Spine Tumors & Non-spine Bone Metastases: Evolution of Hypofractionation

Aster
INTERNATIONAL INSTITUTE OF
ONCOLOGY
Complete Cancer Care

durgapoorna@gmail.com

Dr Durgapoorna
Kochi

30/10; 20/5; 8Gy

- MC (90%) - Met - lung, prostate, breast, kidney
- Overall pain response rates of ~ 60%
- Complete pain response rates ~ 10–25%

Rich, Shayna E., et al. "Update of the systematic review of palliative radiation therapy fractionation for bone metastases." Radiotherapy and Oncology 126.3 (2018): 547-557.

Chow, Ronald, et al. "Single vs multiple fraction palliative radiation therapy for bone metastases: Cumulative meta-analysis." Radiotherapy and Oncology 141 (2019): 56-61

Better survival

- Improved systemic Rx
- Also local modalities
- Target mutations - melanoma, lung

- Durable symptom mx
- Potential late side effects with large volume
- Cure!!

However

- Longer time to start
- Resource
- Increased toxicity

- Only after Liver & lung - dose fall off in mm
- Serial
- Catastrophic

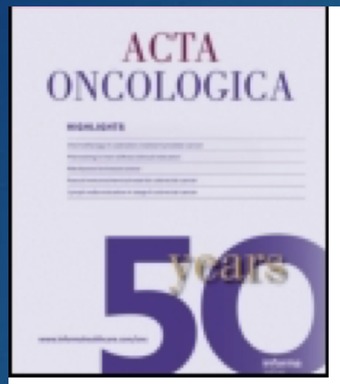
- Minimal inter fraction change & little intrafraction movement
- On board imaging - Xray, CT
- Planning - arcs, IMRT

Osborn, Virginia W., Anna Lee, and Yoshiya Yamada. "Stereotactic body radiation therapy for spinal malignancies." Technology in Cancer Research & Treatment 17 (2018): 1533033818802304.

SBRT

- An external beam radiation therapy method used to very precisely deliver a high dose of radiation to an extracranial target within the body, using either a single dose or a small number of fractions.
- Tumor antigen-specific immune response, endothelial/vascular injury, or increased cell kill secondary to higher delivered dose

Potters, Louis, et al. "American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the performance of stereotactic body radiation therapy." International journal of radiation oncology, biology, physics 76.2 (2010): 326-332.



Acta Oncologica

ISSN: 0284-186X (Print) 1651-226X (Online) Journal homepage: https://www.tandfonline.com/loi/ionc20

Stereotactic High Dose Fraction Radiation Therapy of Extracranial Tumors Using An Accelerator: Clinical experience of the first thirty-one patients

Henric Blomgren, Ingmar Lax, Ingemar Näslund & Rut Svanström

To cite this article: Henric Blomgren, Ingmar Lax, Ingemar Näslund & Rut Svanström (1995) Stereotactic High Dose Fraction Radiation Therapy of Extracranial Tumors Using An Accelerator: Clinical experience of the first thirty-one patients, Acta Oncologica, 34:6, 861-870, DOI: 10.3109/02841869509127197

To link to this article: https://doi.org/10.3109/02841869509127197

https://strawberryindigo.wordpress.com/2013/07/28/the-leap/leap-of-faith-fish/

MSKCC

- 811 spine metastases in 657 patients,
- Median of 24 Gy ; median follow-up of 26.9 months
- Local failure <1% - 12 Months ; 3.1% at 48 months
- Median 17.09 Gy vs 23.56 - local failure 14% vs 2.1% at 48 months
- Independent of histology

Yamada, Yoshiya, et al. "The impact of histology and delivered dose on local control of spinal metastases treated with stereotactic radiosurgery." Neurosurgical focus 42.1 (2017): E6.

UPMC

- 500 spinal mets
- 12.5 to 25 Gy single
- Long term pain control - 86%
- Long term control - 90%; 88% of prior RT

Gerszten, Peter C., et al. "Radiosurgery for spinal metastases: clinical experience in 500 cases from a single institution." Spine 32.2 (2007): 193-199.

MDACC

- N=61
- 16 to18 Gy - nonrenal cell histologies (n=30)
- 16 to 24 Gy - renal cell (n=33)
- Mean FU - 20 Months
- Local control - 88%

Garg, Amit K., et al. "Phase 1/2 trial of single-session stereotactic body radiotherapy for previously unirradiated spinal metastases." Cancer 118.20 (2012): 5069-5077.

NOMS Framework

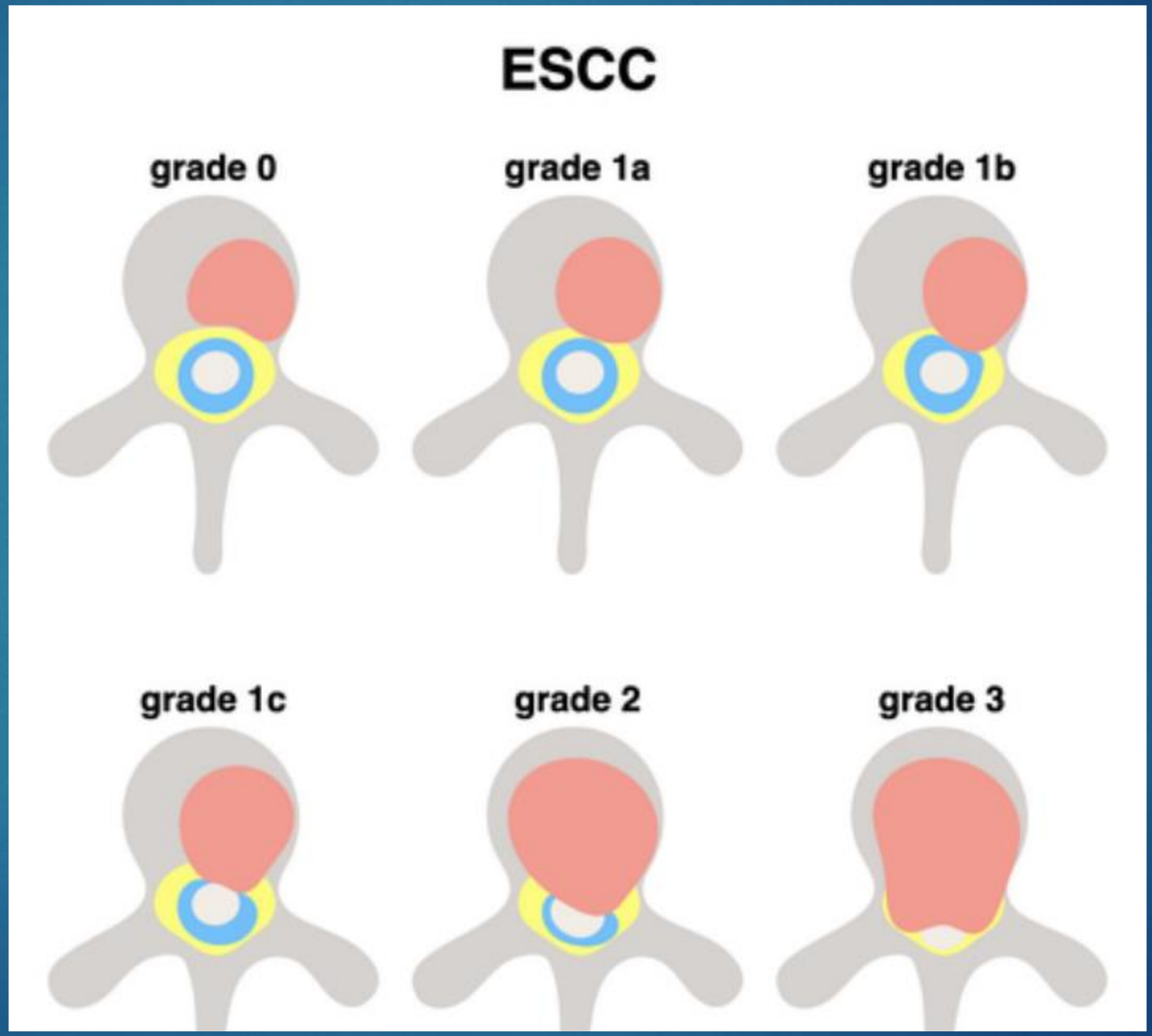
Neurologic	Oncologic	Mechanical	Systemic	Decision
Low-grade ESCC + no myelopathy	Radiosensitive	Stable		cEBRT
	Radiosensitive	Unstable		Stabilization → cEBRT
	Radioresistant	Stable		SRS
	Radioresistant	Unstable		Stabilization → SRS
High-grade ESCC ± myelopathy	Radiosensitive	Stable		cEBRT
	Radiosensitive	Unstable		Stabilization → cEBRT
	Radioresistant	Stable	Tolerate surgery	Decomp/stab → SRS
	Radioresistant	Stable	Unable to tolerate	cEBRT
	Radioresistant	Unstable	Tolerate surgery	Decomp/stab → SRS
	Radioresistant	Unstable	Unable to tolerate	Stabilization → cEBRT

Laufer, Ilya, et al. "The NOMS framework: approach to the treatment of spinal metastatic tumors." The oncologist 18.6 (2013): 744-751.

SINS Score

Location:	
• junctional: occiput-C2, C7-T2, T11-L1, L5-S1	3 points
• mobile spine: C3-C6, L2-L4	2 points
• semirigid: T3-T10	1 point
• rigid: S2-S5	0 point
Pain:	
• mechanical pain: improves with recumbency or pain with movement or spinal loading	3 points
• occasional pain but not mechanical	1 point
• painless lesion	0 point
Bone lesion:	
• lytic	2 points
• mixed	1 point
• blastic	0 point
Radiographic spinal alignment:	
• subluxation/translation	4 points
• de novo deformity (kyphosis/scoliosis)	2 points
• normal alignment	0 point
Vertebral body collapse:	
• >50% collapse	3 points
• <50% collapse	2 points
• no collapse with >50% vertebral body involved	1 point
• none of the above	0 point
Posterior spinal element involvement:	
• bilateral	3 points
• unilateral	1 point
• none of the above	0 point

Bilsky grade



MDACC

- N=63
- 30/5 vs 27/3 - no diffce
- N=149; 27 TO 30/3
- Less pain, opioid at 6 mo
- PFS 80.5% - 1 Yr & 72.5% - 2 yrs

Chang, Eric L., et al. "Phase I/II study of stereotactic body radiotherapy for spinal metastasis and its pattern of failure." Journal of Neurosurgery: Spine 7.2 (2007): 151-160.
Wang, Xin Shelley, et al. "Stereotactic body radiation therapy for management of spinal metastases in patients without spinal cord compression: a phase 1–2 trial." The lancet oncology 13.4 (2012): 395-402.

PAINFUL SPINAL METS

INSTANT ONCOLOGY

Saghal et al. 2021[1]

RECRUITED 2016-19

ECOG PS 0-2 • Only 8% were PS2, median age 64 ∴ fitter than the "typical" palliative patient.
MRI-confirmed
SINS ≤ 12 (Spinal Instability Neoplasia Score)[3]
≥2 points on the Brief Pain Inventory[4] • Worst pain in the past 24h? Scale of 0-10

Exclusions:
- MSCC/cauda equina
- Previous RTX to target
- CTX 1 week pre/post
- Spinal decompression • Surgery is still gold standard for MSCC if eligible.

MRI spine, BPI, SINS, QoL, analgesia requirement

Random 1:1

8/1 with single posterior field is SoC, faster to plan, faster to treat, just as effective + easier to retreat[5]

Conventional 20/5 on consecutive days parallel opposed pair or 3DCRT

SABR 24/2 on consecutive days

Allowed to target ≤3 consecutive vertebral segments
ie. only suitable for limited spinal disease

F/u @ 1m, 3m, 6m

✓ High protocol adherence
But 13% died before 3m assessment

✓ Central blinded review of all MRIs

! SABR not done by SABR specialists
✓ Pre-RTX local peer review of plans
✓ Retrospective central review of plans
↳ found ≤5% minor protocol deviations

✓ Phase 2/3 RCT
- Designed as Phase 2 in 2015 to test feasibility
- Converted to Phase 2/3 in 2017 to test superiority of SABR
- ! Sample size adjusted in 2018 based on results of (ref.2) ← CAUTION

✓ Publically-funded, researcher-led
✓ n = 229 from 18 centres, CAN+AUS

! Median f/u 6.7m • Longer f/u preferable in this fit population, for both pain response + late tox
Harder to retreat after SABR
Esp. vertebral compression # + myelopathy

✓ Stratified by:
- Radioresistant tumours (26%) • Defined as... GI, melanoma, sarcoma, RCC
- Soft tissue mass (63%)
- Centre

Baseline characteristics:
✓ Mostly balanced, but
! SABR group on ↑analgesia (2.7×)
! EBRT group had ↑thoracic sites, mechanical pain, collapse

Main primaries: breast, GU, GI, lung

! No data on disease burden
- how many were oligometastatic?
- how many lines of SACT?

OUTCOMES

Pain score 0 +no analgesia increase

Complete pain response	@ 1m:	17%	vs.	26%
	@ 3m:	14%	vs.	35%
	@ 6m:	16%	vs.	32%
Partial/complete pain response	@ 1m:	46%	vs.	56%
	@ 3m:	39%	vs.	53%
	@ 6m:	31%	vs.	41%

→ PRIMARY OUTCOME: RR 1.33 (95% CI 1.14-1.55)
↳ adjusted OR 3.47 (95% CI 1.77-6.80)

What about cost-effectiveness?[3]
SABR $9000/#
Conventional $10187/#

! No data on re-treatment rates

Defined according to (ref.6)
↳ Local progression @ 6m: 10% vs. 3%

Deaths @ 6m: 26% vs. 23%

EORTC QLQ-C30+ QLQ-BM22
QoL: No significant differences apart from financial burden

Adverse events: G3 pain 4% vs. 5%
CTCAE 4.0
Otherwise, very low in both groups

* TAKE HOME *

SABR 24/2 may be more effective than conventional, but factor in
- patient age, fitness, prognosis
- disease burden
- time + resources to plan
- retreatment potential

c.f. Pielkenrood et al. 2021[8] Single centre Phase 2
n=110 < conventional 8/1, 20/5 or 30/10 / SABR 18/1, 30/3 or 35/5
No benefit to pain @3m, underpowered

c.f. Sprave et al. 2018[2] Single centre Phase 2 (limited spinal disease)
n=55 < conventional 30/10 / SABR 24/1
Some benefit @6m but not @3m

c.f. Ryu et al. 2019[9] Phase 3 RCT
n=353 < conventional 8/1 / SABR 16-18/1
Well tolerated but no benefit to pain

clinical ONCOLOGY · RCR The Royal College of Radiologists

Original Investigation

April 20, 2023

Stereotactic Radiosurgery vs Conventional Radiotherapy for Localized Vertebral Metastases of the Spine

Phase 3 Results of NRG Oncology/RTOG 0631 Randomized Clinical Trial

Samuel Ryu, MD[1]; Snehal Deshmukh, MS[2,3]; Robert D. Timmerman, MD[4]; et al

» Author Affiliations

JAMA Oncol. 2023;9(6):800-807. doi:10.1001/jamaoncol.2023.0356

- **Objective** - whether patient-reported pain relief improved with SRS vs cEBRT - 1 to 3 vertebral metastases.
- 353 patients enrolled , 339 analyzed.
- 16 or 18 Gy to involved vertebral level(s) only vs 8 Gy to the involved vertebra plus 1 above & below
- **Conclusions and Relevance** - Superiority of SRS for the primary end point not found.
- No spinal cord complications at 2 years after SRS.
- Further investigation - oligometastases, where durability of cancer control essential.

ARTICLE IN PRESS

Radiotherapy and Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Guidelines

ESTRO clinical practice guideline: Stereotactic body radiotherapy for spine metastases

M Guckenberger [a,*], N Andratschke [a], C Belka [b,c,d], D Bellut [e], F Cuccia [f], M Dahele [g], RS Guninski [a], M Josipovic [h,i], P Mancosu [j], G Minniti [k,s], M Niyazi [t], U Ricardi [l], P Munck af Rosenschold [m], A Sahgal [n], Y Tsang [o], WFAR Verbakel [p], F Alongi [q,r]

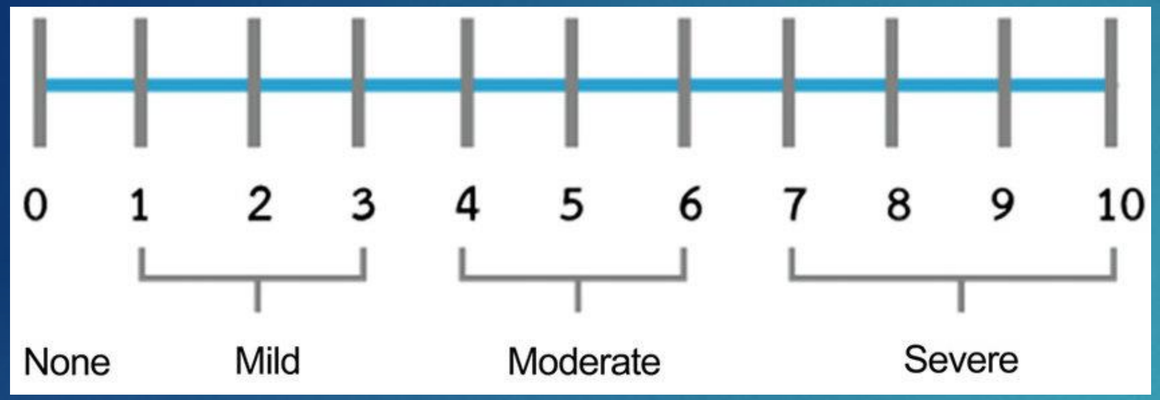
4 key questions - 22 recommendations and 5 statements

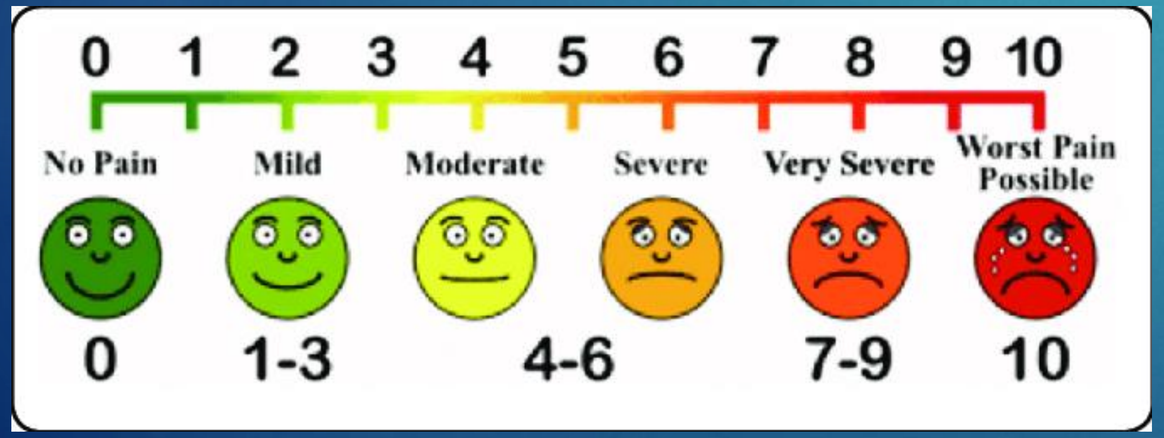
- 1) What is the overall pain response rate, complete pain response rate and duration of pain response after SBRT for painful vertebral metastases? How does pain response after SBRT compare to conventional palliative radiotherapy?
- 2) What is the local control (LC) after SBRT for spine metastases? What is the role of spine SBRT in oligo-metastatic disease (OMD)?
- 3) What is the practice of spinal SBRT to optimize safety and efficacy according to available evidence?
- 4) What is the toxicity profile of spine SBRT?

Table 1 Key question 1 recommendations, strength of recommendation and level of evidence.

	KQ 1 Recommendations	Strength of Recommendation	Level of Evidence (Refs)
1.	For patients who are candidates to receive SBRT for painful vertebral metastases from solid malignancies, a baseline and post-SBRT pain assessment is recommended using either Brief Pain Inventory Index (BPI), Visual Analog Score (VAS) or Numeric Rating Scale (NRS).	Strong	High 4, 5, 6, 7, 8, 9
2.	For patients with painful vertebral metastases from solid malignancies, SBRT should be considered due to higher complete pain response rates in carefully selected patients who are not frankly unstable (SINS>12), who have no or minimal epidural disease (Bilsky 0–1), up to 3 contiguous vertebral segments in the radiation treatment volume and a prolonged life expectancy where durable local and control is also intended.	Conditional	Moderate 4, 5, 6, 7, 8, 9

Pain scales





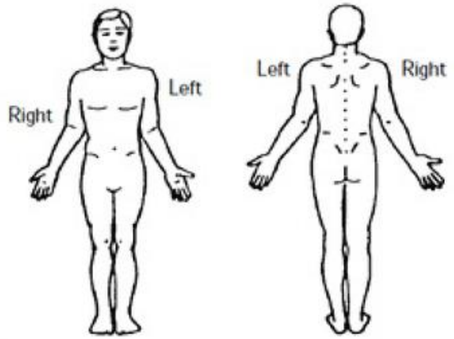
Date: ____ /____ /____ Time: _____

Name: _____ _____ _____
Last First Middle intial

1) Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

1. Yes 2. No

2) On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3) Please rate your pain by circling the one number that best describes your pain at its **worst** in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No pain — Pain as bad as you can imagine

4) Please rate your pain by circling the one number that best describes your pain at its **least** in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No pain — Pain as bad as you can imagine

5) Please rate your pain by circling the one number that best describes your pain on **average**.

0 1 2 3 4 5 6 7 8 9 10
No pain — Pain as bad as you can imagine

6) Please rate your pain by circling the one number that tells how much pain you have **right now**.

0 1 2 3 4 5 6 7 8 9 10
No pain — Pain as bad as you can imagine

7) What treatments or medications are you receiving for your pain?

_____

_____

8) In the past 24 hours, how much **relief** have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0% 10 20 30 40 50 60 70 80 90 100%
No relief — Complete relief

9) Circle the one number that describes how, during the past 24 hours, pain has **interfered** with your:

A. General activity

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

C. Walking ability

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

D. Normal work (includes both work outside the home and housework)

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

F. Sleep

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

G. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

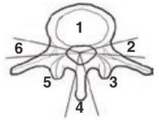
Table 2 Key question 2 recommendations, strength of recommendation and level of evidence.

	KQ 2 Recommendations	Strength of Recommendation	Level of Evidence (Refs)
1.	For patients with vertebral metastases from solid malignancies, SBRT should be practiced with a prescription dose higher than the equivalent of 1x18Gy (BED_{10} = 50 Gy_{10}). For de novo spine metastases, high dose spine SBRT practice includes 1x20Gy, 1x24Gy, 2x12Gy, 3x10Gy, and 5x7Gy. Based on these schemes there is an expectation of local control (LC) ranging from 80 to 90% at 1–2 years.	Strong	Moderate/expert opinion 6, 10, 11, 12, 13
2.	For patients with painful vertebral metastases from solid malignancies meeting the eligibility criteria for spine SBRT, a fractionated approach using 2x12Gy is conditionally recommended as the preferred palliative SBRT dose and fractionation.	Conditional	Moderate [6]
3.	For patients with vertebral metastases from solid malignancies, single fraction SBRT with 16 or 18 Gy is not recommended as an alternative to conventional low-dose palliative radiotherapy (1x8Gy) if pain relief and/or quality of life are the primary treatment goals.	Strong	Moderate [10]

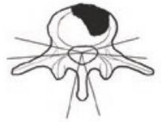
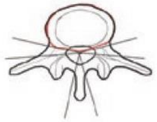
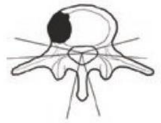
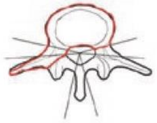
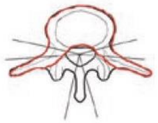
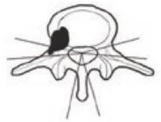
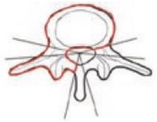
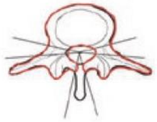
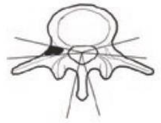
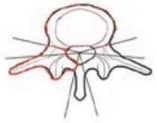
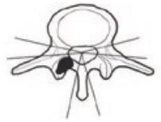
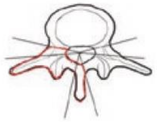
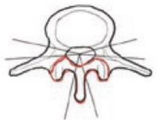
4.	For patients with vertebral metastases from solid malignancies, where local therapy for OMD is supported by disease-specific guidelines and/or the tumor board, then spine SBRT is recommended for the majority of eligible patients. In selected patients, more aggressive combined modality approaches involving (separation) surgery and SBRT may be needed to optimize LC and functional outcomes.	Strong	Expert opinion/ moderate 11, 14, 15, 16, 17, 18, 19
5.	For patients with vertebral metastases from solid malignancies, when SBRT is performed in the context of concomitant targeted/immuno- therapy, a potential risk for unexpected and/or increased toxicity should be discussed between spine SBRT practitioners and medical oncologists.	Strong	Expert opinion 20, 21

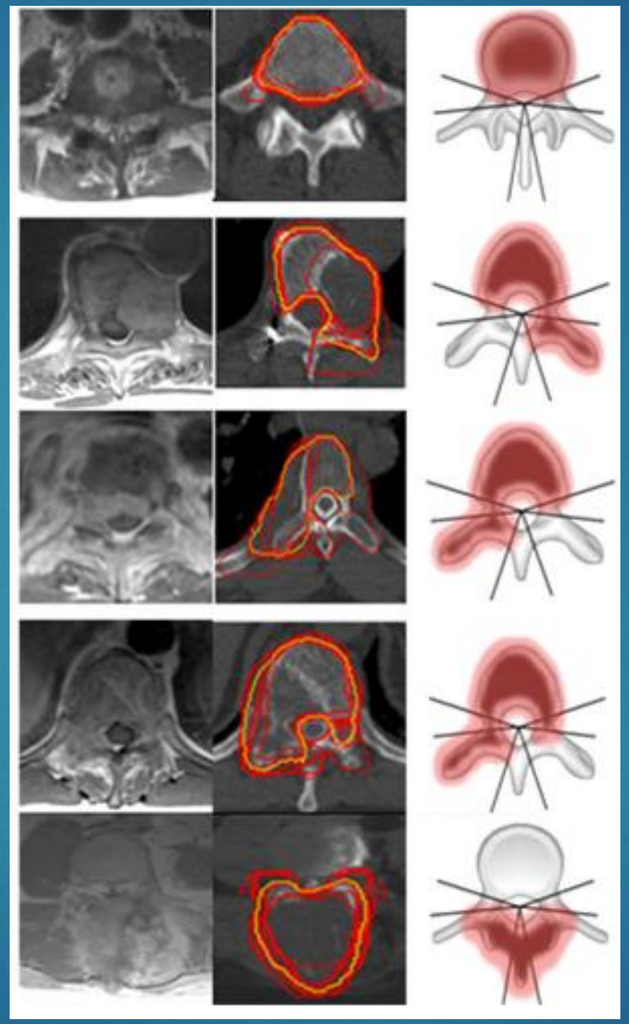
Target volume recommendations

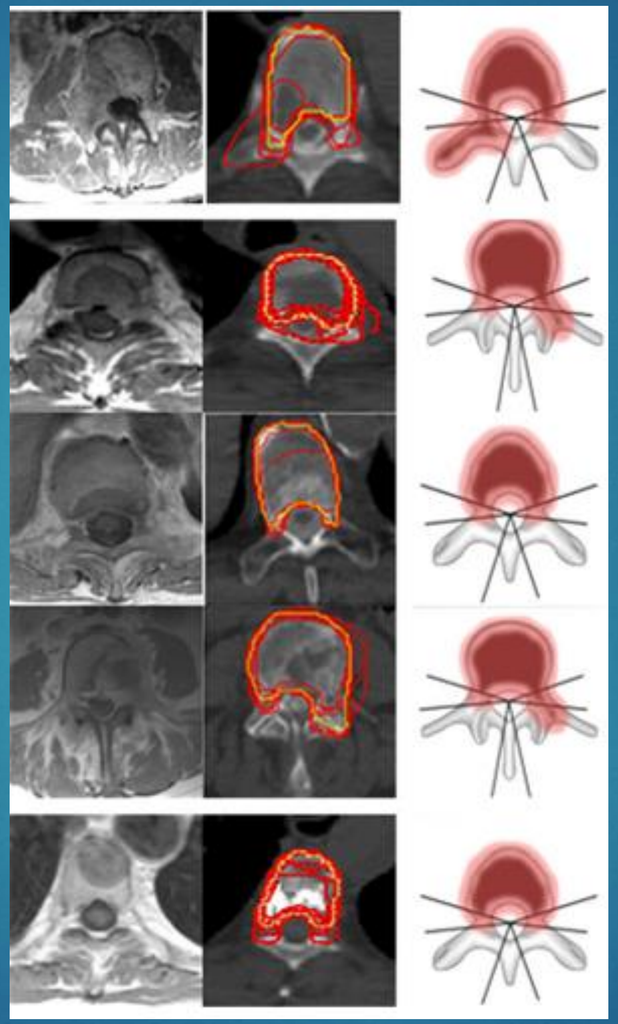
Criteria	Inclusion	Cautionary/Relative Contraindication	Exclusion
Radiographic	Spinal/paraspinal metastatic tumor	>3 contiguous segments	
	Bilsky epidural disease grade 0-1	Bilsky epidural disease grade 2	Bilsky epidural disease grade 3
	Maximum of 2-3 contiguous or 3 noncontiguous segments	Spinal malalignment	
Patient	Age >18 years		Inability to lie flat and tolerate treatment
	KPS ≥40–50		Contraindication to MRI and/or CT myelogram
	Oligometastatic disease	Widespread metastatic disease	Symptomatic spinal cord compression or cauda equina syndrome
	Life expectancy of at least 3 months		
Tumor	Histologic proof of malignancy	Radiosensitive histology such as myeloma/lymphoma	
	Oligometastatic spinal metastasis	>50% baseline vertebral fracture	
Previous Treatment	Previous external beam irradiation	Previous SBRT to the same level	EBRT within 90 days prior to SBRT
	Postoperative		Systemic radionuclide within 30 days prior to SBRT
Spinal Instability	No spinal instability (SINS score 0-6 points)	Potential spinal instability (SINS score 7–12 points)	Frank spinal instability (SINS score > 12 points)



1: vertebral body
2,6: pedicle
3,5: lamina and transverse processes
4: spinous process

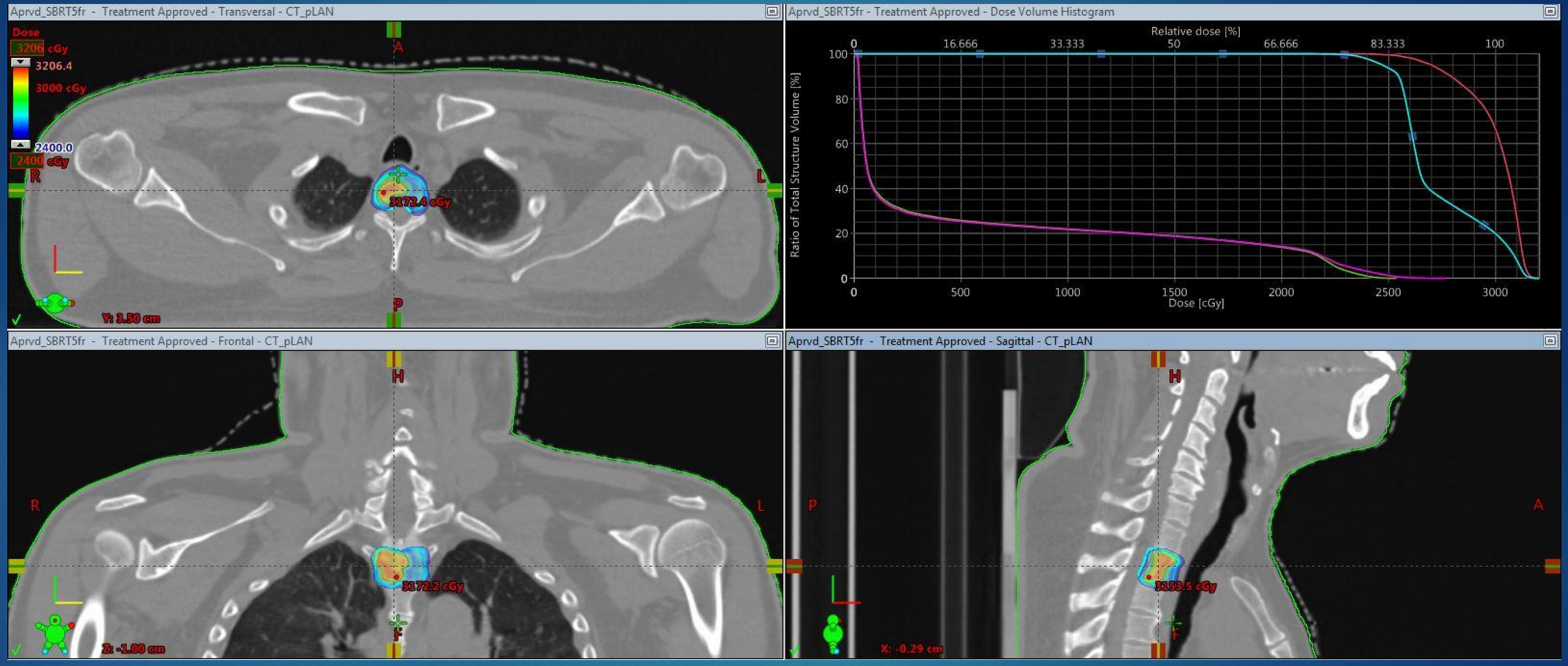
GTV	GTV description	CTV	CTV description
	Any portion of the vertebral body		Include the entire vertebral body
	Lateralized within the vertebral body		Include the entire vertebral body and the ipsilateral pedicle/ transverse process
	Diffusely involves the vertebral body		Include the entire vertebral body and the bilateral pedicles/ transverse process
	Involves vertebral body and unilateral pedicle		Include entire vertebral body, pedicle, ipsilateral transverse process, and ipsilateral lamina
	Involves vertebral body and bilateral pedicles/transverse processes		Include entire vertebral body, bilateral pedicles/transverse process, and ipsilateral lamina
	Involves unilateral pedicle		Include pedicle, ipsilateral transverse process, and ipsilateral lamina, ± vertebral body
	Involves unilateral pedicle		Include lamina, ipsilateral pedicle/ transverse process, and spinous process
	Involves spinous process		Include entire spinous process and bilateral laminae





GTV involvement	ISRC GTV anatomic classification	ISRC bony CTV recommendation	CTV description
Any portion of the vertebral body	1	1	Include the entire vertebral body
Lateralized within the vertebral body	1	1, 2	Include the entire vertebral body and the ipsilateral pedicle/transverse process
Diffusely involves the vertebral body	1	1, 2, 6	Include the entire vertebral body and the bilateral pedicles/transverse processes
GTV involves vertebral body and unilateral pedicle	1, 2	1, 2, 3	Include entire vertebral body, pedicle, ipsilateral transverse process, and ipsilateral lamina
GTV involves vertebral body and bilateral pedicles/transverse processes	3	2, 3, 4	Include entire vertebral body, bilateral pedicles/transverse processes, and bilateral laminae
GTV involves unilateral pedicle	2	2, 3 ± 1	Include pedicle, ipsilateral transverse process, and ipsilateral lamina, ± vertebral body
GTV involves unilateral lamina	3	2, 3, 4	Include lamina, ipsilateral pedicle/transverse process, and spinous process
GTV involves spinous process	4	3, 4, 5	Include entire spinous process and bilateral laminae

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


Aprvd_SBRT5fr - Treatment Approved - Transversal - CT_pLAN
Dose
3206 cGy
3206.4
3000 cGy
2400.0
2400 cGy
A
R
L
P
3172.4 cGy
Y: 3.50 cm
Aprvd_SBRT5fr - Treatment Approved - Dose Volume Histogram
Relative dose [%]
0
16.666
33.333
50
66.666
83.333
100
Ratio of Total Structure Volume [%]
Dose [cGy]
0
500
1000
1500
2000
2500
3000
Aprvd_SBRT5fr - Treatment Approved - Frontal - CT_pLAN
H
R
L
F
3172.2 cGy
Z: -1.00 cm
Aprvd_SBRT5fr - Treatment Approved - Sagittal - CT_pLAN
H
P
A
F
3153.5 cGy
X: -0.29 cm

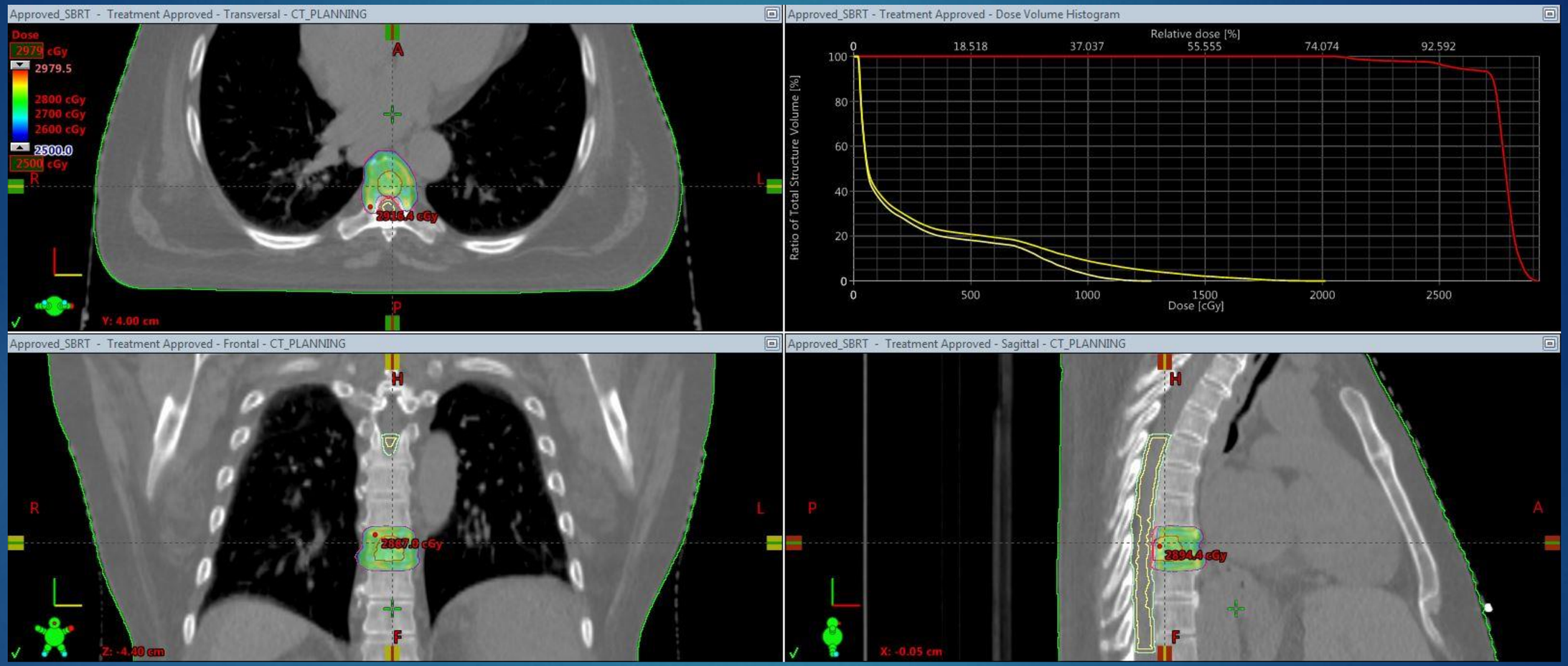

Approved_SBRT - Treatment Approved - Transversal - CT_PLANNING
Dose
2979 cGy
2979.5
2800 cGy
2700 cGy
2600 cGy
2500.0
2500 cGy
A
R
L
P
Y: 4.00 cm
Approved_SBRT - Treatment Approved - Dose Volume Histogram
Relative dose [%]
0
18.518
37.037
55.555
74.074
92.592
Ratio of Total Structure Volume [%]
100
80
60
40
20
0
0
500
1000
1500
2000
2500
Dose [cGy]
Approved_SBRT - Treatment Approved - Frontal - CT_PLANNING
H
R
L
F
Z: -4.40 cm
Approved_SBRT - Treatment Approved - Sagittal - CT_PLANNING
H
P
A
F
X: -0.05 cm

Table 3 Key question 2 statements and level of evidence.

	KQ 2 Statements	Level of Evidence (Refs)
1.	For patients with vertebral metastases from solid malignancies, very high dose single fraction spine SBRT (e.g. 1x24Gy) is associated with high rates of LC. However, the gains in local control should be balanced with a higher risk of vertebral compression fracture.	Expert opinion 11, 14, 22, 23, 24, 25
2.	For patients with vertebral metastases from solid malignancies, MRI is the preferred modality for assessing local control. CT and/or PET/CT are alternative modalities with the caveat that they are less sensitive for epidural disease. The possibility of post-SBRT imaging changes and pseudo-progression should be kept in mind. In selected patients tumor markers (e.g. PSA) may be used for follow-up.	Expert opinion 26, 27
3.	For patients with vertebral metastases from solid malignancies, spine SBRT practitioners should be alert for clinically relevant but less common toxicities, like plexopathy and myositis.	Expert opinion [19]

Table 4 Key question 3 recommendations, strength of recommendation and level of evidence.

	KQ 3 Recommendations	Strength of Recommendation	Level of Evidence (Refs)
1.	Patients with vertebral metastases of solid malignancies treated with SBRT should be appropriately positioned in a reproducible supine position. Above the cervical-thoracic junction (e.g. thoracic 4 vertebra and above), patient-specific rigid fixation is recommended (e.g. thermoplastic head and neck mask). Below the cervical-thoracic junction, near-rigid body immobilization, or no immobilization combined with intra-fraction positional verification/spine tracking, is recommended.	Strong	High 4, 5, 9, 10, 28
2.	For patients with vertebral metastases of solid malignancies treated with SBRT, target and organ-at-risk volumes should be delineated on a simulation CT with slice thickness ≤ 1.5 mm, co-registered to T1 and T2 MRI series. Volumetric MRI images acquired in the radiotherapy treatment position are conditionally recommended.	Strong	High 4, 5, 9, 10, 28
3.	For patients with vertebral metastases of solid malignancies treated with SBRT, the overall geometric treatment uncertainty should allow a GTV/CTV to PTV margin ≤ 3 mm. A minimum PTV margin of 1 mm is recommended.	Strong	Moderate 5, 9

4.	For patients with vertebral metastases of solid malignancies treated with SBRT, radiotherapy treatment should be performed using an intensity modulated delivery technique (i.e. fixed beam IMRT, VMAT, helical tomotherapy, robotic RT). The use of fast delivery techniques, such as using flattening filter free beams, is conditionally recommended.	Strong	High 4, 5, 9, 10, 28
5.	For patients with vertebral metastases of solid malignancies treated with SBRT, a treatment planning strategy of prioritizing organ-at-risk sparing over target coverage should be utilized where the PTV is close to or overlaps with the critical organ-at-risk (i.e. spinal cord, cauda equina, oesophagus). A “cropped PTV” approach and planning organ-at-risk volume (PRV) safety margins is conditionally recommended in the planning optimization process only.	Strong	High 4, 5, 9, 10, 28
6.	For patients with vertebral metastases of solid malignancies treated with SBRT, online image guidance procedures should be performed before each daily delivery session (e.g. using cone beam CT, stereoscopic × ray, in-room MR). Intra-fraction treatment verification imaging is conditionally recommended at least once during each treatment fraction. Six-degree of freedom (6DoF) patient positioning correction is conditionally recommended. When 6DoF is performed, verification imaging after pitch and roll corrections is conditionally recommended.	Strong	High 4, 5, 9, 10, 28

7.	The start-up of an SBRT program for patients with vertebral metastases of solid malignancies should include radiation oncologist, medical physicist, and radiation therapist. Each SBRT case should be discussed in a multi-disciplinary setting, including medical oncologist, radiation oncologist, spine surgeon, and neuro-radiologist. The discussion with medical physicist and radiation therapist regarding the technical feasibility is conditionally recommended.	Strong	Expert opinion
8.	Each SBRT case should undergo patient specific quality assurance. All centers should audit their own SBRT technique and evaluate the positioning precision and accuracy of their equipment and this will inform center specific PTV margins.	Strong	Expert opinion

- T1, T2, STIR images
- 1mm thickness
- 18 to 24 Gy in 1 fraction
- 24 Gy in 2 fractions
- 24 to 30 Gy in 3 fractions
- 30 Gy in 4 fractions
- 30 to 40 Gy in 5 fractions
- 12- 14Gy to spine; 16-18 Gy to thecal sac

- Modulated treatment planning system.
- Dose calculation grid size < 1.5 mm
- Modern dose calculation algorithm
- End-to-end tolerance of<2 mm, max PTV 3 mm
- Six degrees of freedom (6DoF) couches
- Verification imaging, especially after large pitch & roll corrections (e.g. > 1°
- QA

Table 5 Key question 4 recommendations, strength of recommendation and level of evidence.

	KQ 4 Recommendations	Strength of Recommendation	Level of Evidence (Refs)
1.	For patients with vertebral metastases of solid malignancies, pre-SBRT assessment of spinal stability using the validated SINS score is recommended.	Strong	High 4, 5
2.	For patients with vertebral metastases of solid malignancies, pre-SBRT assessment of surgical stabilization is recommended in case of intermediate instability (score 7–12) and especially instability (score 13–18) based on the SINS score.	Strong	Expert opinion
3.	For patients with vertebral metastases of solid malignancies, pre-SBRT assessment of epidural involvement using the validated Bilsky grade is recommended.	Strong	Moderate 29, 30
4.	For patients with vertebral metastases of solid malignancies, SBRT is not recommended in the situation of symptomatic MSCC (spinal cord or cauda equina).	Strong	High 4, 5, 7

5.	For patients with vertebral metastases of solid malignancies, the following procedures are recommended to keep the risk of radiation induced myelopathy at a very low level: • Appropriate imaging (volumetric T1/T2 MRI or alternatively CT myelography) for accurate localization of the spinal cord and/or thecal sac. • Use of PRV concept for the spinal cord. • Adherence to accepted dose constraints for the PRV spinal cord. • Priority of the spinal cord dose tolerance over target volume coverage in inverse SBRT planning. • High-precision SBRT delivery.	Strong	High 4, 5, 7
6.	For patients with vertebral metastases of solid malignancies, it is recommended to prioritize adequate coverage of the GTV over sparing of nerve roots due to the low risk of radiation induced radiculopathy.	Strong	High 5, 31
7.	For patients with vertebral metastases of solid malignancies, the routine use of prophylactic treatment with steroids is not recommended due to the low risk of post-SBRT pain flare.	Conditional	Moderate 5, 32, 33

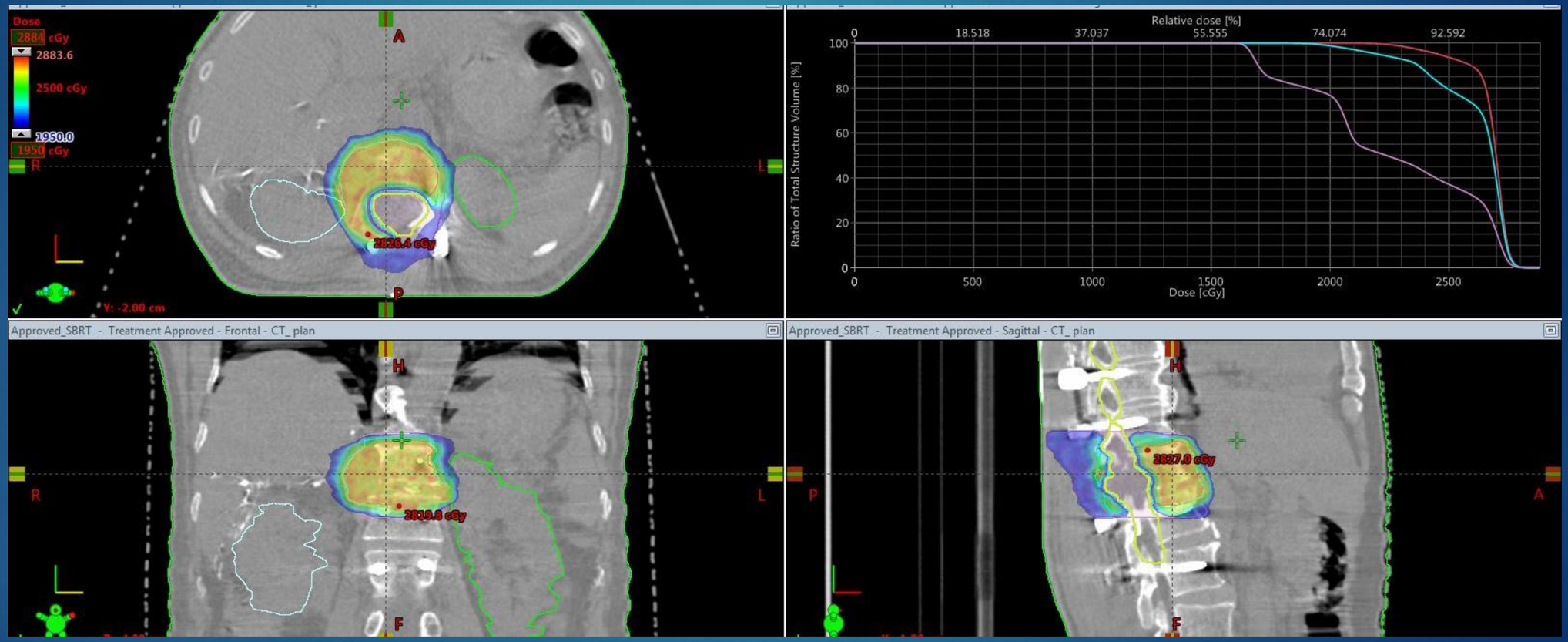
Table 6 Key question 4 statements and level of evidence.

	KQ 4 Statements	Level of Evidence (Refs)
1.	For patients with vertebral metastases of solid malignancies, fractionated SBRT is not associated with an increased risk of vertebral fracture when compared to CRT.	High 5, 22
2.	For patients with vertebral metastases of solid malignancies, single-fraction SBRT with doses > 20 Gy is associated with an increased risk of vertebral fracture as compared to CRT and compared to fractionated SBRT.	High 5, 14, 25

Work flow

- Pre-treatment assessments
  - Clinical examination including neurological function assessment
  - Quantitative pain assessment using validated instruments such as the visual analogue scale (VAS) or brief pain inventory (BPI)
  - Spinal instability assessment using the Spinal Instability Neoplastic Score (SINS)
  - Epidural spinal cord compression assessment using the score developed by Bilsky et al.
- SBRT planning
  - High-resolution CT imaging
  - High-resolution MR imaging: T1 without contrast; T1 with contrast in presence of paraspinal or epidural disease; T2 non-contrast
  - Careful rigid image-registration
  - Target volume definition following international consensus recommendations
  - IMRT treatment planning
  - VMAT and flattening-filter-free (FFF) technologies to minimize SBRT delivery times
  - Daily pre-treatment image-guided patient set-up
  - Passive or active intra-fraction motion control
- Follow-up
  - Clinical follow-up using pre-treatment assessments
  - Imaging follow-up using high-resolution CT and / or MR imaging

Post op



Caption

Largest

- N= 186
- 24 single vs 27 to 30/3 vs 18 to 26 in 5-6
- Local progression at 1 yr - 16.4% vs 4.1% vs 22.6%

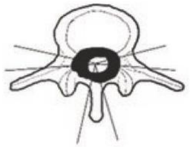
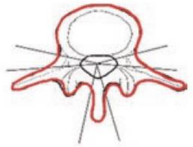
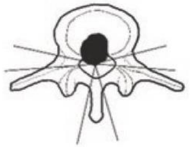
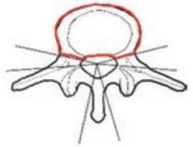
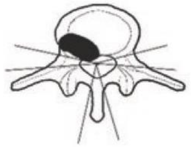
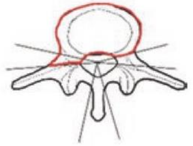
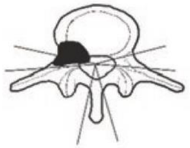
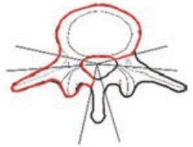
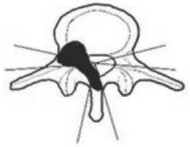
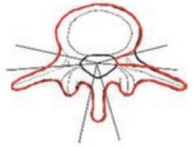
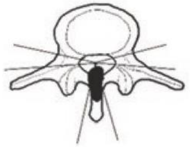
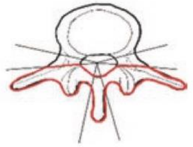
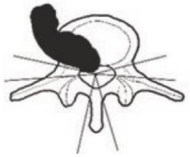
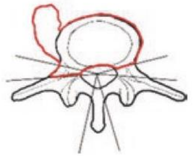
Laufer, Ilya, et al. "The NOMS framework: approach to the treatment of spinal metastatic tumors." The oncologist 18.6 (2013): 744-751.

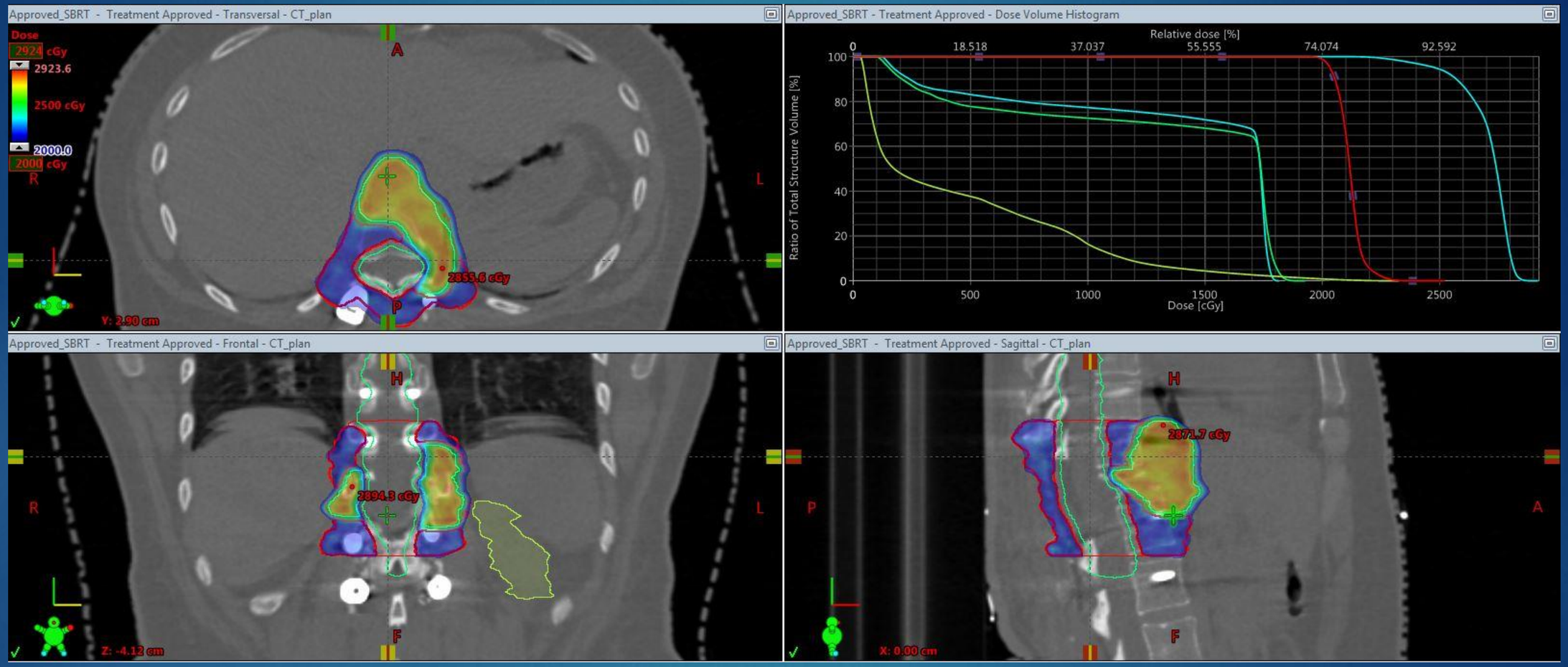
ISRS guideline post op

Treatment planning

- All patients should undergo an axial high-resolution 1.5 Tesla T1/T2 MRI of the affected spinal segment including at least one vertebral segment above and below the target volume for both target and OAR delineation. This MRI is fused to the planning CT scan. Use of gadolinium or CT contrast can assist in delineation of soft tissue tumor extension. A CT-myelogram can be considered, especially for cases where hardware artifact obscures canal on the MRI scan. In this scenario it is best to perform a simulation CT myelogram as opposed to a diagnostic CT myelogram that is then fused to the radiation planning CT.
- A 1.5-2 mm PRV should be applied to the spinal cord. The thecal sac does not need a PRV. Spinal cord and thecal sac dose limits vary based on fractionation. Published guidelines for dose constraints can be consulted as indicated.[34-36]
- The preoperative extent of epidural/paraspinal disease should be included in the postoperative CTV. This often requires the use of a "donut" type CTV.[38] A 5 mm superior/inferior CTV expansion including the spinal canal beyond visible epidural disease should also be considered, in addition to a 5 mm margin surrounding any paraspinal soft tissue disease extension while respecting anatomic boundaries. The surgical scar does not need to be included in the CTV. Contouring recommendations have been published by Chan et al and Redmond et al.[38,39]
- A minimum time interval of 1-week from the time of a minimally invasive spinal surgery, and 8-14 days for more invasive surgeries, should be maintained before simulation for SBRT. Delays longer than 4 weeks postoperatively to the initiation of radiation may result in worse tumor control.

Faruqi, Salman, et al. "Stereotactic radiosurgery for postoperative spine malignancy: A systematic review and International Stereotactic Radiosurgery Society Practice Guidelines." Practical Radiation Oncology 12.2 (2022): e65-e78.

Pre-op epidural involvement		Post-op bony CTV	
	Circumferential epidural disease		Include the preoperative body, bilateral pedicles, bilateral transverse processes, bilateral laminae, and spinous process
	Anteriorly in the central body		Include the preoperative body
	Anteriorly in lateral body		Include the preoperative body + ipsilateral pedicle ± lamina
	Anteriorly in the body and unilaterally in the pedicle		Include preoperative body + ipsilateral pedicle, ipsilateral transverse process and ipsilateral lamina
	Anteriorly in the body unilaterally in the pedicle, and posteriorly in the spinous process		Include preoperative body + ipsilateral pedicle, bilateral transverse process, bilateral laminae, and spinous process
	Posteriorly in the spinous process		Include preoperative spinous process, bilateral laminae and bilateral transverse processes
	Any of the above + extensive paraspinal extension		As above + coverage of the entire preoperative extent of paraspinal extension


Approved_SBRT - Treatment Approved - Transversal - CT_plan
Dose
2924 cGy
2923.6
2500 cGy
2000.0
2000 cGy
A
R
L
P
2855.6 cGy
Y: 2.90 cm
Approved_SBRT - Treatment Approved - Dose Volume Histogram
Relative dose [%]
0
18.518
37.037
55.555
74.074
92.592
Ratio of Total Structure Volume [%]
100
80
60
40
20
0
0
500
1000
1500
2000
2500
Dose [cGy]
Approved_SBRT - Treatment Approved - Frontal - CT_plan
H
R
L
F
2894.3 cGy
Z: -4.12 cm
Approved_SBRT - Treatment Approved - Sagittal - CT_plan
H
P
A
F
2871.7 cGy
X: 0.00 cm

https://www.cartoonstock.com/cartoon?searchID=CS179759

Re RT

- 20% after 8Gy/1#
- 2019 NHS Review

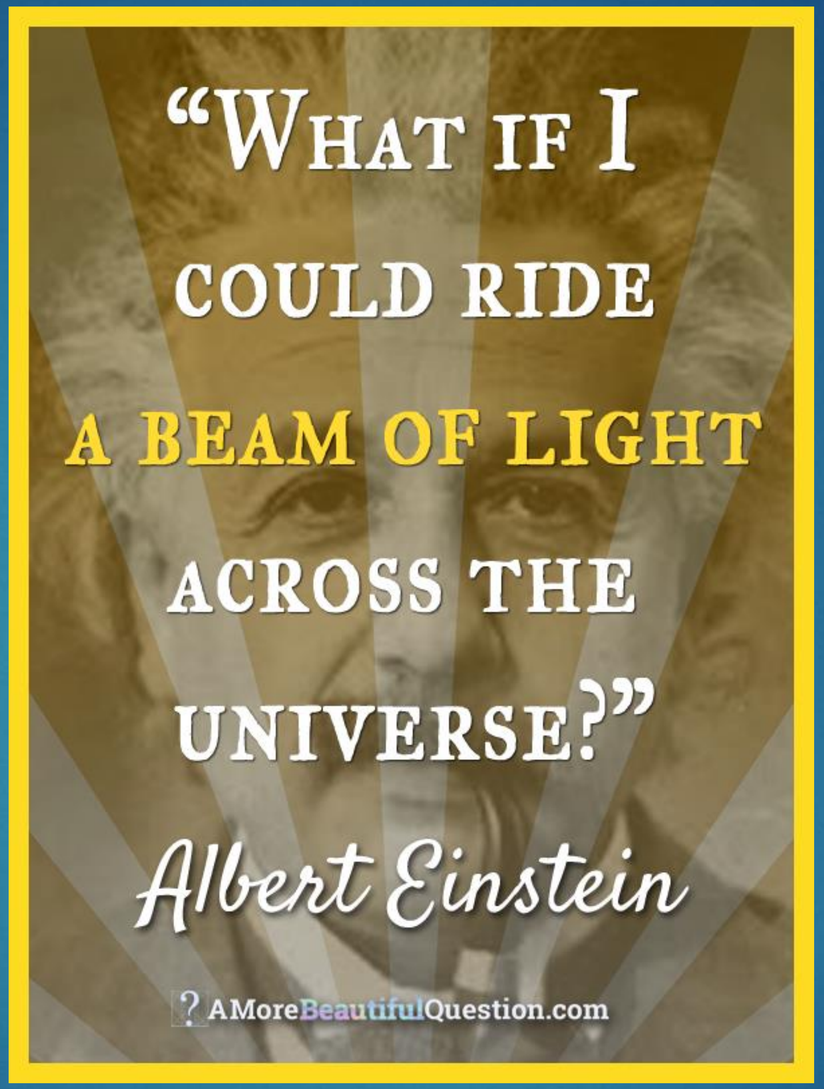
Myrehaug, Sten, et al. "Reirradiation spine stereotactic body radiation therapy for spinal metastases: systematic review: International Stereotactic Radiosurgery Society practice guidelines." Journal of Neurosurgery: Spine 27.4 (2017): 428-435.

ISRS Guidelines

Recommendation	Level of Evidence
Following cEBRT, retreatment w/ SBRT is a recommended therapeutic option in suitable patients based on multidisciplinary assessment	III
Following SBRT, retreatment w/ SBRT is a treatment option in suitable patients based on multidisciplinary assessment	III
For patients w/ clinical features concerning for malignant epidural spinal cord compression, mechanical instability, or baseline vertebral body compression fracture, the radiation oncologist should consult a spine surgeon before the patient undergoes SBRT	II

Toxicity data

Authors & Year	Toxicity Scale	No. of VCFs	No. of Neurological Adverse Events	Grade III–IV Toxicity, Other
Sahgal et al., 2009	NCI-CTCAE v3.0	NR	0	0
Choi et al., 2010	NR	NR	1	0
Garg et al., 2011	NCI-CTCAE v2.0, McCormick scale	NR	2	0
Damast et al., 2011	NR	9	0	0
Mahadevan et al., 2011	NR	NR	4	0
Ahmed et al., 2012	NCI-CTCAE v3.0	1	1	0
Chang et al., 2012	NCI-CTCAE v2.0	12	0	0
Thibault et al., 2014	NR	NR	NR	0
Thibault et al., 2015[22]	NR	0	0	0



https://amorebeautifulquestion.com/wp-content/uploads/2014/03/Einstein-Light-Beam2.png

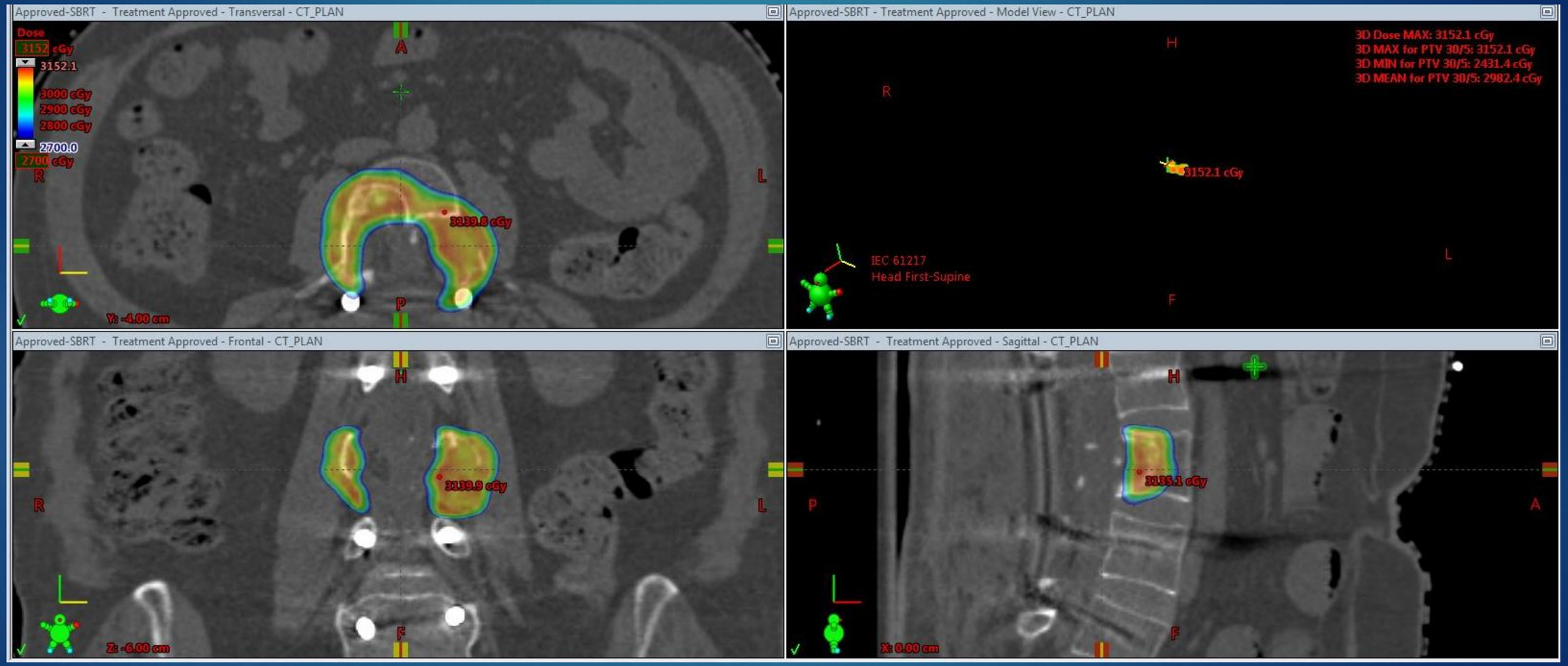
Primary Spine Tumours

Chordoma

- n=12; 16 Gy, 24 Gy single
- n=12; 24 Gy in 1 fraction or 24-36 Gy in 3 fractions
- Upfront, Local control 80% vs 57% salvage
- n=20; median dose 37.5 Gy / 5 ; local relapse free survival 90% at 28 months

Jung, Edward W., et al. "Single-fraction spine stereotactic body radiation therapy for the treatment of chordoma." Technology in Cancer Research & Treatment 16.3 (2017): 302-309.
Yamada, Yoshiya, et al. "Preliminary results of high-dose single-fraction radiotherapy for the management of chordomas of the spine and sacrum." Neurosurgery 73.4 (2013): 673-680.
Lockney, Dennis T., et al. "Spinal stereotactic body radiotherapy following intralesional curettage with separation surgery for initial or salvage chordoma treatment." Neurosurgical Focus 42.1 (2017): E4.

Neurogenic tumours



FU

- Clinical follow-up
- Spine MRI - 3-monthly in year one then 3–6 monthly
- Interpretation of post-SBRT images challenging

Radiation myelopathy - 0.4%

- Total dose -median re-RT point dose maximum - 123.4 Gy in Myelopathy group vs 25 Gy in the non
- Limit cumulative BED to <140 Gy for thecal sac Dmax; maximum SBRT BED to 50 Gy
- At least 5-month b/n treatments
- Dose/ #

Sahgal, Arjun, et al. "Reirradiation human spinal cord tolerance for stereotactic body radiotherapy." International Journal of Radiation Oncology* Biology* Physics 82.1 (2012): 107-116.
Gibbs, Iris C., et al. "Delayed radiation-induced myelopathy after spinal radiosurgery." Neurosurgery 64.2 (2009): A67-A72.

HYTEC - 5%

- 12.4–14.0 Gy in 1 fraction
- 17.0–19.3 Gy in 2 fractions
- 20.3–23.1 Gy in 3 fractions
- 23.0–26.2 Gy in 4 fractions
- 25.3–28.8 Gy in 5 fractions

Sahgal, Arjun, et al. "Spinal cord dose tolerance to stereotactic body radiation therapy." International Journal of Radiation Oncology* Biology* Physics 110.1 (

Vertebral Compression Fracture

- Dose per fraction >19 Gy
- Lytic tumors
- Baseline spinal misalignment
- Baseline presence of a compression #

Sahgal, Arjun, et al. "Vertebral compression fracture after spine stereotactic body radiotherapy: a multi-institutional analysis with a focus on radiation dose and the spinal instability neoplastic score." Journal of clinical oncology 31.27 (2013): 3426.

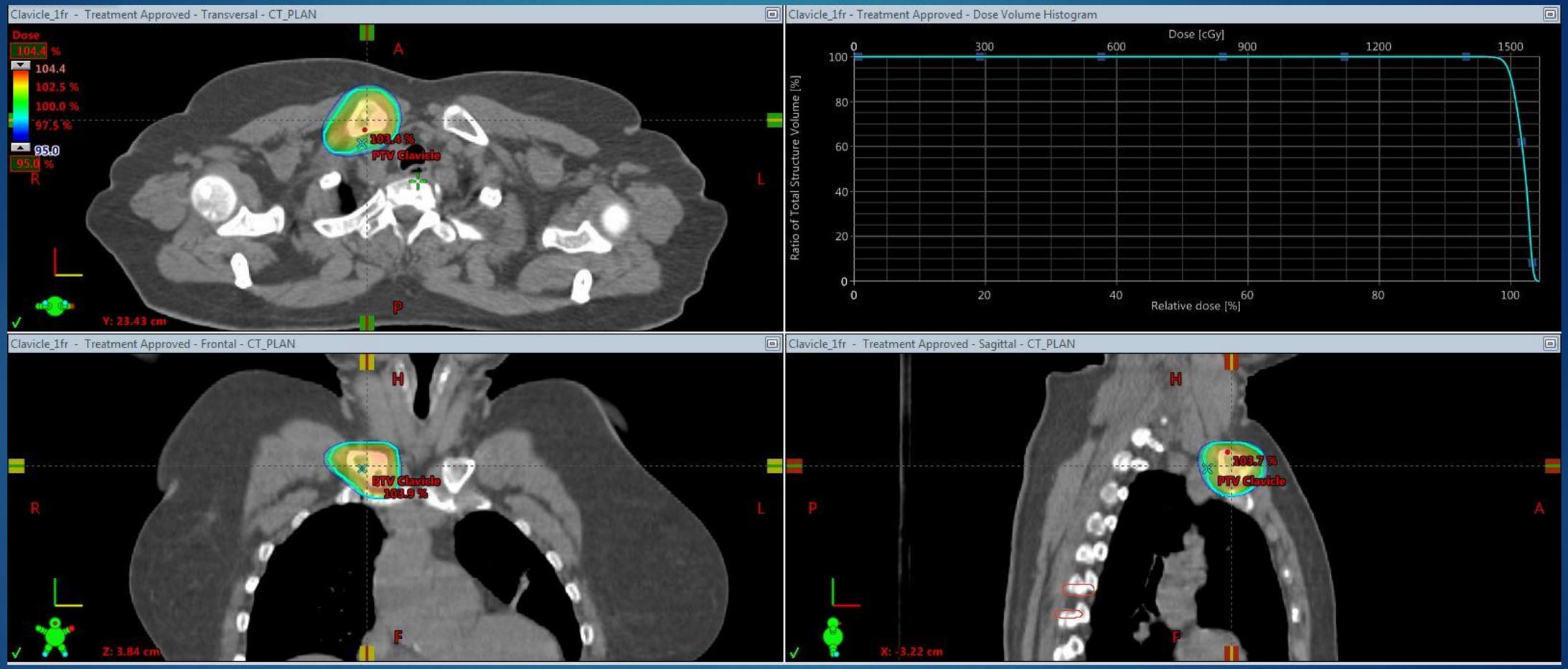
Acute pain flare

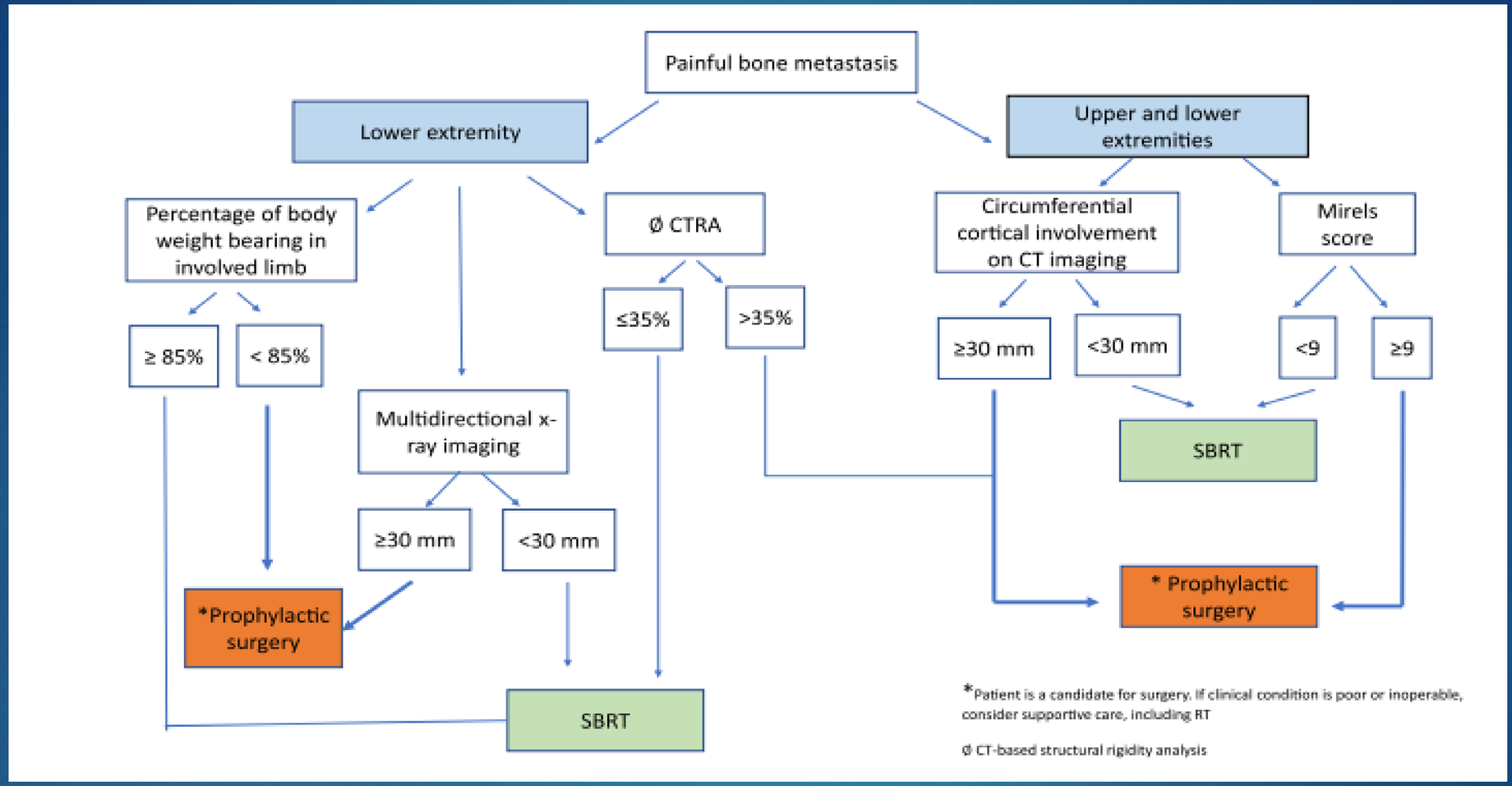
- Single fraction
- Steroids

Kowalchuk, Roman O., et al. "Development and internal validation of a recursive partitioning analysis–based model predictive of pain flare incidence after spine stereotactic body radiation therapy." Practical Radiation Oncology 12.4 (2022): e269-e277.

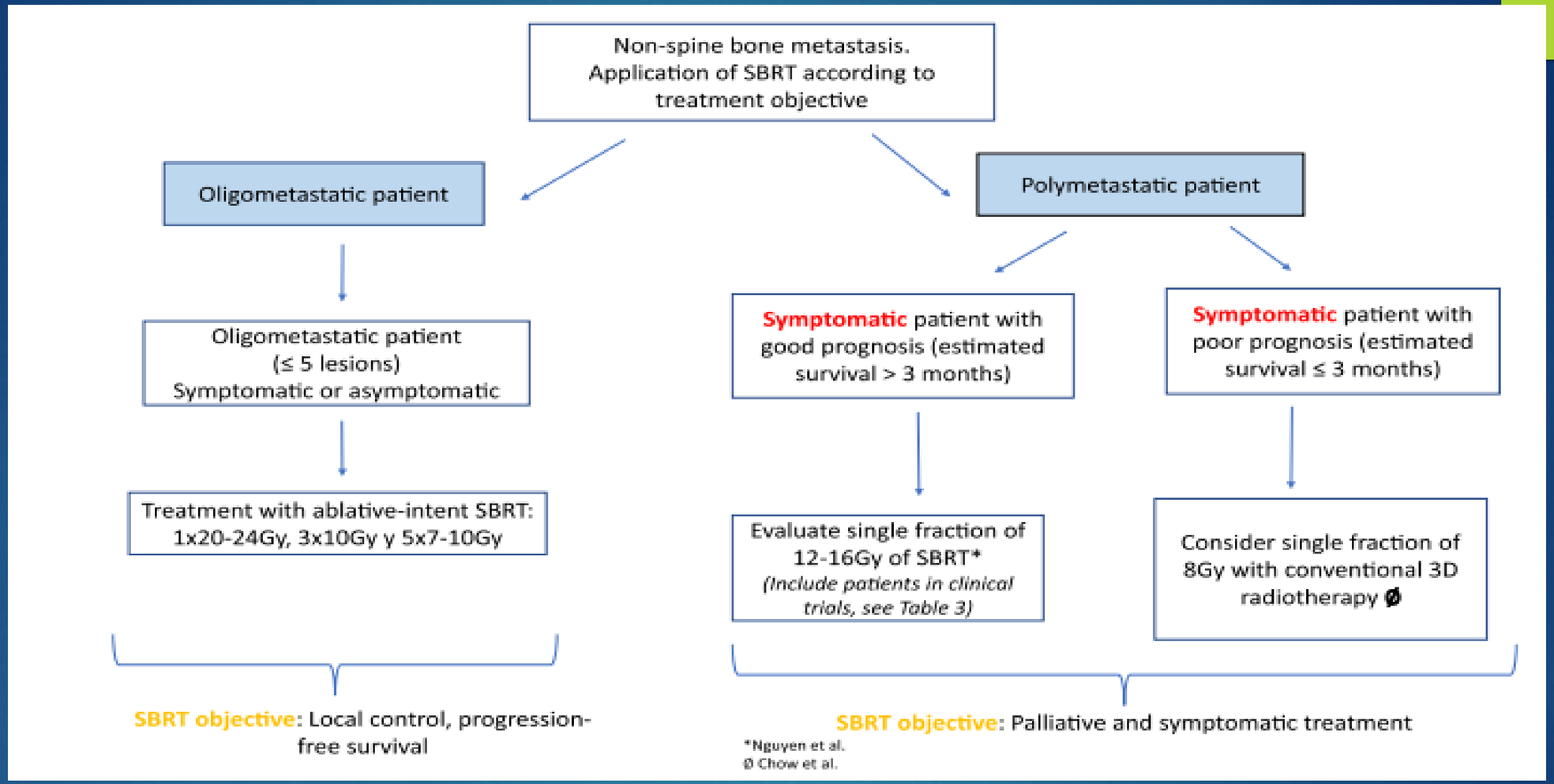
- Plexoplathy
- Myositis
- Esophagitis
- N,V,D

Non spine Bone





Lopez-Campos, Fernando, et al. "SEOR SBRT-SG stereotactic body radiation therapy consensus guidelines for non-spine bone metastasis." Clinical and Translational Oncology 24.2 (2022): 215-226.


Non-spine bone metastasis. Application of SBRT according to treatment objective
Oligometastatic patient
Polymetastatic patient
Oligometastatic patient (≤ 5 lesions) Symptomatic or asymptomatic
Symptomatic patient with good prognosis (estimated survival > 3 months)
Symptomatic patient with poor prognosis (estimated survival ≤ 3 months)
Treatment with ablative-intent SBRT: 1x20-24Gy, 3x10Gy y 5x7-10Gy
Evaluate single fraction of 12-16Gy of SBRT* (Include patients in clinical trials, see Table 3)
Consider single fraction of 8Gy with conventional 3D radiotherapy Ø
SBRT objective: Local control, progression-free survival
SBRT objective: Palliative and symptomatic treatment
*Nguyen et al.
Ø Chow et al.

- Simulation CT in treatment position 1–1.5 mm
- At least 10 cm craniocaudal
- IV contrast as needed
- Limit image artifacts
- 4D-CT if target/ OARs move
- T1W MRI

Palma, David A., et al. "Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial." The Lancet 393.10185 (2019): 2051-2058.

1. The CTV should be based on the GTV plus an intraosseous margin ≤ 5 mm $\pm$ an extraosseous margin ≤ 5 mm.
2. The inclusion of an extraosseous margin should be strongly considered in patients with soft tissue cancers and/or significant disruption of the cortical bone.
3. The CTV must be modified manually to avoid irradiating OARs and uninvolved joint spaces, respecting natural anatomic barriers such as the peritoneal cavity or pleura.

- On board verification
- BED 60-100Gy
- 1 x 20 Gy vs 3 x10 Gy vs 5 x 7 Gy
- 1) moderate-severe cortical erosion≥30% (high risk of #)
- (2) extraosseous involvement
- (3) tumor volume or bulky mass (7 cm or more in diameter)
- (4) HPR
- (5) OAR Dose constraints

Mercier C, Claessens M, Buys A, Gryshkevych S, Billiet C, Joye I, et al. Stereotactic ablative radiation therapy to all lesions in patients with oligometastatic cancers: a phase 1 dose-escalation trial. Int J Radiat Oncol Biol Phys. 2021;109(5):1195–205.

- Moderate-severe cortical erosion≥30% (high risk of #)
- Extraosseous involvement
- Tumor volume or bulky mass (7 cm or more in diameter)
- HPR
- OAR Dose constraints
- Previous RT

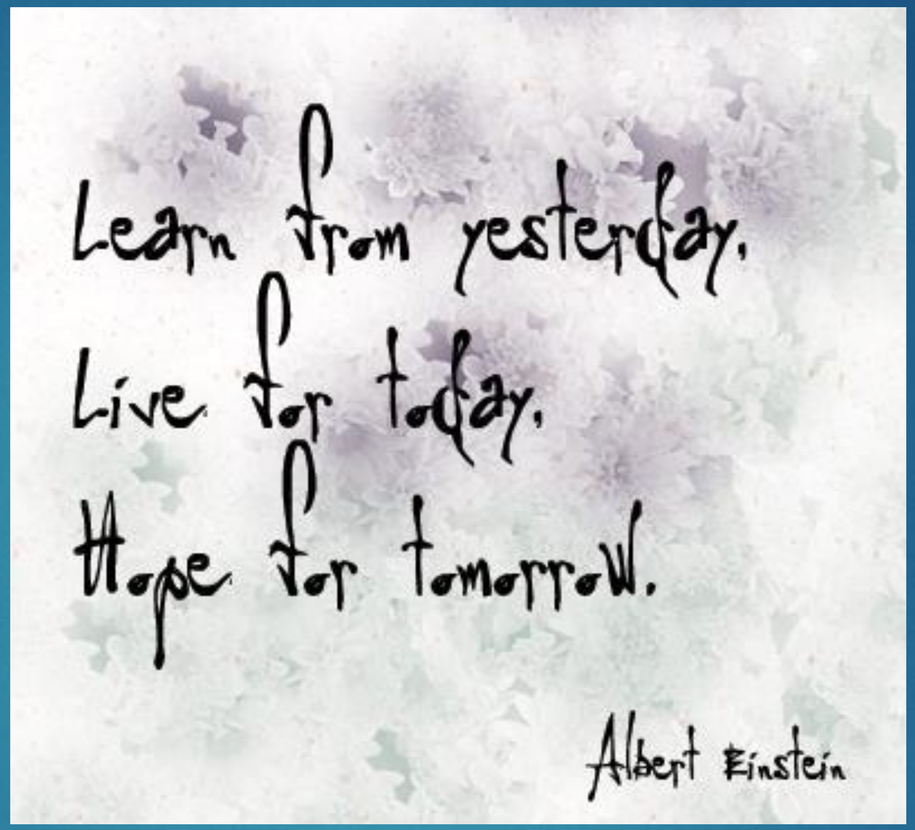
- BOMET-QOL-10 questionnaire

Future

- Toxicity with immuno
- Abscopal
- Technology
- QoL
- Molecular
- Upfront vs Salvage
- Pain control

https://faqsupport.com.au/predict-future-outcomes-with-some-certainty/

Clinicaltrials.gov identifier (NCT number)	Phase/study type	*n*	ARMS AND INTERVENTIONS	Total dose/fractionation	Primary endpoint	Group
NCT04063254	II/Randomized	302	High-dose SBRT vs standard-dose SBRT	12–16 Gy/1fr vs. 8–10 Gy/1fr	Pain response at 3 months	National Taiwan University Hospital
NCT04177056	II/Single arm	45	SBRT	30–35 Gy/5fr	Pain response at 3 months	Juravinski Cancer Centre (Hamilton, Ontario, Canada)
CROME Trial NCT04693377	II/Randomized	40	SBRT vs.SBRT + cryoablation	Not specified	Pain response at 12 months	M.D. Anderson Cancer Center
NCT01429493	II-III/Randomized	120	conventional radiotherapy vs. biological image-guided radiotherapy with conventional dose vs biological image-guided SBRT with dose escalation	8 Gy/1fr vs biological image-guided 8 Gy/1fr vs. biological image-guided SBRT with dose escalation to the PET positive lesion	Pain response at 12 months	University Hospital, Ghent
ROBOMET NCT03831243	III/Randomized	126	EBRT vs SBRT	8 Gy/1fr vs 20 Gy/1fr	Pain response at 1 month	Cancer Research Antwerp, Belgium
STEREO-OS NCT03143322	III/Randomized	196	Systemic treatment + SBRT Vs. systemic treatment alone	35 Gy/5fr vs 27 Gy/3fr	PFS at 12 months	UNICANCER, National Cancer Institute, France
NCT02145286	I-II/Single arm	47	SBRT	Not specified	Optimal dose range with single SBRT	University of Virginia



https://quotesgram.com/img/einstein-quotes-about-learning/8297888/