

STEREOTACTICALLY- GUIDED SPINAL RADIOSURGERY

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1. Introduction

Hamilton et al. first described spinal SRS in 1995 using a linear accelerator. ⁽¹⁴⁾

Advances in radiosurgical technology and techniques have now allowed for safe and effective treatment of many conditions involving the spine. As experience with this treatment has become more accepted and widely used, spinal radiosurgery has even become an important treatment alternative to surgery, primarily because of its appealing non-invasive nature, convenience, and efficacy. ^(4, 7, 8, 19)

Stereotactically-guided spinal radiosurgery has become a pivotal tool in the treatment of metastatic cancers, arteriovenous malformations, gliomas, ependymomas, and peripheral nerve sheath tumors. Metastatic cancer is the single most common use for this technology. Up to 70% of the 1 million individuals in the United States who are diagnosed with cancer will develop spinal metastases. Additionally, nearly 10% of cancer patients develop symptomatic spinal metastases ⁽¹⁵⁾. These spinal lesions, when symptomatic, can cause pain, skeletal instability, and neural compression. Early diagnosis and treatment of these lesions can be critical. Appropriate treatment has the potential to improve patient quality of life and in many circumstances significantly delay or prevent the progression of disease. Although surgery plays a critical role in certain cases, radiation is considered the primary treatment for spinal metastases especially when multiple lesions are present without neurological deficits ⁽⁶⁾.

In this chapter, we will review the basic principles of radiation treatment, including the tolerance of the spinal cord to radiation, histological tumor types,

the physical properties of tissue response to radiation, and the current literature evidence in supporting the safety and efficacy of this technique. Many forms of technology are available for spinal radiosurgery are based on the use of a linear accelerator (linac), which include Cyberknife and Novalis. Other technologies include Gamma Knife, which utilizes radioactive decay, and Proton Beam radiation. Our focus in this chapter will be on the linac based systems, but many of the principles are similar. Early results and experience demonstrate that SRS is both a safe and effective modality for the treatment of spinal lesions.

2. Tumor versus Normal Surrounding tissue: Variable response to Radiation and the role of Stereotaxis

The most important limiting factor with radiation treatment for lesions in the spine is radiation to the spinal cord parenchyma. Occasionally, surrounding tissues such as the esophagus or retroperitoneal organs may also need to be considered. The spinal cord is a particularly sensitive part of the CNS to the effects of radiation making precisely calculated treatment plans a requirement for safe and effective treatment without significant side effects.

Conventional external beam radiotherapy is the classic and established technique utilized for the radiation treatment of spinal lesions. With this form of radiation treatment a dose of 20-40 Gy can safely be delivered to the spine (including the spinal cord) in 5-20 fractions. Numerous studies have found that the risk of radiation myelitis following fractionated

radiation therapy is very small⁽¹¹⁾. With this form of treatment, the factor limiting the total dose delivered is the tolerance of the spinal cord to radiation⁽¹⁰⁾. Early studies evaluating the effects of spinal cord irradiation demonstrated that the risk of myelitis from irradiation of 45-50 Gy in 2 Gy fractions was 0.4 %. This dose subsequently was established as the benchmark for subsequent treatments⁽¹⁶⁾.

Stereotactic spinal radiosurgery has a tremendous advantage over conventional radiation methods in that there is often minimal radiation exposure to normal anatomic structures (eg: spinal cord, bowel, kidney, esophagus). The physics behind SRS/SBRT allows for a geometrical advantage in delivering the radiation, which therefore allows for minimal exposure to the neighboring structures. Furthermore, a major advantage of stereotactic radiosurgery is that the tumor can receive a higher dose and the cord a lower dose than is possible with conventional radiation therapy⁽⁷⁾.

The volume of the cord exposed to radiation plays a role in the development of radiation myelitis. Spinal cord constraint to 10 Gy to 10% of partial cord volume is often utilized⁽²⁰⁾. Also, 12 Gy is considered the maximum tolerant amount of spinal cord radiation. Furthermore, planning software allows for calculation of radiation dosing and in the circumstance of there being a more significant dose to important surrounding structures, modifications in the plan can be performed or the decision to stereotactically fractionate doses can also be entertained.

Mathematical modeling of likelihood of radiation myelitis is most often achieved using the linear-quadratic (LQ) model. The LQ model models biologic response to radiation. The surviving fraction of cells after a dose D is defined as:

$$SF = \exp - (\alpha D + \beta D^2) .$$

The values of α and β depend on the tissue irradiated. The surviving fraction is dependant on cell killing that is linearly related to dose (αD) and quadratically related to dose (βD^2) .

The LQ model is used to arrive at a biologically effective dose (BED). This is defined as:

$BED = nd * (1 + d/(\alpha/\beta))$ where d is the dose per fraction and n is the number of fractions. The alpha beta ratio (α/β) is estimated to be 2 for late responding

normal tissues (including the spinal cord) and 10 for more rapidly dividing malignant cells (or early responding tissues such as tumor).

BED can be used to compare various dose fractionation schemes and extrapolate from the well-studied data in fractionated radiation of the spinal cord. While validated in conventionally fractionated radiation therapy, the LQ model and BED have not been validated for use in hypofractionated radiation or SRS. BED is however, often used as a basis for comparing radiation dose fractionation schemes in hypofractionated treatments. Because of the question in using BED for application in radiosurgical cases, one must take clinical and case specific factors into consideration when making a final decision on fractionation in radiosurgery.

Another consideration in the treatment of tumors is the tumor type and the necessary radiobiological dose to treat. Tumors with a low α/β ratio (eg, sarcomas) may respond to larger fraction sizes⁽¹²⁾. Mechanisms for these radiobiological differences is unclear. Some evidence suggests that single-fraction therapy of more than 15 Gy results in tumor death by apoptosis, perhaps through a sphingomyelinase pathway⁽⁹⁾. However, microvascular damage may also occur in high-dose fractions. Because of this microvascular effect, radiosurgery expanded its applications not only to primary or secondary malignancies, but also in the treatment of vascular lesions such as arteriovenous malformations. Depending on the nidus and location of the spinal AVM, either stereotactic radiosurgery (single dose) or stereotactic radiotherapy (fractionated doses) can be utilized.

Benign tumors such as meningiomas, schwannomas and neurofibromas may also be successfully treated with stereotactic radiosurgery. Much of this treatment strategy began with intracranial lesions such as vestibular schwannomas and meningiomas. Effective doses of radiation at 12-16Gy in a single dose can often be safely delivered with good long-term control.⁽²¹⁾

Metastatic cancer to the spine is the most common indication for spinal radiosurgery. Early diagnosis and treatment of metastatic cancer with stereotactic radiosurgery may prevent the need for open surgery on many of these complex cancer patients.⁽¹⁸⁾ Because this does not directly compromise other cancer treatments such as chemotherapy, these treatments can occur concomitantly.

The most common symptom leading to spinal radiosurgery related to metastatic disease is pain. In fact, pain is often used as an indication for radiation. Pain relief after radiosurgery is a major objective of treatment and when this occurs there is thought to be good success with the treatment.^(10,19) Several reports show that more than 80% of patients who presented with pain improved after radiation⁽¹³⁾. Local tumor control rate of 90% at 6 months was achieved for both metastatic lesions and benign tumors^(5,6). Most radiosurgery failure may be secondary to significant epidural mass in the spinal canal or insufficient radiation dose due to previous radiation.

Twenty-one spinal AVM were treated from 1997-2006 at a single institution⁽²²⁾. AVM obliteration was partial in 4 and complete in 2 of the 6 patients on follow-up angiography. Significant obliteration was observed in nearly every case observed on MRI at 1 year.

Another applications have been used including radiosurgery for the prevention of fibrosis after nerve root exploration⁽¹¹⁾ or to target ganglia and nerve structures in the spine to treat dermatomal pain⁽¹²⁾.

3. Other techniques in Spinal Radiosurgery:

Image guidance systems such as the Exac Trac relies on X-ray confirmation just before and during the radiation treatment to ascertain the position of the patient for added verification. Now, cone beam CT scan is also available as part of the radiosurgery delivery device. Near real-time computer generated image fusion has allowed the development of these stereotactic techniques no longer dependent on a rigid fixation device.⁽¹⁷⁾

In many instances, lesions can be seen in spinal imaging and be of unclear significance. These lesions can be benign or be signs of metastatic disease. Image fusion

in many instances, utilizing PET-CT fusion, can help determine if a lesion has hypermetabolism. These “hot” spots can then be targeted with radiosurgery. Many believe this is beneficial in early detection and improved treatment. In addition, diffusion tensor imaging has also allowed for interesting anatomic analysis of the spinal cord, guiding decision making for radiosurgical treatment.

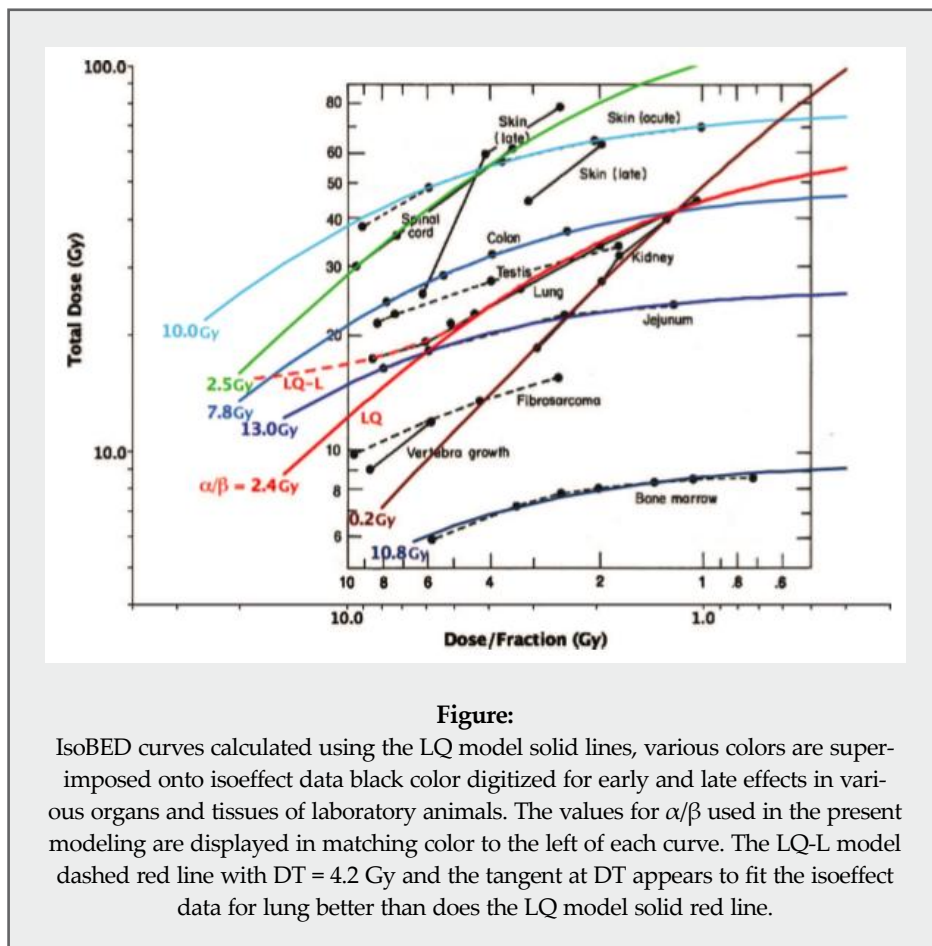


Figure:

IsoBED curves calculated using the LQ model solid lines, various colors are superimposed onto isoeffect data black color digitized for early and late effects in various organs and tissues of laboratory animals. The values for α/β used in the present modeling are displayed in matching color to the left of each curve. The LQ-L model dashed red line with DT = 4.2 Gy and the tangent at DT appears to fit the isoeffect data for lung better than does the LQ model solid red line.

TABLE III. Summary of suggested dose constraints for various critical organs. Note that for serial tissues, the volume-dose constraints are given in terms of the critical maximum tissue volume that should receive a dose equal to or greater than the indicated threshold dose for the given number of fractions used. For parallel tissue, the volume-dose constraints are based on a critical minimum volume of tissue that should receive a dose equal to or less than the indicated threshold dose for the given number of fractions used.

Serial tissue	Max critical volume above threshold	One fraction		Three fractions		Five fractions		End point (Grade II)
		Threshold dose (Gy)	Max point dose (Gy) ^a	Threshold dose (Gy)	Max point dose (Gy) ^a	Threshold dose (Gy)	Max point dose (Gy) ^a	
Optic pathway	<0.2 cc	8	10	15.3 (3.1 Gy/fx)	17.4 (3.5 Gy/fx)	23 (4.6 Gy/fx)	25 (5 Gy/fx)	Neuritis
Cochlea			9		17.1 (3.7 Gy/fx)		25 (5 Gy/fx)	Hearing loss
Brainstem								Cranial neuropathy
Lower mandible	<0.5 cc	10	15	18 (6 Gy/fx)	23.1 (7.7 Gy/fx)	23 (4.6 Gy/fx)	31 (6.2 Gy/fx)	Myelitis
Spinal cord and cauda	<0.35 cc	10	14	18 (6 Gy/fx)	21.9 (7.3 Gy/fx)	23 (4.6 Gy/fx)	30 (6 Gy/fx)	
Spinal cord subvolume (5-6 mm above and below level treated per Rys)	<10% of subvolume	10	14	18 (6 Gy/fx)	21.9 (7.3 Gy/fx)	23 (4.6 Gy/fx)	30 (6 Gy/fx)	Myelitis
Cauda equina	<3 cc	14	16	21.9 (7.3 Gy/fx)	24 (8 Gy/fx)	30 (6 Gy/fx)	32 (6.4 Gy/fx)	Neuritis
Sacral plexus	<3 cc	14.4	16	22.5 (7.5 Gy/fx)	24 (8 Gy/fx)	30 (6 Gy/fx)	32 (6.4 Gy/fx)	Neuropathy
Esophagus ^b	<5 cc	11.9	15.4	17.7 (3.9 Gy/fx)	25.2 (8.4 Gy/fx)	19.5 (3.9 Gy/fx)	35 (7 Gy/fx)	Stricture/ulcer
Brachial plexus	<3 cc	14	17.5	20.4 (6.8 Gy/fx)	24 (8 Gy/fx)	27 (5.4 Gy/fx)	30.5 (6.1 Gy/fx)	Neuropathy
Heart/pericardium	<15 cc	16	22	24 (8 Gy/fx)	30 (10 Gy/fx)	32 (6.4 Gy/fx)	38 (7.6 Gy/fx)	Pericarditis
Gastric antrum	<10 cc	31	37	39 (13 Gy/fx)	45 (15 Gy/fx)	47 (9.4 Gy/fx)	53 (10.6 Gy/fx)	Aneurysm
Trachea and large bronchi ^b	<4 cc	10.5	20.2	15 (5 Gy/fx)	30 (10 Gy/fx)	16.5 (3.3 Gy/fx)	40 (8 Gy/fx)	Stricture/ulcer
Bronchus-small airways	<0.5 cc	12.4	13.3	18.9 (6.3 Gy/fx)	23.1 (7.7 Gy/fx)	21 (4.2 Gy/fx)	33 (6.6 Gy/fx)	Stricture with atelectasis
Liv	<1 cc	22	30	28.8 (9.6 Gy/fx)	34.9 (11.6 Gy/fx)	33 (7 Gy/fx)	43 (8.6 Gy/fx)	Pain or fracture
Skin	<30 cc	23	26	30 (10 Gy/fx)	33 (11 Gy/fx)	36.5 (7.3 Gy/fx)	39.5 (7.9 Gy/fx)	Ulceration
Stomach	<10 cc	11.2	12.4	16.5 (5.5 Gy/fx)	23.2 (7.4 Gy/fx)	18 (3.6 Gy/fx)	32 (6.4 Gy/fx)	Ulceration/ulcer
Duodenum ^b	<3 cc	11.2	12.4	16.5 (5.5 Gy/fx)	22.2 (7.4 Gy/fx)	18 (3.6 Gy/fx)	32 (6.4 Gy/fx)	Ulceration
	<10 cc	9		11.4 (3.8 Gy/fx)		12.5 (2.5 Gy/fx)		
Jejunum/Ileum ^b	<5 cc	11.9	15.4	17.7 (3.9 Gy/fx)	25.2 (8.4 Gy/fx)	19.5 (3.9 Gy/fx)	35 (7 Gy/fx)	Enteritis/stricture
Colon ^b	<20 cc	14.3	18.4	24 (8 Gy/fx)	28.2 (9.4 Gy/fx)	25 (5 Gy/fx)	38 (7.6 Gy/fx)	Colitis/stenosis
Rectum ^b	<20 cc	14.3	18.4	24 (8 Gy/fx)	28.2 (9.4 Gy/fx)	25 (5 Gy/fx)	38 (7.6 Gy/fx)	Proctitis/stenosis
Bladder wall	<15 cc	11.4	18.4	16.8 (5.6 Gy/fx)	28.2 (9.4 Gy/fx)	18.3 (3.6 Gy/fx)	38 (7.6 Gy/fx)	Cystitis/stenosis
Penile bulb	<3 cc	14	34	21.9 (7.3 Gy/fx)	42 (14 Gy/fx)	30 (6 Gy/fx)	50 (10 Gy/fx)	Impotence
Femoral heads (right and left)	<10 cc	14		21.9 (7.3 Gy/fx)		30 (6 Gy/fx)		Necrosis
Renal hilum/vascular trunk	<2/3 volume	10.6	18.6 (6.2 Gy/fx)			23 (4.6 Gy/fx)		Malfunction/hypertension

Figure:

53 year old female with metastatic breast cancer who developed neck pain. A mass was seen at C2. Stereotactic radiosurgery was administered with a dose of 12 Gy to 90%. Images show the initial lesion seen and a new MRI 1.5 years later.

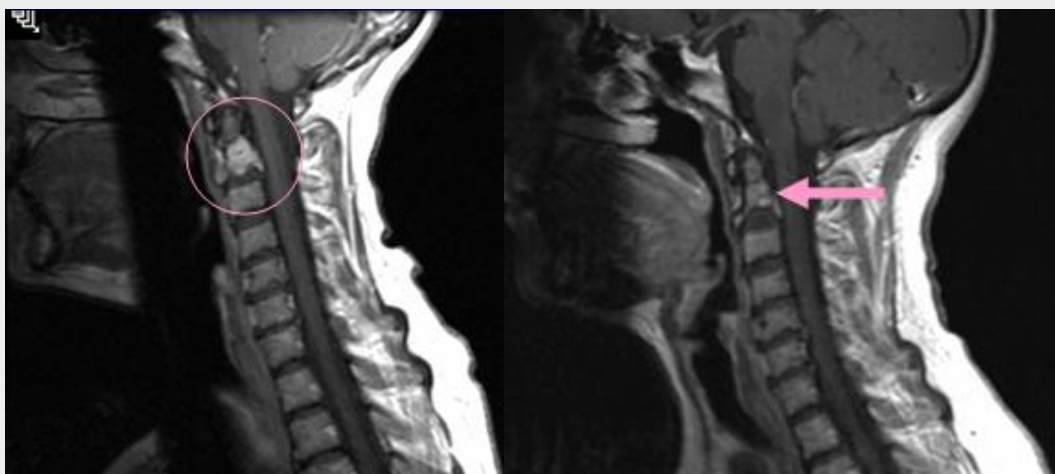


Figure:

Example of large metastatic focus that can be safely treated with stereotactic radiosurgery and avoidance of dangerous dose to spinal cord.

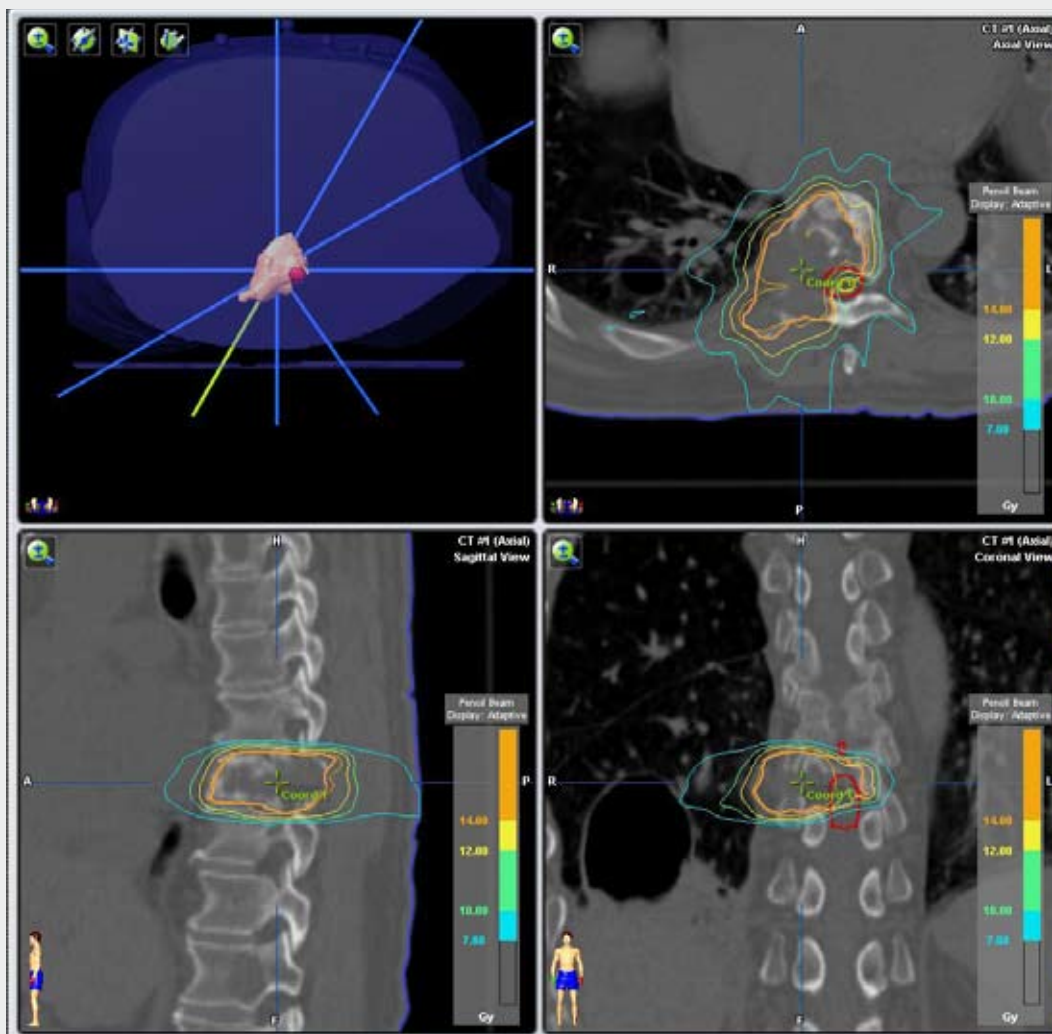
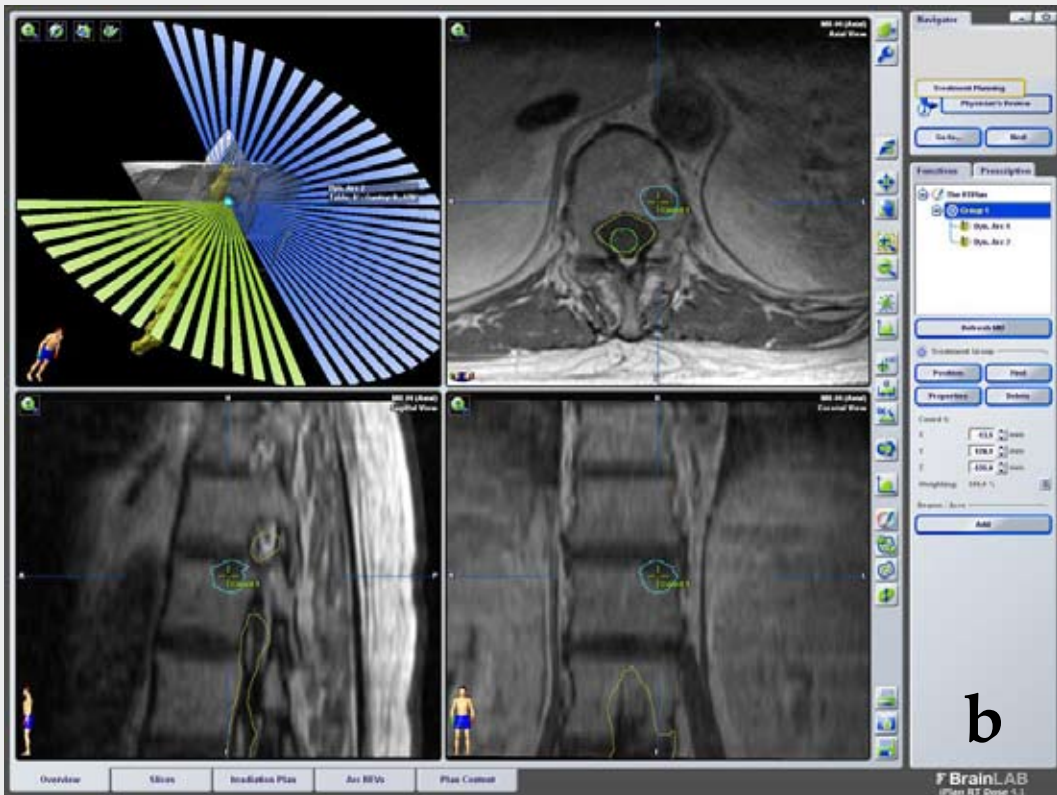
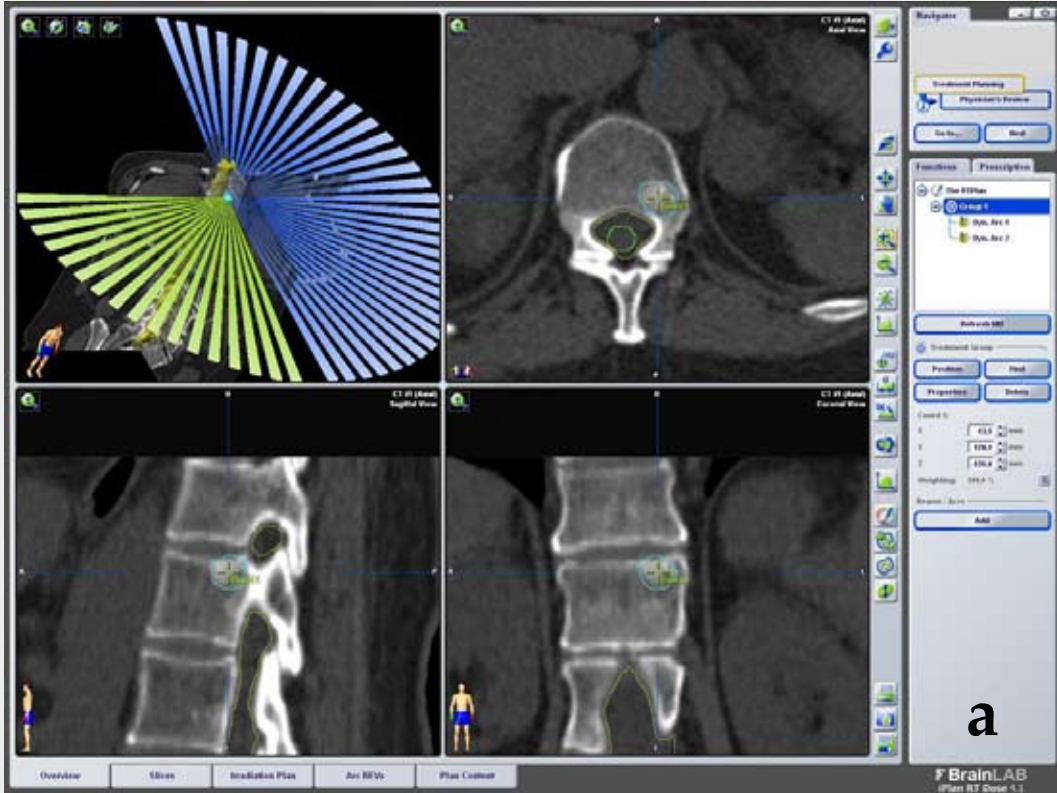
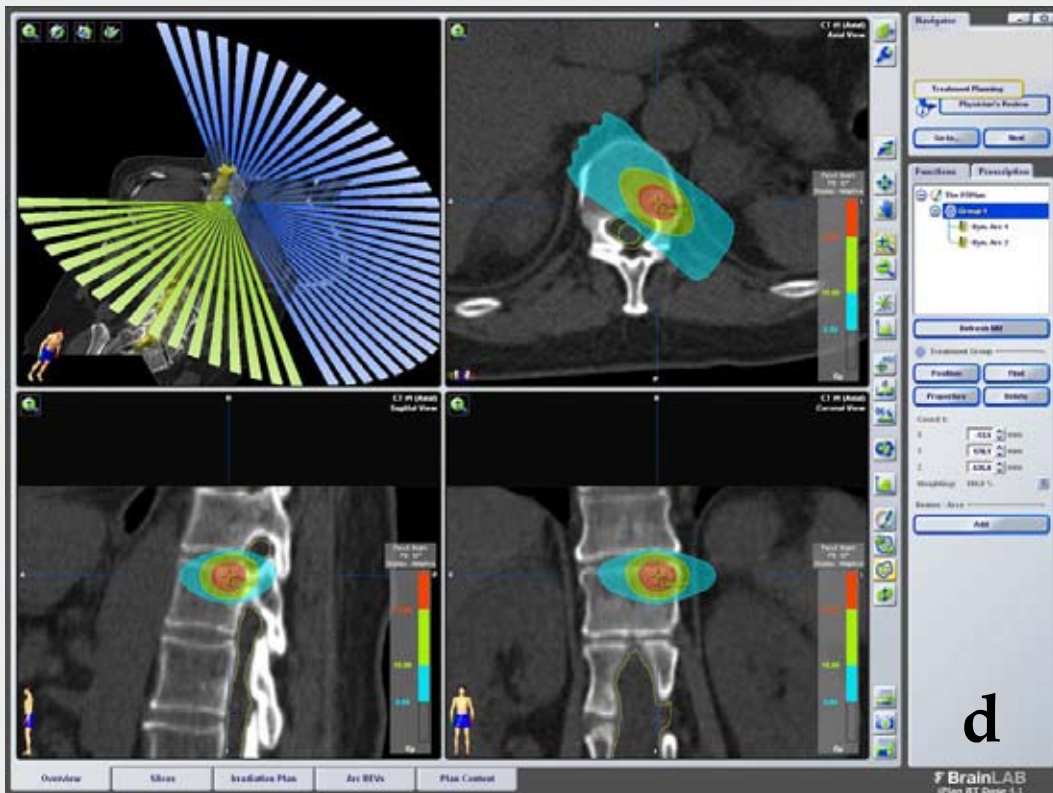
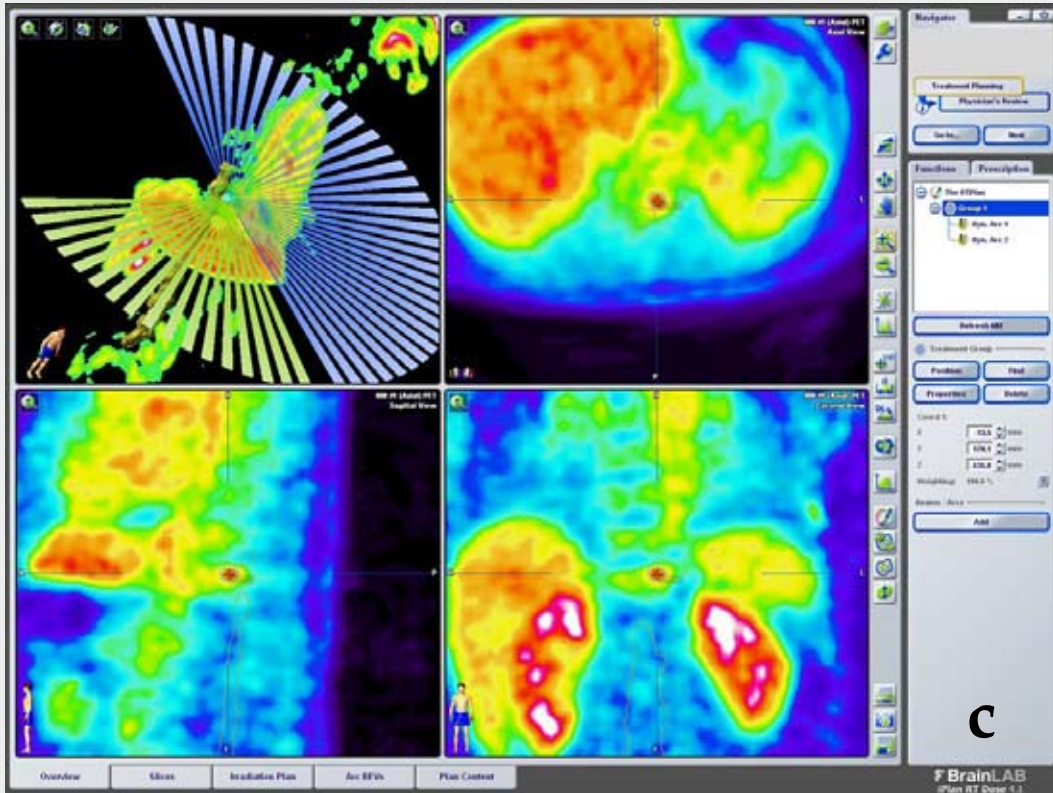


Figure:

Imaging showed a lower thoracic metastatic lesion on the left just in front of the pedicle-body junction.

A) CT scan demonstrates osteoblastic activity in this region. B) MRI demonstrates a non-enhancing mass that's T1 hypointense. C) PET imaging shows this spot as being hypermetabolic D) Final treatment plan with very safe dose affecting lower spinal cord, but high dose given to metastatic lesion.





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