose tolerance

High-dose, single-fraction image-guided intensity-modulated radiotherapy for metastatic spinal lesions.

Yamada Y, Bilsky MH, Lovelock DM, Venkatraman ES, Toner S, Johnson J, Zatcky J, Zelefsky MJ, Fuks Z.

Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

103 consecutive spinal **metastases in 93 patients.**

Max pointed dose to the spinal cord 14 Gy (to any portion of the spinal cord instead of a dose volume constraint) without any case of spinal cord toxicity

Int J Radiat Oncol Biol Phys. 2008 Jun 1;71(2):484-90

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Open question
spinal cord dose tolerance: clinical evidences

Partial Volume Tolerance of the Spinal Cord and Complications of Single-Dose Radiosurgery

Samuel Ryu, Jian-Yue Jin, Ryan Jin, Jack Rock, Munther Ajlouni, Benjamin Movsas, Mark Rosenblum, Jae Ho Kim
Henry Ford Hospital, Detroit, Michigan.

conclusion : partial volume tolerance of the spinal cord is at least 10 Gy to 10% of the spinal cord volume defined as 6 mm above and below the radiosurgery target

CANCER February 1, 2007 / Volume 109 / Number 3

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Open question
Spinal cord dose tolerance

Delayed radiation-induced myelopathy after spinal radiosurgery

Gibbs IC, Patil C, Gerszten PC, Adler JR Jr, Burton SA.
Stanford University Medical Center
University of Pittsburgh School of Medicine, University of Pittsburgh Medical Center

- **1075 treated patients**
- **6 patients developed delayed myelopathy** (age range, 25–61 years)
- Treatment schedules: 12.5–20 Gy in 1 fraction
  18 to 22 Gy in 2 fractions
  18 to 24 Gy in 3 fractions
  14 to 24 Gy in 4 fractions
  25 Gy in 5 fractions

CONCLUSION: ..... We recommend limiting the volume of spinal cord treated above an 8-Gy equivalent.
But.... radiation injury **occurred over a spectrum of dose parameters** that prevented identification of specific dosimetric factors contributing to this complication

Neurosurgery. 2009 Feb;64(2 Suppl)

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Open question **spinal cord dose tolerance:** clinical evidences

- Reports of myelopathy from SRS to spinal lesions appear rare (<1%) when the maximum pointed spinal cord dose is limited to 13 Gy in a single fraction or 20 Gy in three fractions

- long-term data are insufficient to calculate a dose–volume relationship for myelopathy when the partial cord is treated with a hypofractionated regimen

QUANTEC: ORGAN SPECIFIC PAPER

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, 2010

problems

⇢ if a single dose of 8 Gy seems to be tolerated …..the maximum partial volume tolerance at different dose levels cannot be defined

Multicenter italian experience Dosimetry

Fractionations	96 pts single-session SRS
	Mean 13,4 Gy (6-25 Gy)
	61 pts multi-sessions SRS (2 to 6)
	Mean 24,6 Gy (9-40 Gy)
Isodose line	from 70% to 80%
Max dose to spinal canal	9-26 Gy
N.C.I.	1,58
H.I.	1,36

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Results

- All patients experienced a significant pain relief (when present)
- All patient experienced an initial improvement in quality of life
- About 50% of the patients had a neurological improvement

Results

Local Control

- 3 months 91 %
- 6 months 74 %
- 12 months 71 %

Results
Pain

PAIN (VAS)	PRE TREATMENT EVALUATION	3 MONTHS FOLLOW-UP	LAST FOLLOW-UP
MEAN	58	33	36
SD	± 18	± 19	± 26
MEDIAN	60	30	35
RANGE	(30-100)	(0-70)	(0-100)

Pre-treatment vs 3 months: $p < 0,01$
Pre-treatment vs last follow-up: $p < 0,001$

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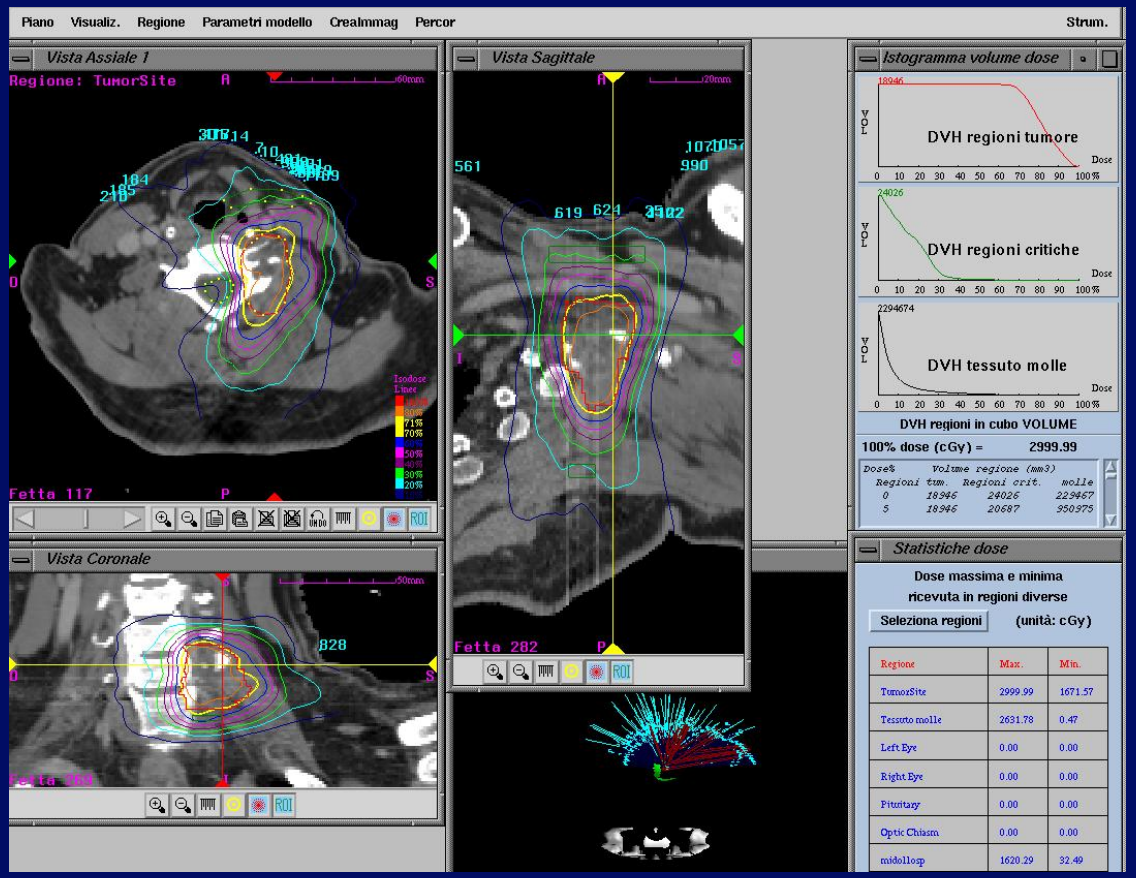
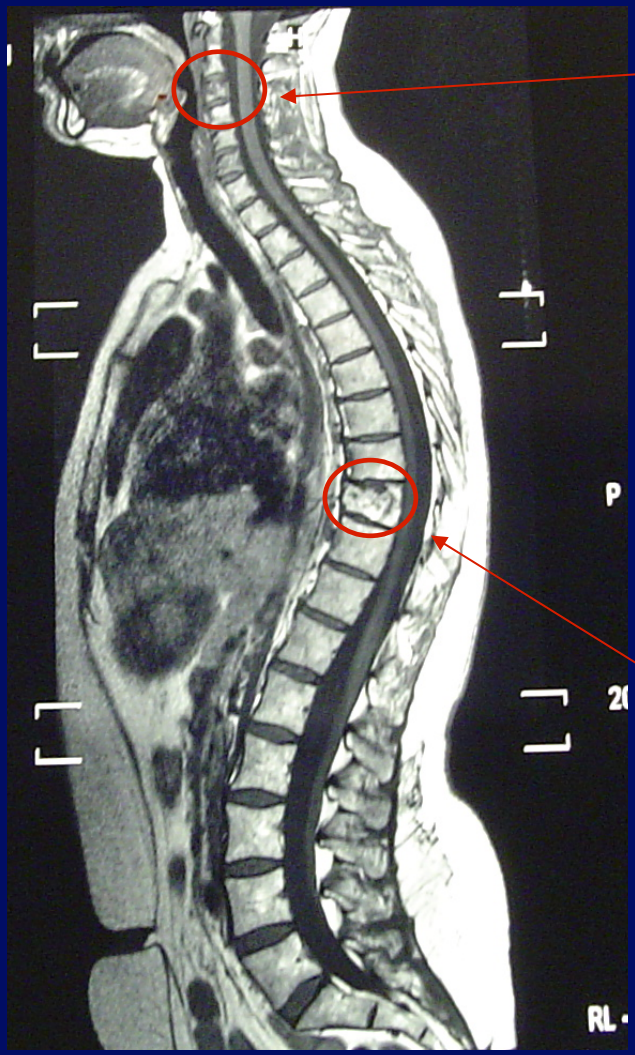
Retreatment renal cell carcinoma

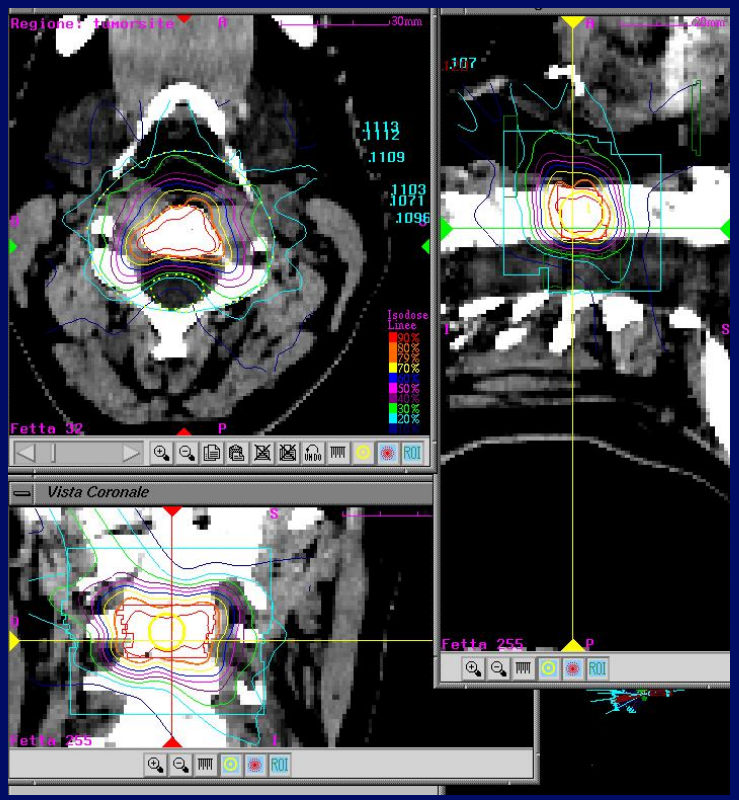


Breast Mets



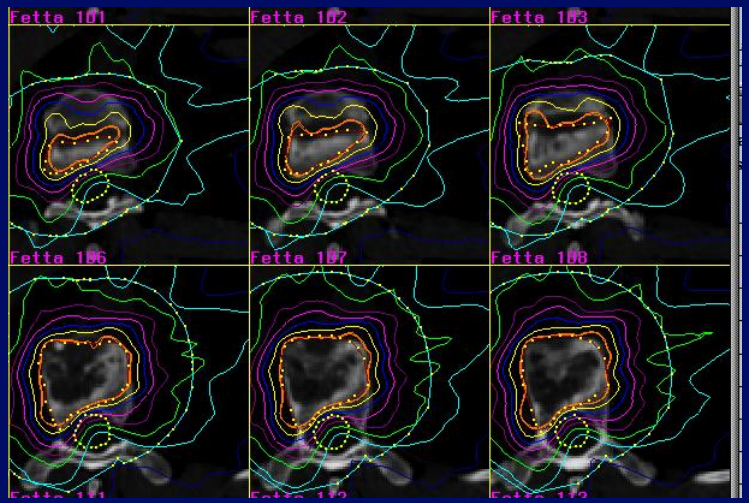
C3

24 Gy, 80%, 4 fr
May ‘06

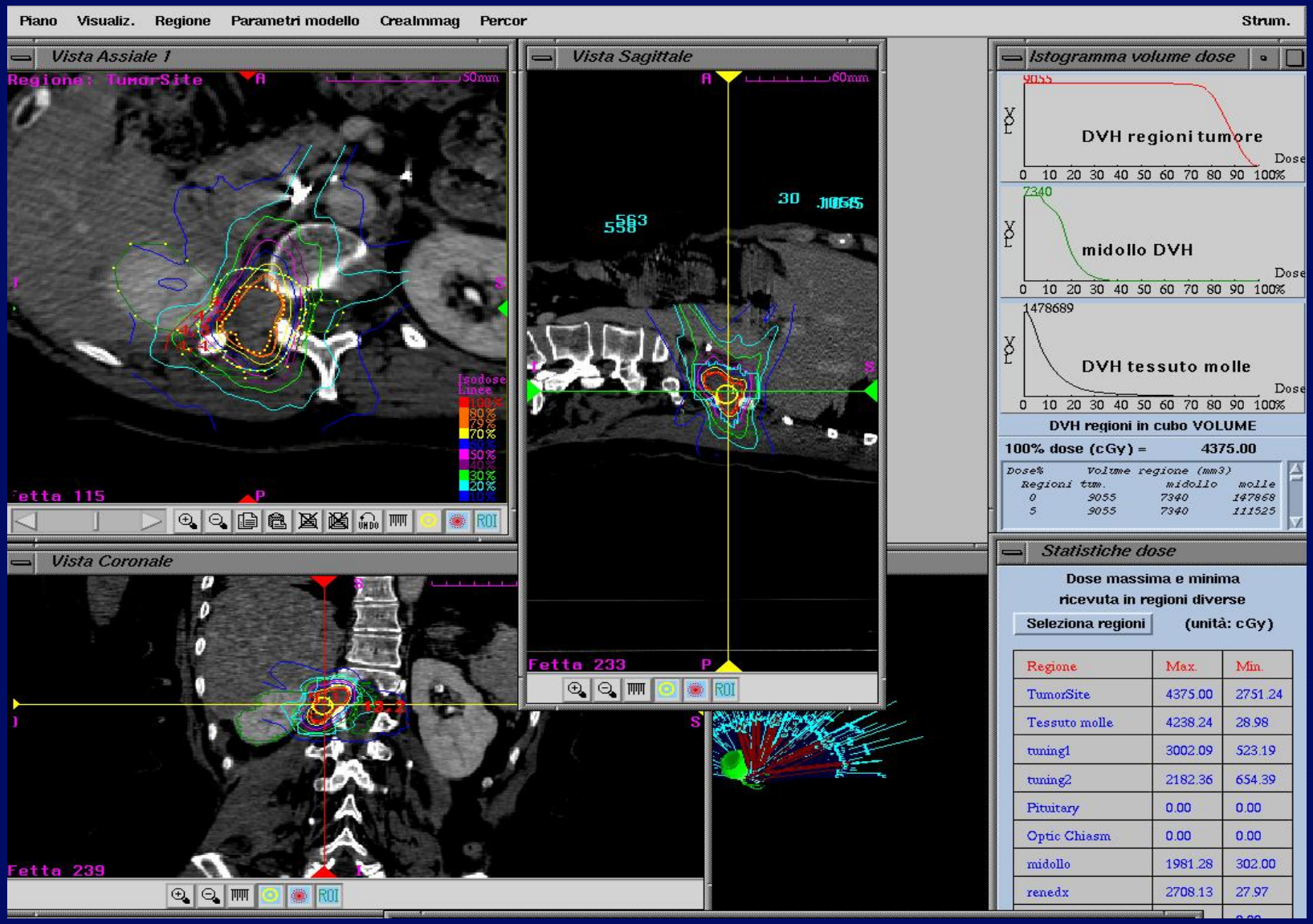


D9

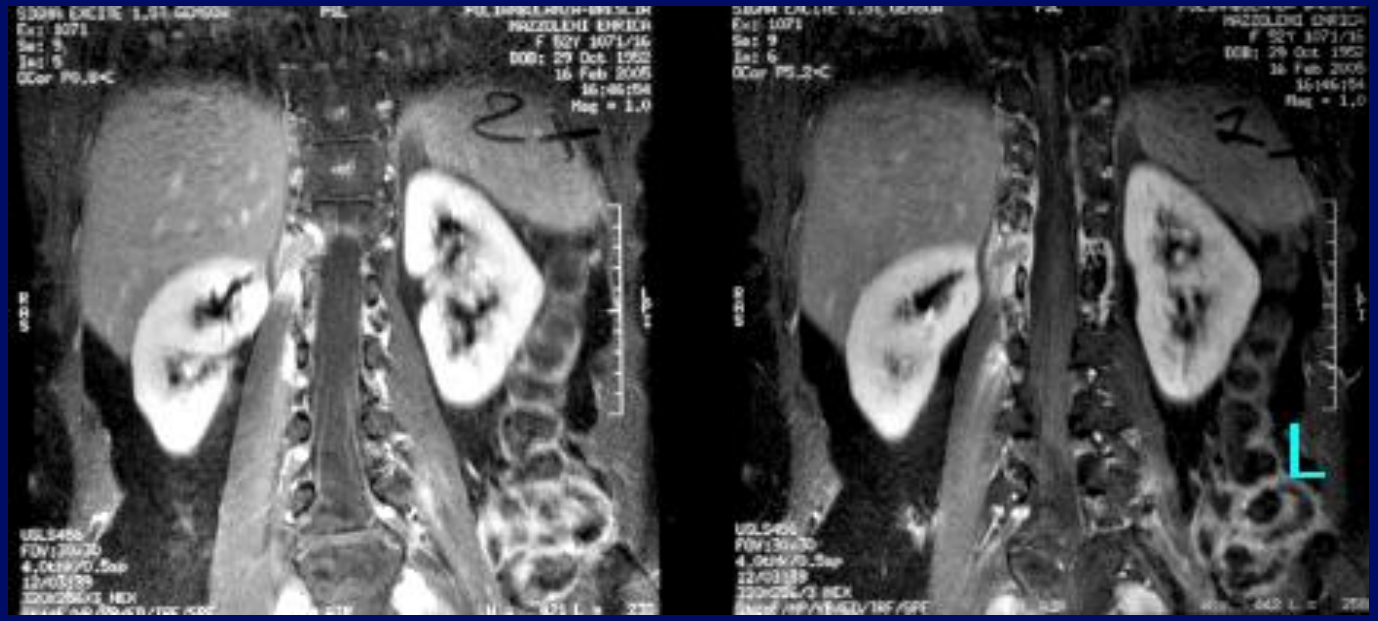
28 Gy, 75%, 4 fr
Aug ‘05



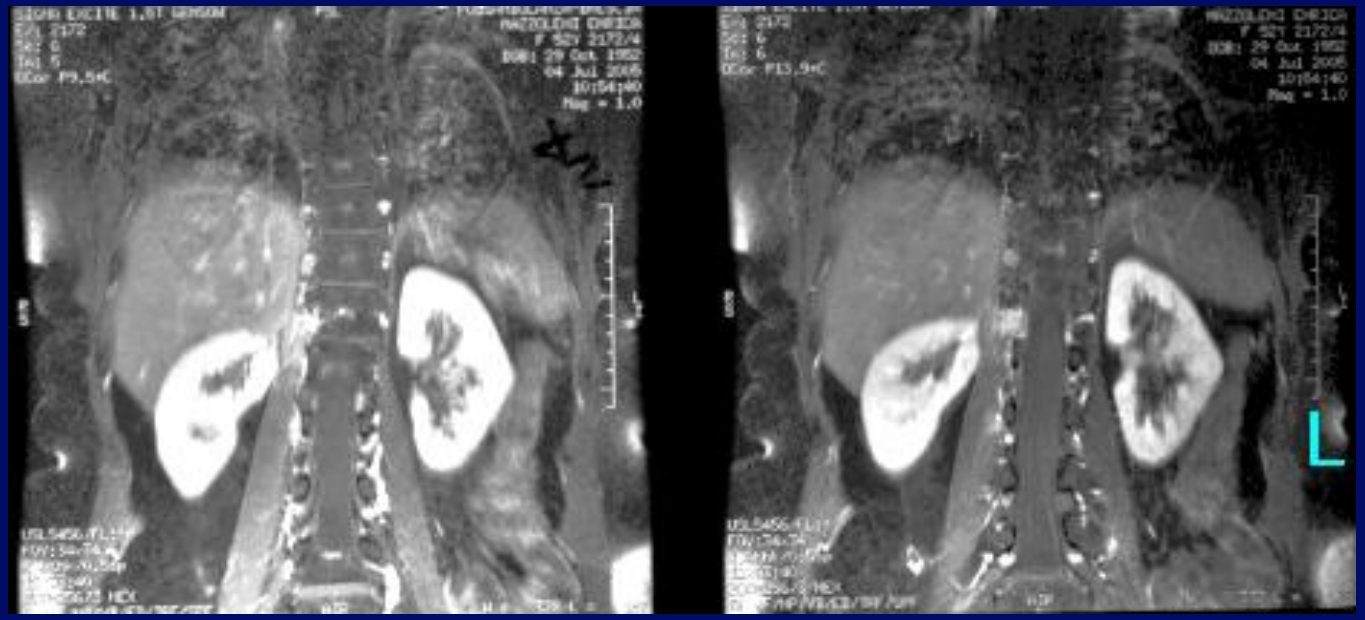
3 years after treatment


Piano
Visualiz.
Regione
Parametri modello
CreaImmag
Percor
Strum.
Vista Assiale 1
Regione: TumorSite
50mm
Isodose Linee
100%
90%
70%
50%
30%
20%
Fetta 115
Vista Sagittale
60mm
Fetta 233
Vista Coronale
Fetta 239
Istogramma volume dose
DVH regioni tumore
midollo DVH
DVH tessuto molle
Dose
0 10 20 30 40 50 60 70 80 90 100%
DVH regioni in cubo VOLUME
100% dose (cGy) = 4375.00
Dose% Volume regione (mm3)
Regioni tum. midollo molle
0 9055 7340 147868
5 9055 7340 111525
Statistiche dose
Dose massima e minima
ricevuta in regioni diverse
Seleziona regioni
(unità: cGy)
Regione Max. Min.
TumorSite 4375.00 2751.24
Tessuto molle 4238.24 28.98
tuning1 3002.09 523.19
tuning2 2182.36 654.39
Pituitary 0.00 0.00
Optic Chiasm 0.00 0.00
midollo 1981.28 302.00
renedx 2708.13 27.97

Mts ovaric carcinoma, 35Gy, 5 fz

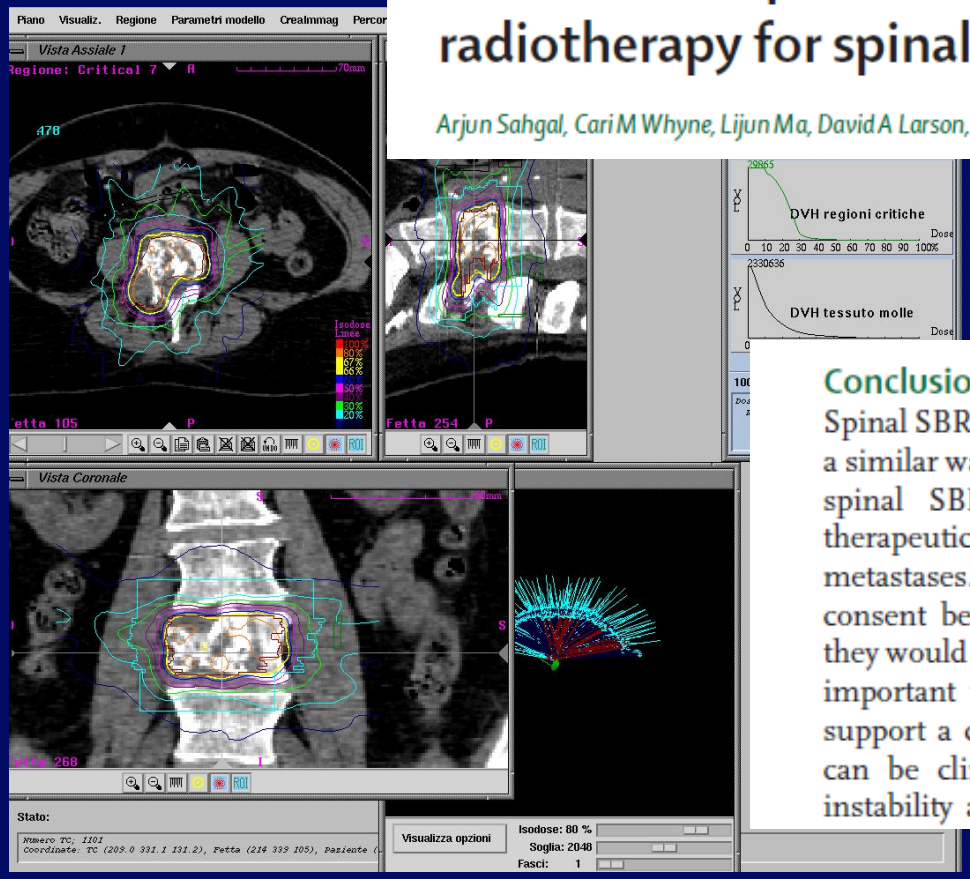


Before treatment



6 months after treatment

Breast cancer mts, 28 Gy, 4 fr



Vertebral compression fracture after stereotactic body radiotherapy for spinal metastases

Arjun Sahgal, Cari M Whyne, Lijun Ma, David A Larson, Michael G Fehlings

Conclusion

Spinal SBRT is an emerging therapy that is developing in a similar way to brain stereotactic radiosurgery, such that spinal SBRT could eventually become a standard therapeutic intervention for some patients with spinal metastases. Crucially, patients must give appropriate consent because there are serious adverse events that they would not be at risk of if treated conventionally. One important toxic effect is SBRT-induced VCF, and data support a crude risk ranging from 11% and 39%. VCF can be clinically significant, resulting in mechanical instability and a need for surgical intervention. As the

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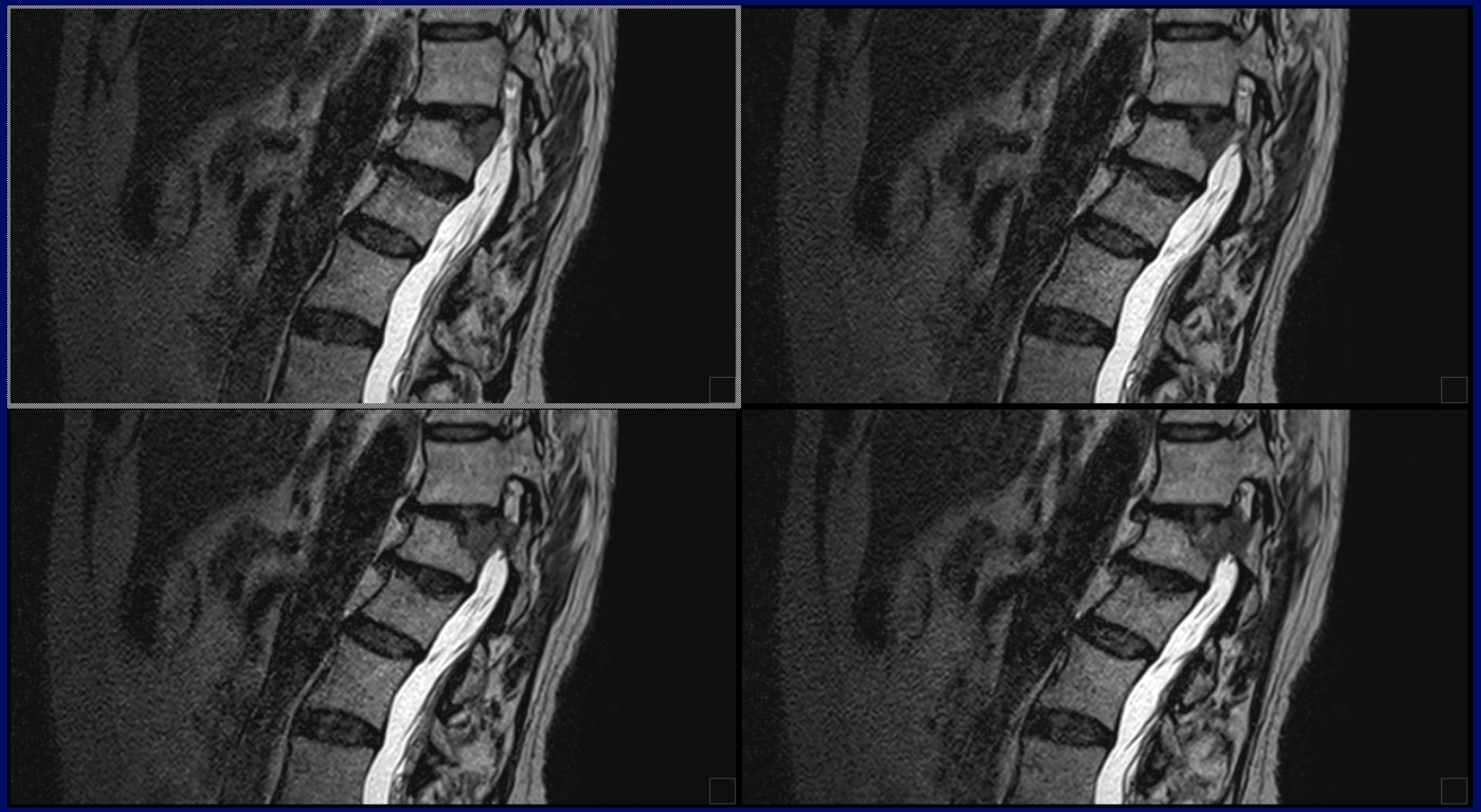
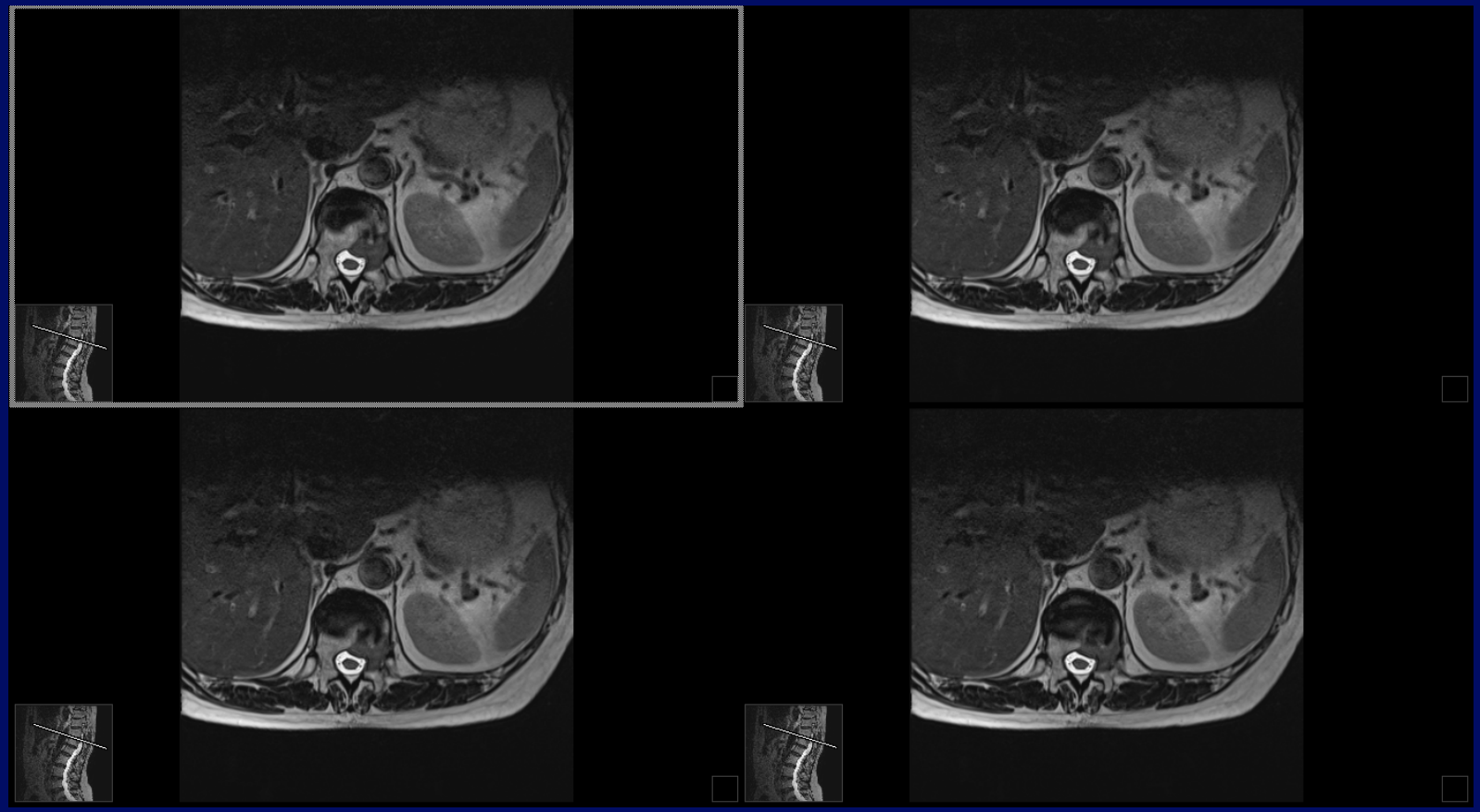
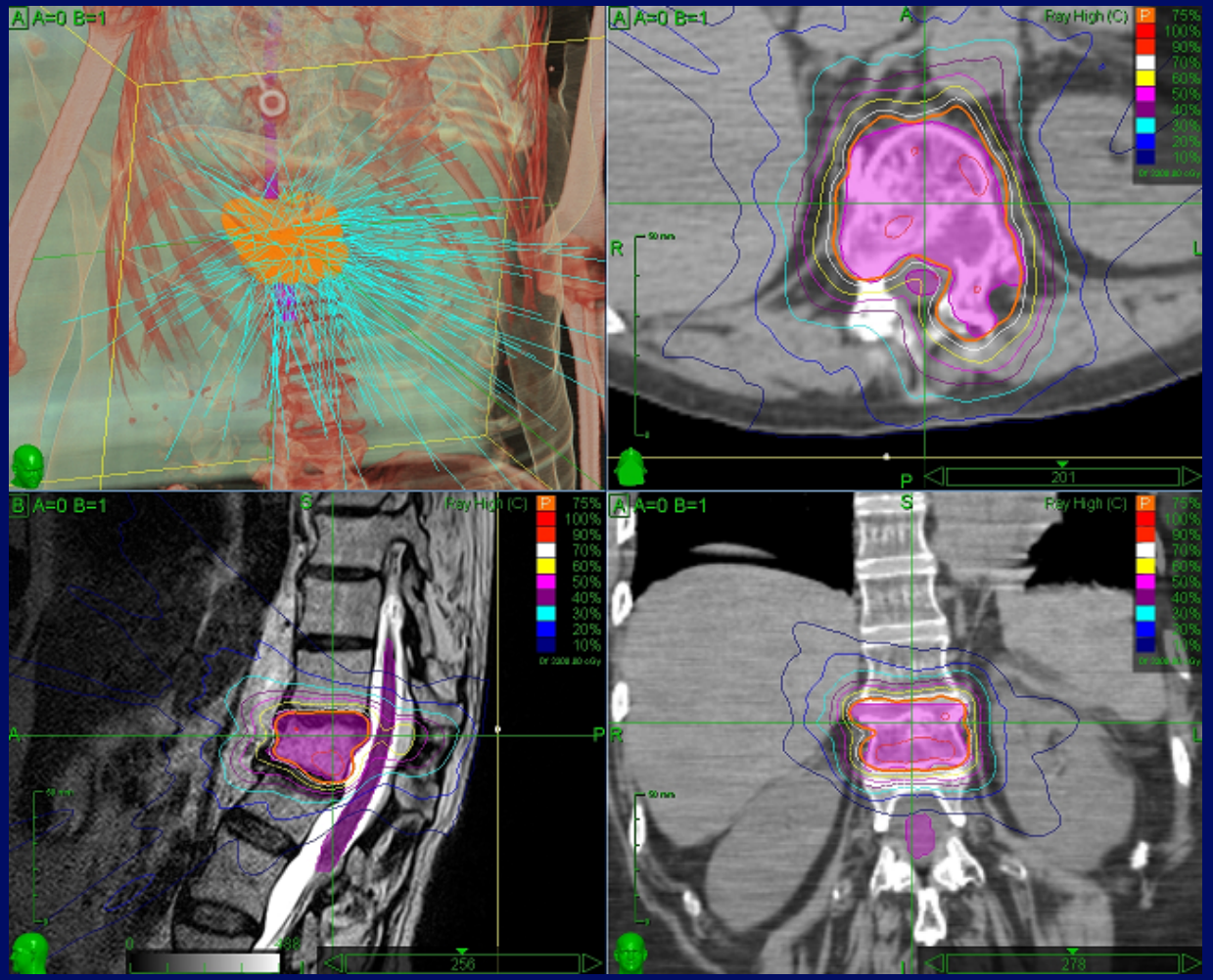
CA, f 57 anni
Ca mammella
Mts D12



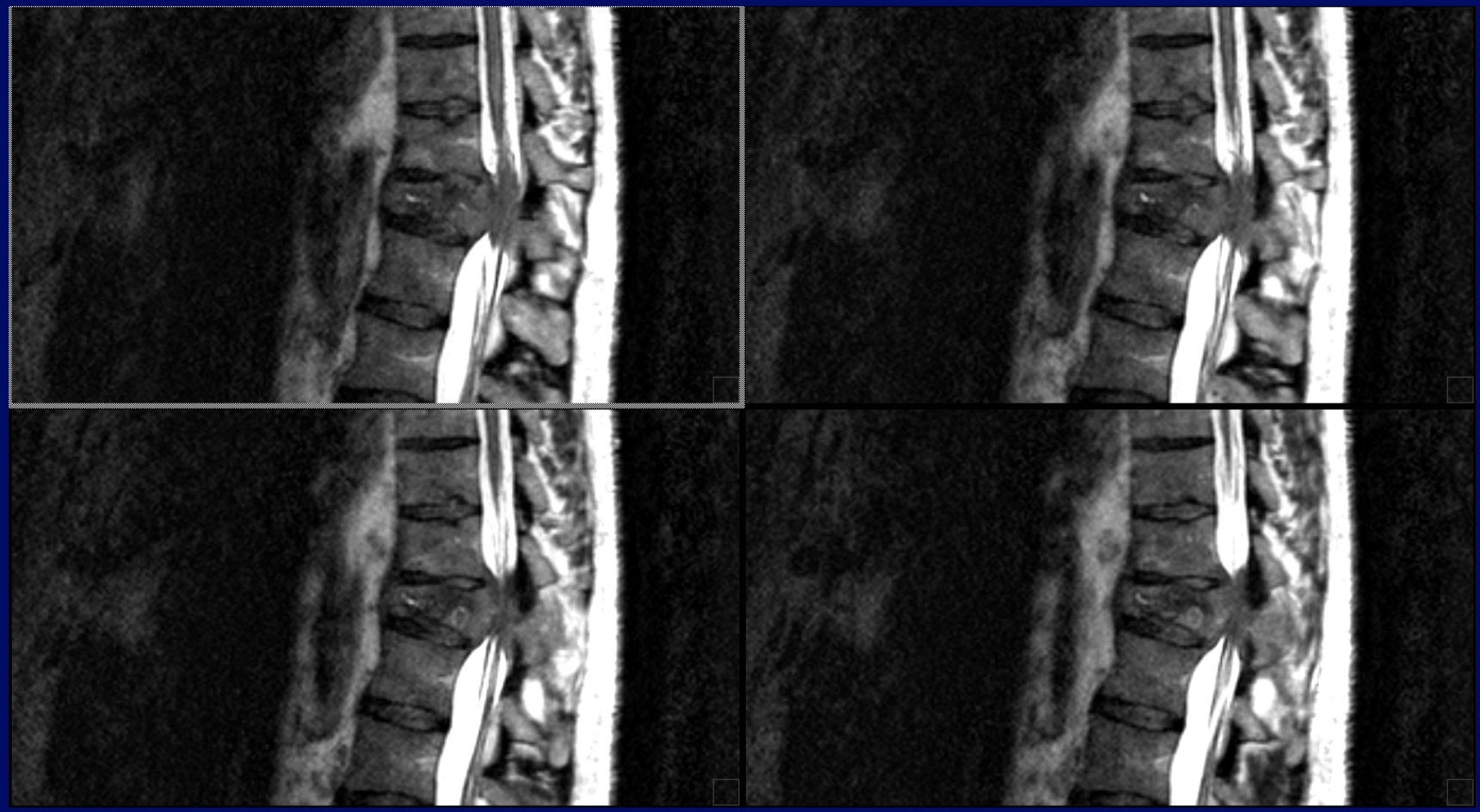
CA, f 57 anni
Ca mammella
Mts D12



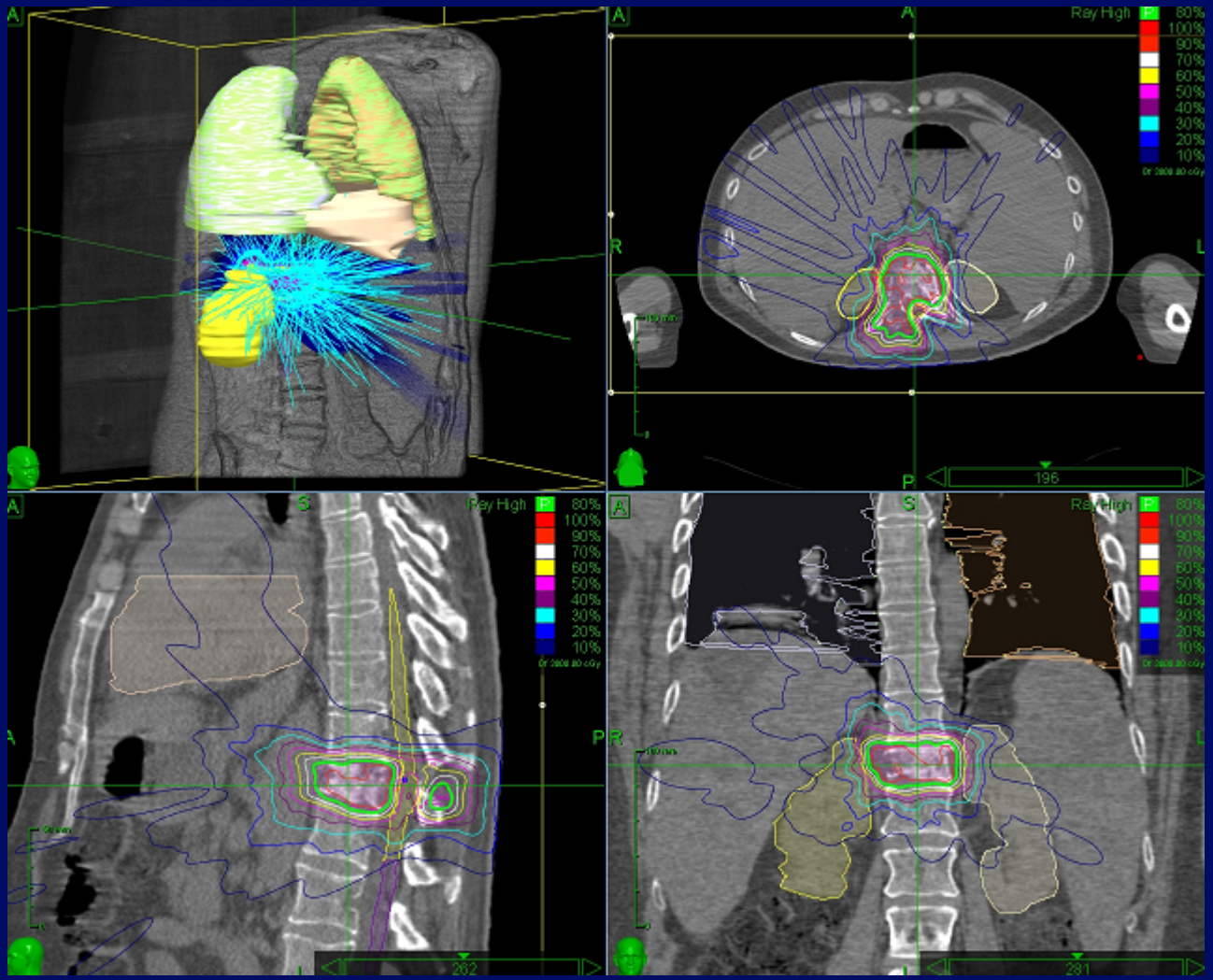
CA, f 57 anni
Ca mammella
Mts D12



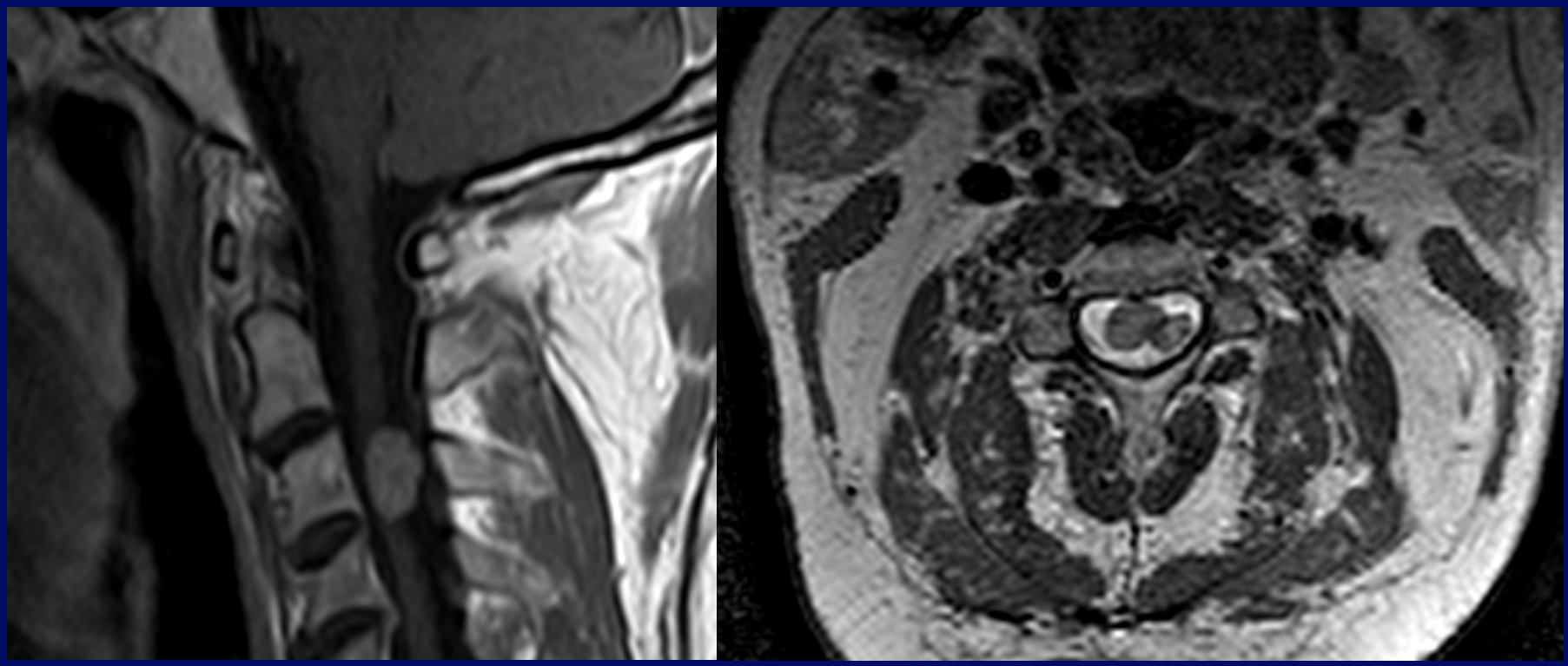
MR, m 49 anni
LH
Mts D12



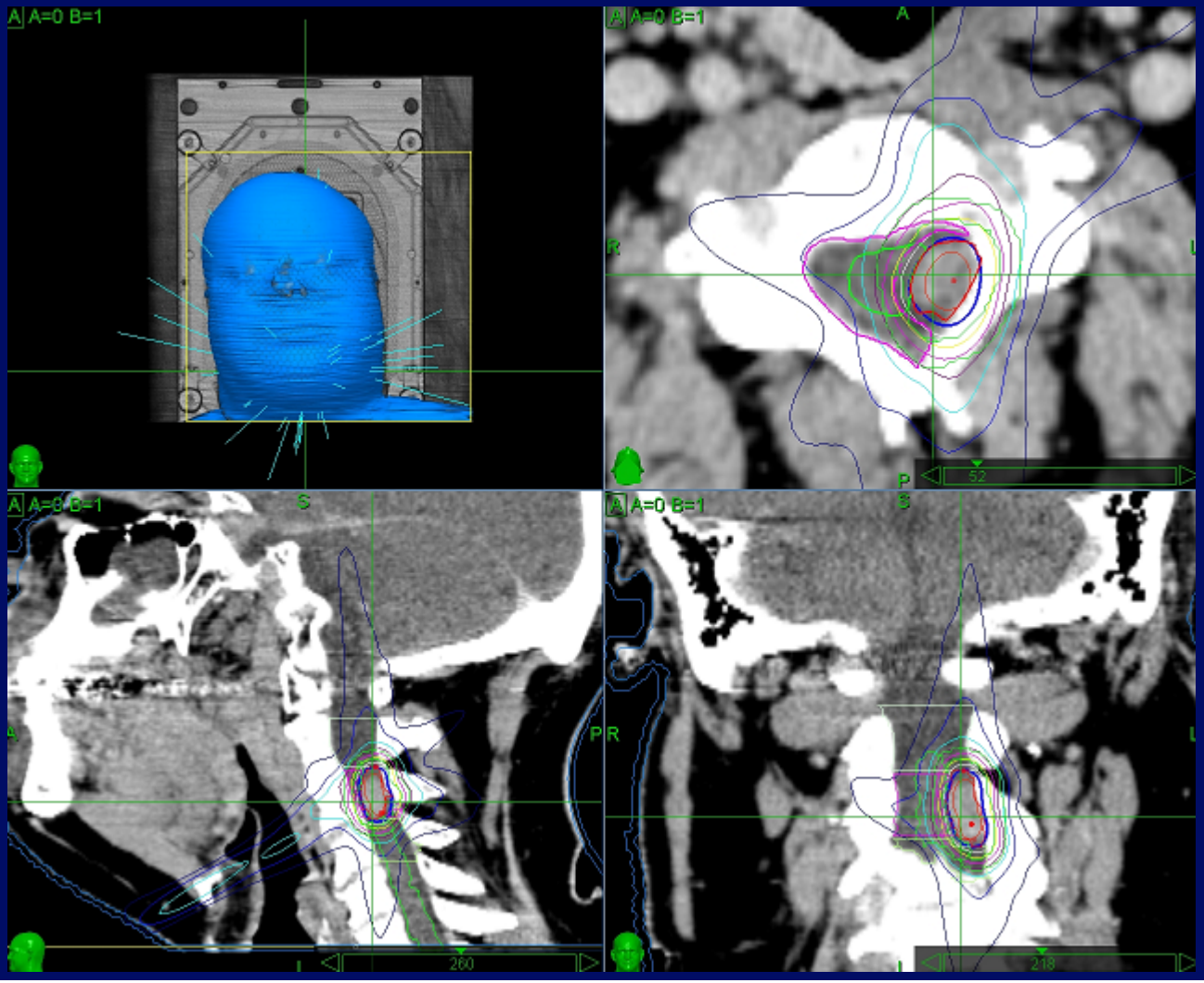
MR, m 49 anni
LH
Mts D12



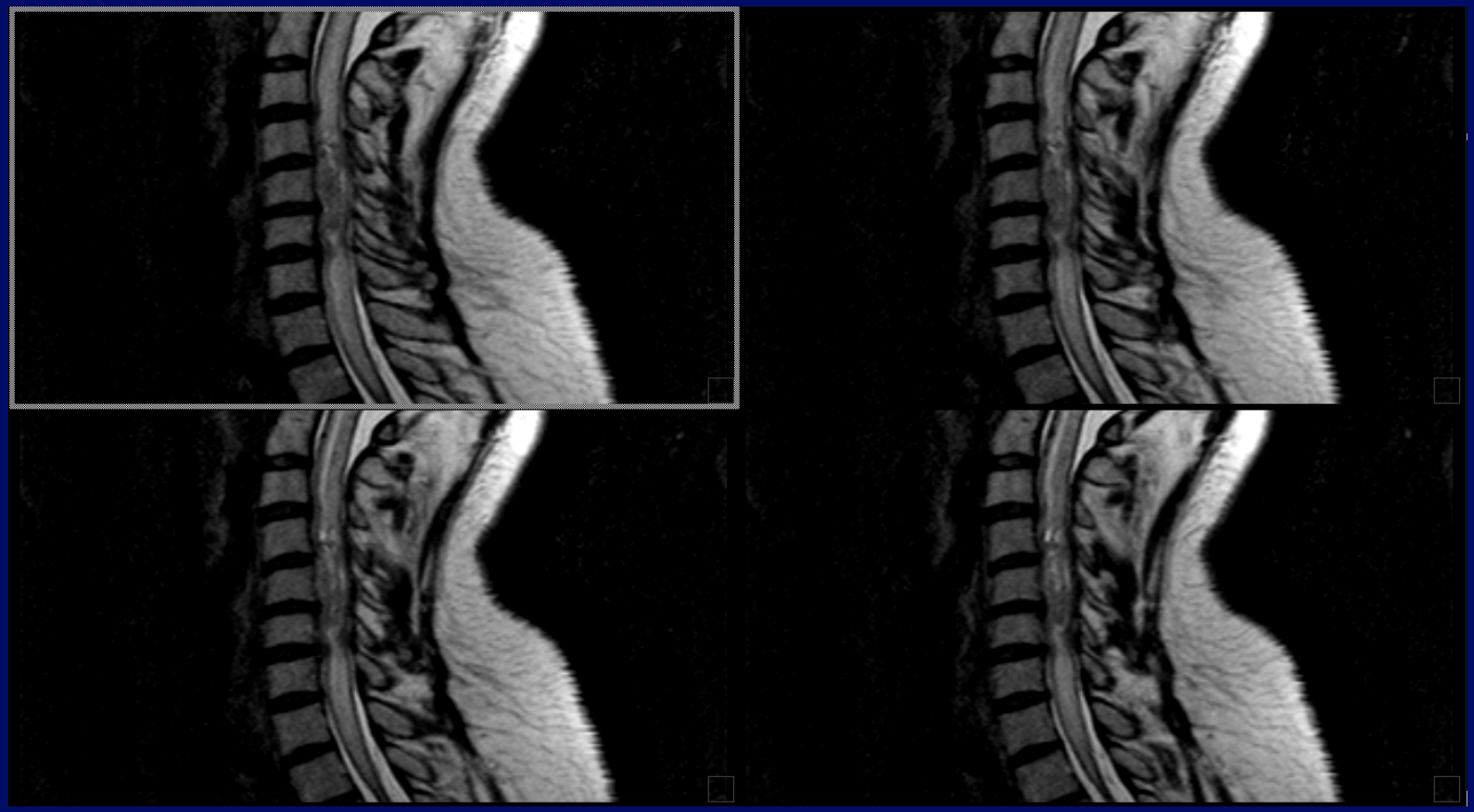
CA, m 45 anni
Ca Timico
Mts C3



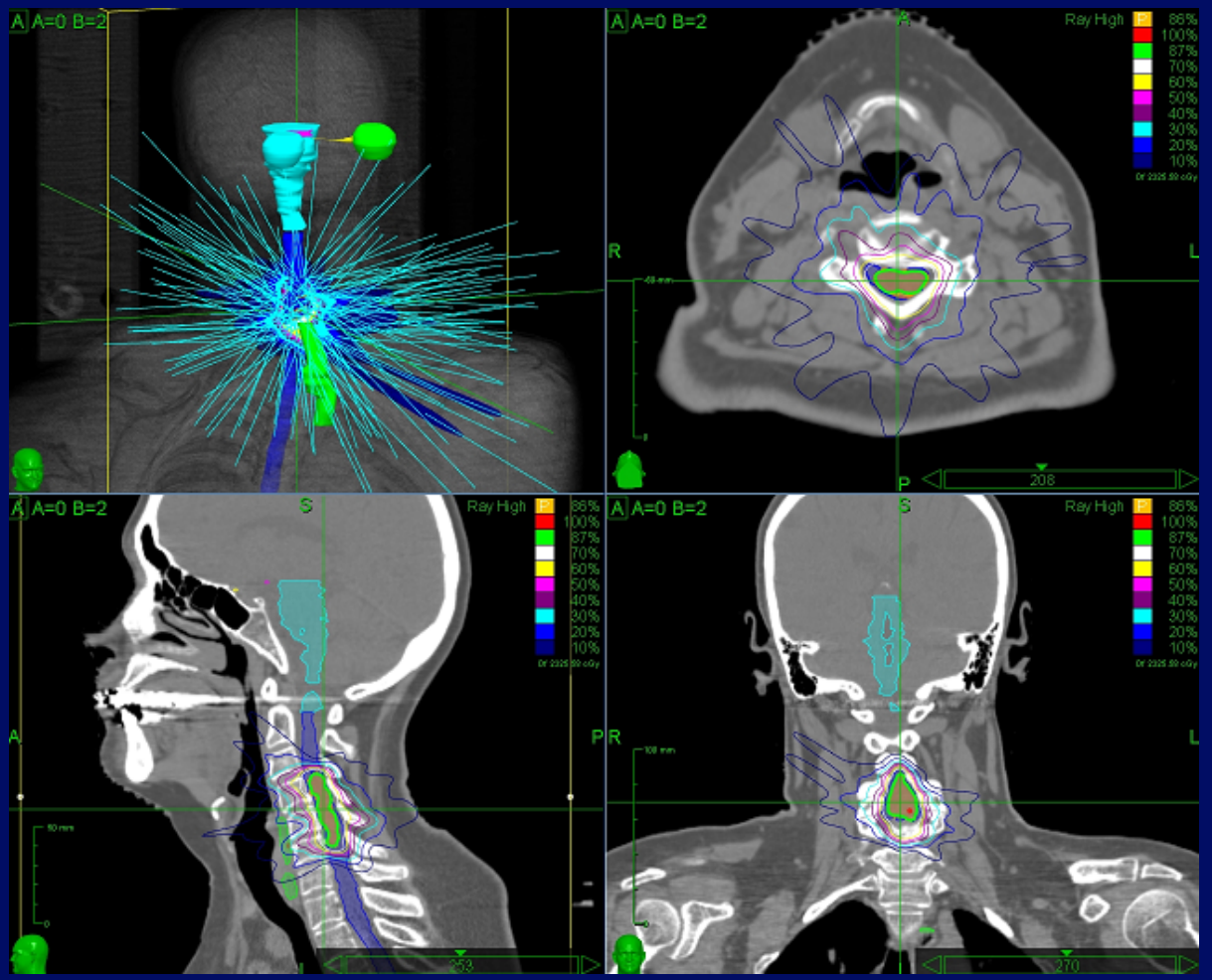
CA, m 45 anni
Ca Timico
Mts C3



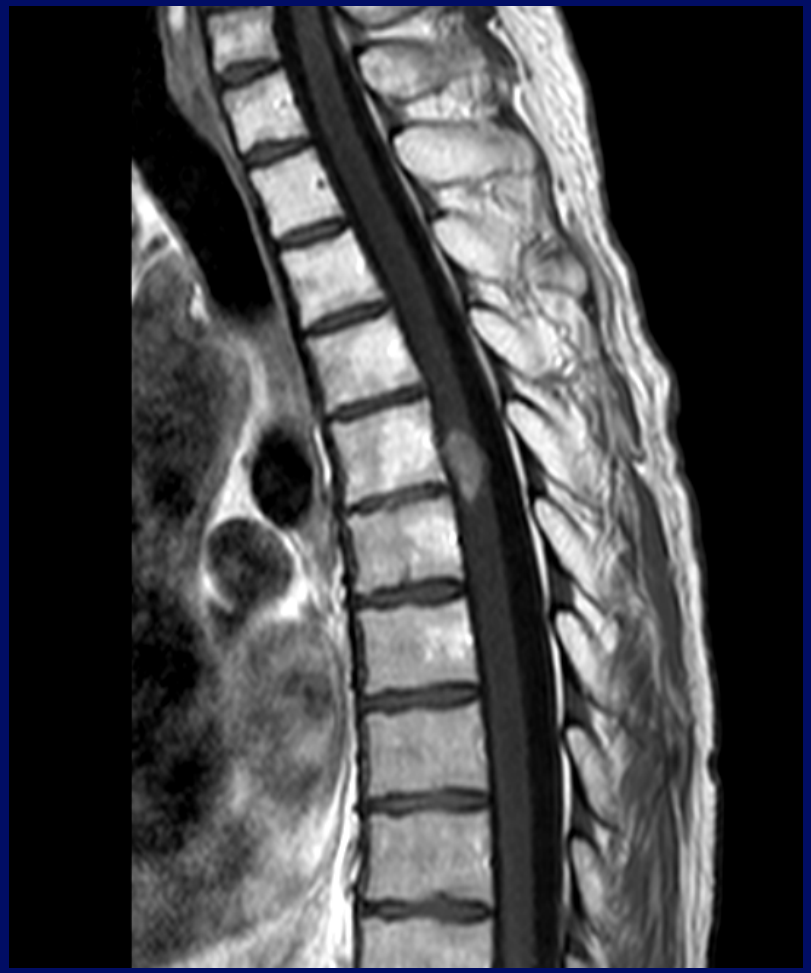
BA, f 47 anni
Ca mammella
Mts C4-C6



BA, f 47 anni
Ca mammella
Mts C4-C6



CR, m 41 anni
Ca polmone
Mts D5-D6



CR, m 41 anni
Ca polmone
Mts D5-D6