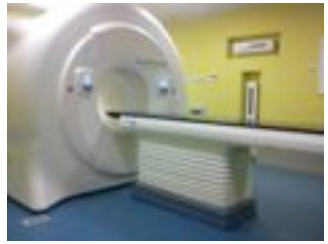
La Radioterapia stereotassica ablativa

Metastasi ossee

Gianluca Mortellaro

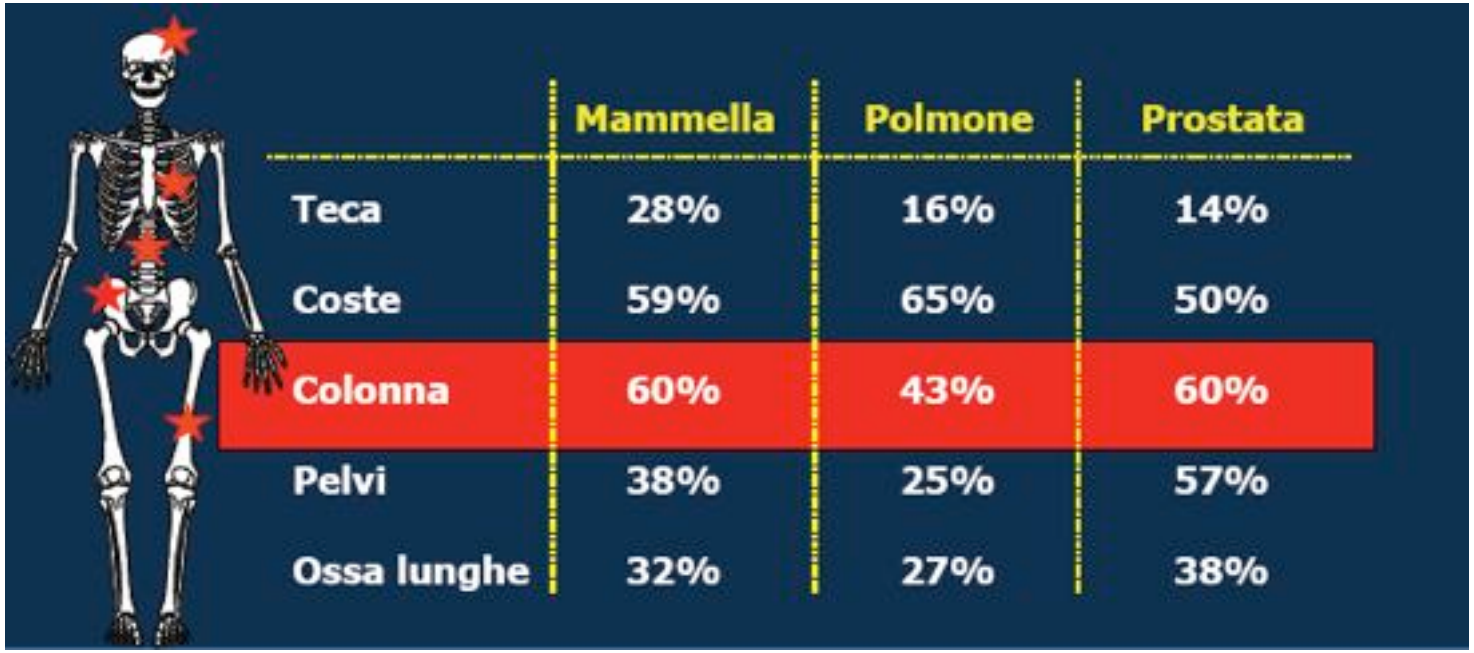
U.O.C. Radioterapia

ARNAS Civico Palermo



Metastasi ossee

- 40-70 % dei pazienti oncologici



	Mammella	Polmone	Prostata
Teca	28%	16%	14%
Coste	59%	65%	50%
Colonna	60%	43%	60%
Pelvi	38%	25%	57%
Ossa lunghe	32%	27%	38%

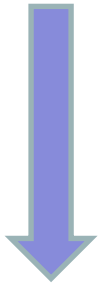
- Rachide dorsale 70%
- Rachide lombo-sacrale 20%
- Rachide cervicale 10%

Prognosi

Survival from Time of Initial Distant Recurrence Relative to Site of the Recurrence

Site of initial recurrence	No. of patients	Median survival (mos)
Bone (all)	116	35
Bone: 1 site	47	53
Bone: 2 sites	22	38
Bone: ≥ 3 sites	44	22
Bone: unspecified[a]	3	—
Lung	43	19
Pleura	16	19
Liver	12	11
Brain	10	12
Distant lymph nodes	10	26
Others	17	12
Multiple with bone	42	10
Multiple without bone	29	13
Total	295	

Nuove tecniche di imaging



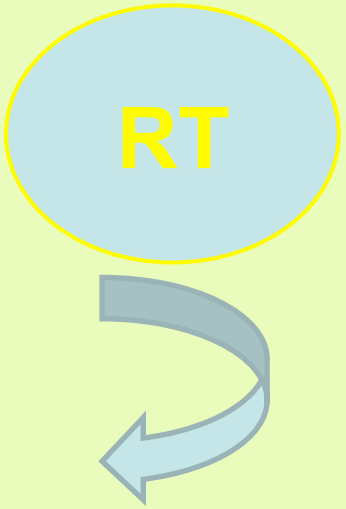
Aumento della percentuale di evidenza Di condizione di malattia oligometastatica

Jacobson AF et al. Cancer 2001

"…**the goals** of radiation therapy in patients with bone metastases are to palliate pain, decrease the use of narcotic analgesic, improve ambulation and restore function, and prevent complications of pathological fracture and spinal cord compression…"

Anderson PR, Coia LR - Semin Radiat Oncol - 2000

- **Controllo dolore**
- **Riduzione assunzione analgesici**
- **Preservazione mobilità e funzione**
- **Prevenzione fratture patologiche**
- **Prevenzione compressione midollare**
- **Controllo progressione malattia**

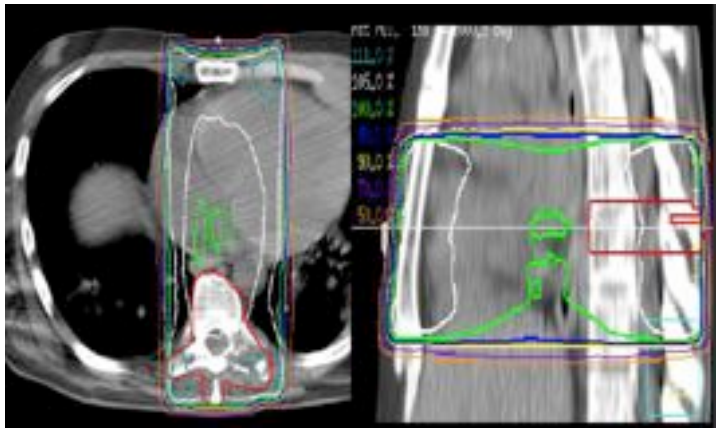


MIGLIORARE LA QUALITÀ DI VITA

Radioterapia convenzionale

- **Trattamento sintomatico dolore**

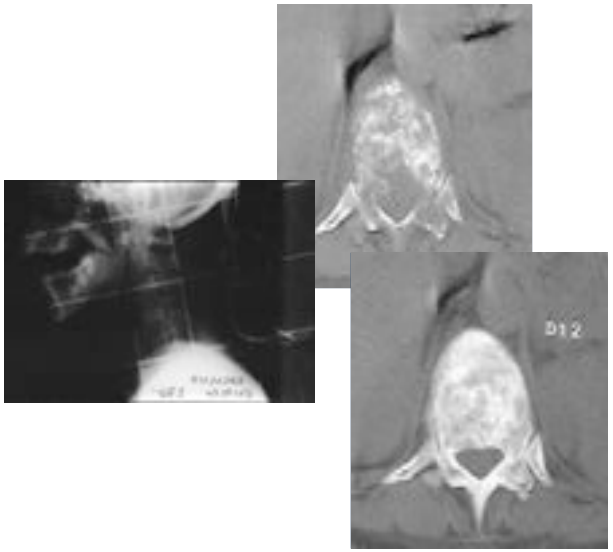
(risposta parziale nell'80-90% dei pazienti, e risposta completa nel 30-50%.**)**



- Picco risposta → 12-20 settimane
- Durata risposta → 3-12 mesi

– **Effetto citocida sulle cellule neoplastiche**
  - riduzione dei fenomeni meccanici

– **Induzione apoptosi**
  - espressione o inibizione di mediatori chimici
  - riduzione della stimolazione degli osteoclasti



ology (2003) 15: 345–352
S0936-6555(03)00113-4

Overview

Palliation of Metastatic Bone Pain: Single Fraction versus Multifraction Radiotherapy – A Systematic Review of Randomised Trials

W. M. Sze*, M. D. Shelley†, I. Held§, T. J. Wilt¶, M. D. Mason‡

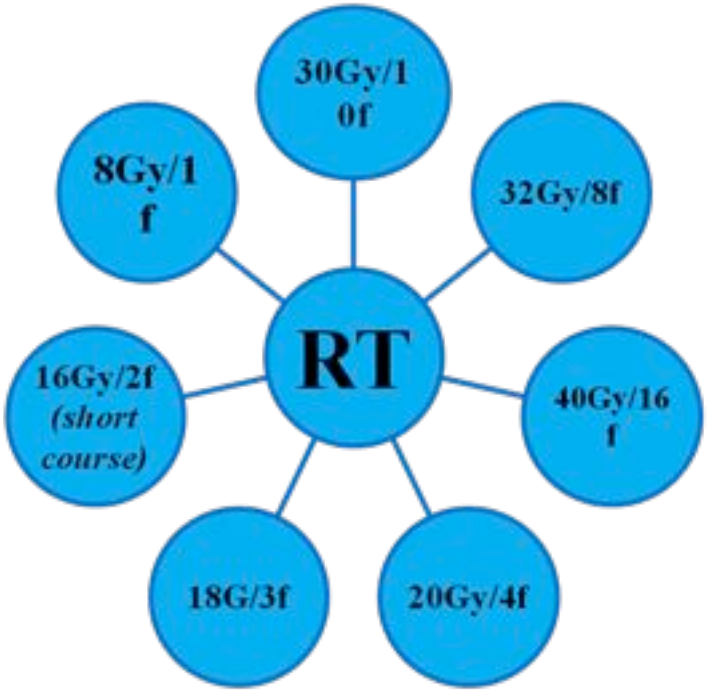
*Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital, Hong Kong, PR China; †Cochrane Unit, Velindre NHS Trust, Cardiff, U.K.; ‡Section of Oncology and Palliative Medicine, Velindre NHS Trust, Cardiff, U.K.; §Department of Oncology, Wrexham Maelor Hospital, Wrexham, U.K.; ¶Minneapolis VA Center for Chronic Disease Outcomes Research, Minneapolis, MN, U.S.A.

CLINICAL INVESTIGATION Bone

META-ANALYSIS OF DOSE-FRACTIONATION RADIOTHERAPY TRIALS FOR THE PALLIATION OF PAINFUL BONE METASTASES

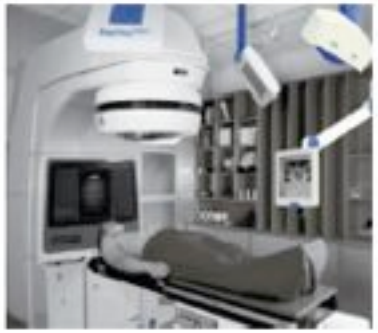
JACKSON SAI-YIU WU, M.D., F.R.C.P.C.,* REBECCA WONG, M.B.CH.B., M.SC., F.R.C.P.C.,† MARY JOHNSTON, B.SC.,‡ ANDREA BEZJAK, M.D.C.M., M.SC., F.R.C.P.C.,† AND TIMOTHY WHELAN, B.M.B.CH., F.R.C.P.C.,* ON BEHALF OF THE CANCER CARE ONTARIO PRACTICE GUIDELINES INITIATIVE SUPPORTIVE CARE GROUP§

*Division of Radiation Oncology, Hamilton Regional Cancer Centre, and Department of Medicine, McMaster University, Hamilton, Ontario, Canada; †Department of Radiation Oncology, Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada; ‡Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada; §Program in Evidence-Based Care, Cancer Care Ontario, Ontario, Canada



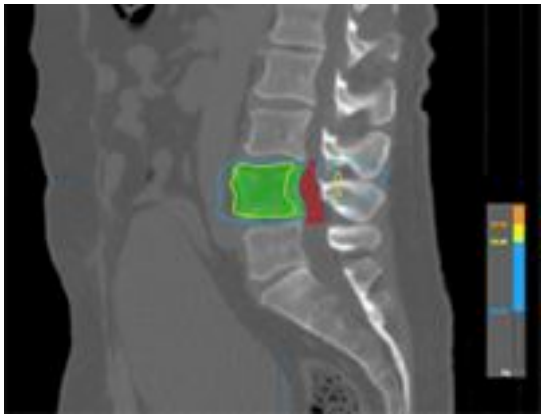
898 pazienti			
Studio randomizzato fase III	**8Gy/1f** (455 pz)		**30Gy/10f** (443 pz)
Controllo dolore	**65%**		**66%**
Fratture patologiche	**5%**		**4%**
Tossicità acuta (grado 2-4)	*10%*	**p = 0.002**	*17%*
Ritrattamento	*18%*	**p < 0.001**	*9%*

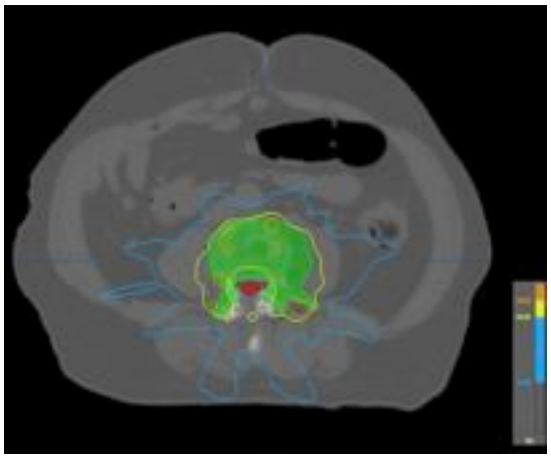
EVOLUZIONE TECNOLOGICA



2D ⇨ 3D ⇨ 4D ⇨ IMRT ⇨ IGRT ⇨ VMAT ⇨ SBRT ⇨ SART

RADIOTERAPIA STEREOTASSICA VERTEBRALE (SBRT-SART)





- Alta conformità di dose
- Dose radiante più alta su lesione localizzata
- Maggior risparmio midollo spinale
- Ridotto rischio di mielite radio-indotta

- Regimi ipofrazionati (1-5 frazioni)

  BED 43 -82 Gy_{10}

SBRT:indicazioni

Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 4, pp. 965–976, 2011

0360-3016/$ - see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2010.11.026

ASTRO GUIDELINE

PALLIATIVE RADIOTHERAPY FOR BONE METASTASES: AN ASTRO EVIDENCE-BASED GUIDELINE

Stephen Lutz, M.D.,* Lawrence Berk, M.D., Ph.D.,† Eric Chang, M.D.,‡
Edward Chow, M.B.B.S.,§ Carol Hahn, M.D.,¶
Peter Hoskin, M.D.,‖ David Howell, M.D.,# Andre Konski, M.D.,** Lisa Kachnic, M.D.,††
Simon Lo, M.B., Ch.B.,‡‡ Arjun Sahgal, M.D.,§§ Larry Silverman, M.D.,¶¶
Charles von Gunten, M.D., Ph.D., F.A.C.P.,‖‖ Ehud Mendel, M.D., F.A.C.S.,##
Andrew Vassil, M.D.,*** Deborah Watkins Bruner, R.N., Ph.D.,††† and William Hartsell, M.D.‡‡‡

Table 3. Suggested inclusion and exclusion criteria for patients enrolled in trials to evaluate stereotactic body radiotherapy for spinal bone metastases

Characteristic	Inclusion	Exclusion
Radiographic	1) Spinal or paraspinal metastasis by MRI (50, 51) 2) No more than 2 consecutive or 3 noncontiguous spine segments involved (50–53)	1) Spinal MRI cannot be completed for any reason (50, 51) 2) Epidural compression of spinal cord or cauda equina 3) Spinal canal compromise >25% (58) 4) Unstable spine requiring surgical stabilization (50, 51, 54, 57) 5) Tumor location within 5 mm of spinal cord or cauda equina (50, 51) (relative*)
Patient	1) Age ≥18 y (50, 54) 2) KPS of ≥40–50 (50, 51, 54, 55) 3) Medically inoperable (or patient refused surgery) (50, 51)	1) Active connective tissue disease (50) 2) Worsening or progressive neurologic deficit (50–52, 57) 3) Inability to lie flat on table for SBRT (50–52) 4) Patient in hospice or with <3-month life expectancy
Tumor	1) Histologic proof of malignancy (50, 51, 56) 2) Biopsy of spine lesion if first suspected metastasis 3) Oligometastatic or bone only metastatic disease (50)	1) Radiosensitive histology such as MM[50-52] 2) Extraspinal disease not eligible for further treatment[51]
Previous treatment	Any of the following: 1) Previous EBRT <45-Gy total dose 2) Failure of previous surgery to that spinal level (50–52) 3) Presence of gross residual disease after surgery	1) Previous SBRT to same level 2) Systemic radionuclide delivery within 30 days before SBRT (50–52) 3) EBRT within 90 days before SBRT (50–52) 4) Chemotherapy within 30 days of SBRT (50–53)

Patiente

IINCLUSIONE ≥18 y ; KPS ≥40–50
Inoperabile-rifiuto pz

ESCLUSIONE
Mallattia connettivale attiva
peggioramento o progressione del deficit neurologico
incapacità a mantenere la posizione sul lettino per SBRT
Aspettativa di vita < 3 mesi o paziente in hospice

Tumore

INCLUSIONE istologia di neoplasia
(renale,polmonare,melanoma, mammella,prostata)
Biopsia della lesione metastatica (se è la prima presentazione metastatica)
paziente oligometastatico o sola malattia ossea

ESCLUSIONE Istologia radiosensibile come il MM
malattia extraspinale non eleggibile per altri trattamenti

Lutz S. Astro EB-Guidelines IJROBP 2011

Precedente trattamento

Uno dei seguenti:

Precedente EBRT <45-Gy dose totale

Fallimento di precedente chirurgia a livello vertebrale

Presenza di residuo di malattia post-chirurgia

Quadro radiologico

INCLUSIONE Metastasi vertebrali o paravertebrali visibili alla MRI; coinvolgimento di non oltre 2 segmenti consecutivi o 3 non contigui coinvolti

ESCLUSIONE RM non eseguibile; compressione epidurale; interessamento del canale midollare >25%

Instabilità che richiede stabilizzazione chirurgica

localizzazione tumorale entro 5 mm dal midollo o cauda equina

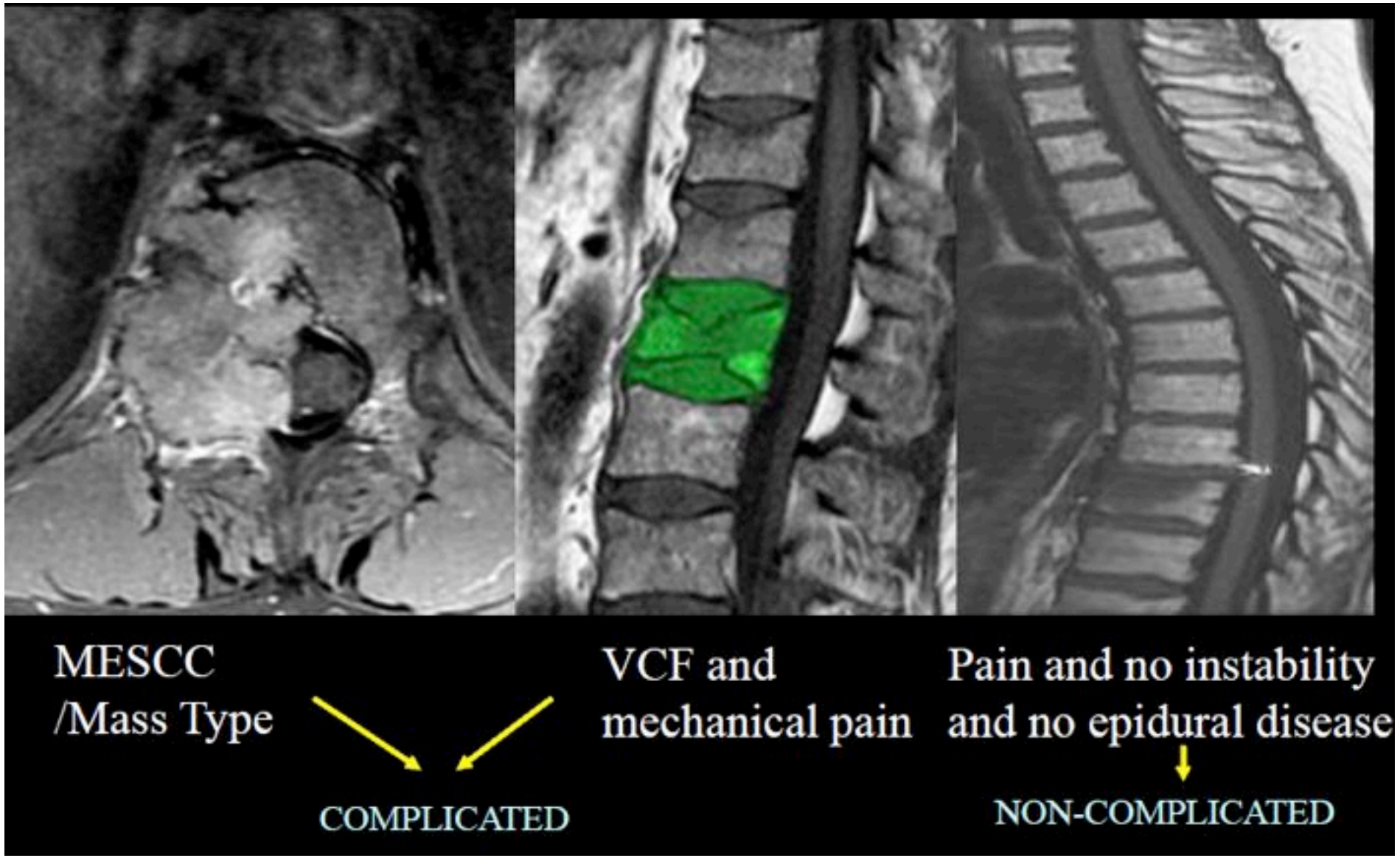
Metastasi vertebrali non complicate

- tumore contenuto nell'osso
- normale allineamento vertebrale e assenza di fratture
- dolore non posizionale
- 5% può progredire in MESCC (metastatic epidural spinal cord compression) o frattura

Metastasi vertebrali complicate

- instabilità meccanica
- masse bulky
- MESCC

  Surgical candidates


MESCC
/Mass Type
VCF and
mechanical pain
Pain and no instability
and no epidural disease
COMPLICATED
NON-COMPLICATED

FRAZIONAMENTI

IPOFRAZIONAMENTO	**20 Gy/5frx;**
	30 Gy/5frx;
	24 Gy/3frx
	27 Gy/3frx;
DOSE SINGOLA	**10- 24 Gy**

SCENARIO CLINICO

- **controllo del dolore?**
- **controllo locale?**
- **quale frazionamento?**
- **volumi?**
- **tossicità?**
- **valutazione risposta clinica?**

→ **Clinical outcomes**

Clinical outcome SBRT

Table 4. Summary of current data for spinal SBRT for spinal metastases

Study	Patients (*n*), tumors (*n*), histologic type	Fractionation	Repeat RT	Pain relief	Complete response	Local control/ definition	Investigator	Year	Reference
Cohort study	69, 127, various histologic types	Mean: 15.5 Gy/2 Fx	15 patients	61/69	NR	96.8% FFP at 10 mo 123/127 (97%)	Tsai	2009	63
Cohort study	38							009	64
Cohort study	93							008	65
Cohort study	32							008	66
Phase I-II study with defined stopping rules	63							007	51
Cohort study	393 histologic types							007	57
Cohort study	49, 61, various histologic types	10–16 Gy/1 Fx	0	52/61	NR	57/61/imaging and pain	Ryu	2005	56
Cohort study	21, 21	Median 20 Gy/5 Fx	20 patients	NR	NR	19/21/imaging	Yamada	2005	67
Cohort study	5, 5	10 Gy/1 Fx	5 patients	NR	NR	5/5/imaging and/or pain	Hamilton	1995	68

Guideline statement

Stereotactic body RT is a technology that delivers high doses to metastatic spinal disease with a steep dose gradient that might allow superior sparing of the adjacent neural structures, including the spinal cord and cauda equina. The published efficacy and safety data for SBRT have mostly been from retrospective single-institution studies, and some of the measured endpoints in these studies were different from those used to evaluate other treatment types (Tables 3, 4 and 5). Given that the complexities of dosing and target delineation for SBRT have yet to be fully defined, the Task Force strongly suggests that these patients be treated only within available clinical trials and that SBRT should not be the primary treatment of vertebral bone lesions causing spinal cord compression.

Table 5. Summary of current data for spinal SBRT for spinal metastases reporting on specific histologic types

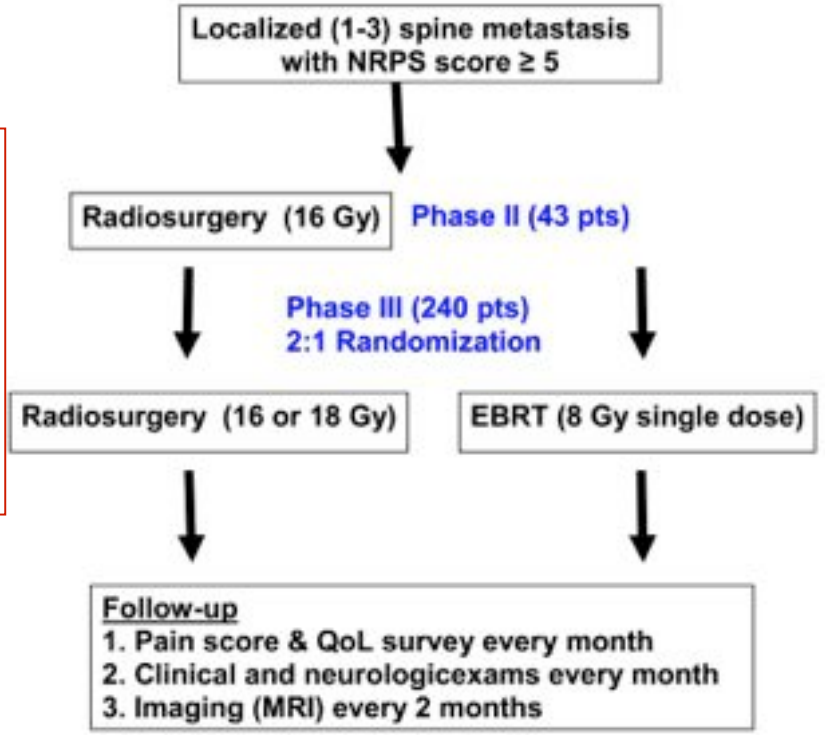
	Patients (*n*), tumors (*n*), histologic type	Fractionation	Repeat treatment	Pain relief	CR	Local control/ definition	Investigator	Year	Reference
Cohort study	48, 55, renal cell	30 Gy/5 Fx; 24 Gy/3 Fx; 24 Gy/1 Fx	22 patients	52% of patients had durable response and were pain free at 12 mo	52% of patients had durable response and were pain free at 12 mo	43/55, 1-y FFP 82%/imaging	Nguyen	2009	69
Cohort study	NR, 93, renal cell	Mean maximum intratumor dose 20 Gy/1 Fx*	NR	94%	NR	87%/imaging	Gerszten	2007	57
Cohort study	NR, 83, breast	Mean maximum intratumor dose 20 Gy/1 Fx*	NR	96%	NR	100%/imaging	Gerszten	2007	57
Cohort study	NR, 80, lung	Mean maximum intratumor dose 20 Gy/1 Fx*	NR	93%	NR	100%/imaging	Gerszten	2007	57
Cohort study	NR, 38, melanoma	Mean maximum intratumor dose 20 Gy/1 Fx*	NR	96%	NR	75%/imaging	Gerszten	2007	57

Int J Radiat Oncol Biol Phys. 2011 October 1; 81(2): S131–S132. doi:10.1016/j.prro.2013.05.001.

RTOG 0631 Phase II/III Study of Image-Guided Stereotactic Radiosurgery for Localized (1-3) Spine Metastases: Phase II Results

Samuel Ryu, M.D.[1], Stephanie L Pugh, Ph.D[2], Peter C. Gerszten, M.D., MPH[3], Fang-Fang Yin, Ph.D.[4], Robert D. Timmerman, M.D.[5], Ying J. Hitchcock, M.D.[6], Benjamin Movsas, M.D.[1], Andrew A. Kanner, M.D.[7], Lawrence B. Berk, M.D.[8], David S. Followill, Ph.D.[9], and Lisa A. Kachnic, M.D.[10]

RTOG 0631 Phase II/III Schema



Int J Radiat Oncol Biol Phys. 2010 Mar 15;76(4):1185-92. doi: 10.1016/j.ijrobp.2009.03.062. Epub 2009 Jul 23.

Management of spinal metastases from renal cell carcinoma using stereotactic body radiotherapy.

Nguyen QN[1], Shiu AS, Rhines LD, Wang H, Allen PK, Wang XS, Chang EL.

Author information

[1]Department of Radiation Oncology, The University of Texas, M.D. Anderson Cancer Center, Houston, Texas 77030, USA.

Abstract

PURPOSE: To evaluate the outcomes associated with stereotactic body radiotherapy (SBRT) in the management of spinal metastases from renal cell carcinoma (RCC).

METHODS AND MATERIALS: SBRT was used in the treatment of patients with spinal metastases from RCC. Patients received either 24 Gy in a single fraction, 27 Gy in three fractions, or 30 Gy delivered in five fractions. Effectiveness of SBRT with respect to tumor control and palliation of pain was assessed using patient-reported outcomes.

RESULTS: A total of 48 patients with 55 spinal metastases were treated with SBRT with a median follow-up time of 13.1 months (range, 3.3-54.5 months). The actuarial 1-year spine tumor progression free survival was 82.1%. At pretreatment baseline, 23% patients were pain free; at 1 month and 12 months post-SBRT, 44% and 52% patients were pain free, respectively. No Grade 3-4 neurologic toxicity was observed.

CONCLUSIONS: The data support SBRT as a safe and effective treatment modality that can be used to achieve good tumor control and palliation of pain associated with RCC spinal metastases. Further evaluation with randomized trials comparing SBRT to conventional radiotherapy may be warranted.

55 lesioni spinali trattate

Frazionamenti

30 Gy in 5 fz
27 Gy in 3 fz
24 Gy in singola fz

Spine progression free survival a un anno 82%

Complete Pain Relief Rates for Pain Using BPI

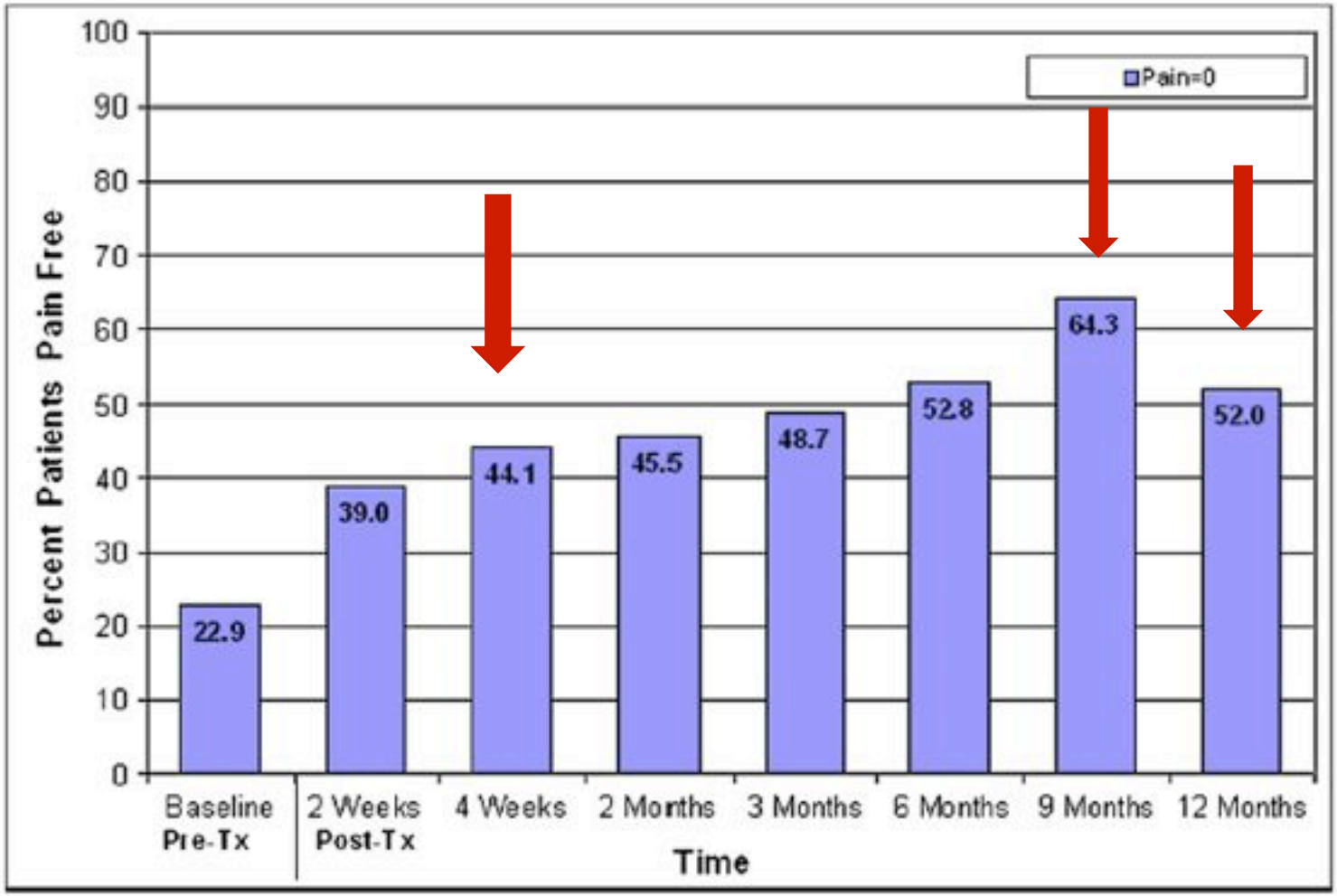


Fig. 3. Percentage of patients completely pain-free as assessed by Brief Pain Inventory.

Review Article

Stereotactic Body Radiosurgery for Spinal Metastatic Disease: An Evidence-Based Review

William A. Hall,[1] Liza J. Stapleford,[1] Costas G. Hadjipanayis,[2] Walter J. Curran,[1] Ian Crocker,[1] and Hui-Kuo G. Shu[1]

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Correspondence should be addressed to Hui-Kuo G. Shu, hgshu@emory.edu

Received 25 January 2011; Accepted 2 May 2011

Table 2: 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.

Frazionamenti e dosi

Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 4, pp. 1151–1157, 2011

0360-3016/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2009.12.038

CLINICAL INVESTIGATION **Metastasis**

PREDICTORS OF LOCAL CONTROL AFTER SINGLE-DOSE STEREOTACTIC IMAGE-GUIDED INTENSITY-MODULATED RADIOTHERAPY FOR EXTRACRANIAL METASTASES

CARLO GRECO, M.D.,* MICHAEL J. ZELEFSKY, M.D.,* MICHAEL LOVELOCK, PH.D.,† ZVI FUKS, M.D.,* MARGIE HUNT, M.S.,† KENNETH ROSENZWEIG, M.D.,* JOAN ZATCKY, B.S., N.P.,* BALEM KIM, B.A.,* AND YOSHIYA YAMADA, M.D.*

Departments of *Radiation Oncology and †Medical Physics, Memorial Sloan-Kettering Cancer Center, New York, NY

in remarkable outcomes. A dose–response relationship has been reported for single-dose stereotactic radiosurgery of brain metastases, with approximately 50% freedom from local relapse at 1 to 2 years after 15–18 Gy compared with ≥80% after 22–24 Gy, regardless of the histologic phenotype of the primary tumor (10, 11). Similar dose–response data for extracranial sites are not available. Recent studies using sin-

Table 1. Patient characteristics

All lesions (n = 124)	n
Gender	
Male	71
Female	32
Age (y), median (range)	64 (33–91)
Treatment site	
Bone	94
Lymph node	14
Lung	8
Liver	6
Other soft tissues	2
Histologic type	
Prostate	42
Renal cell	35
Colorectal	15
Sarcoma	5
Non–small cell lung cancer	4
Cholangiocarcinoma	4
Breast	3
Melanoma	3
Bladder	2
Leydig cell	2
Small-cell lung cancer	2
Thyroid cancer	2
Esophageal	1
Germ cell	1
Chordoma	1
Ovarian	1
Pancreatic	1

SD-SBRT

Table 2. Distribution by prescription dose (all lesions, n = 124)

Planning target volume dose (Gy)	n
18	10
20	2
21	3
22	38
23	1
24	70

Overall 2-year actuarial LC rate 64%
The median time to local failure 9.6 months
Complete responses occurred in 22% of treatments (21 of 95)

18 Gy: 0 complete response
21 Gy: 1/3
22 Gy: 8/38
24 Gy: 12/71

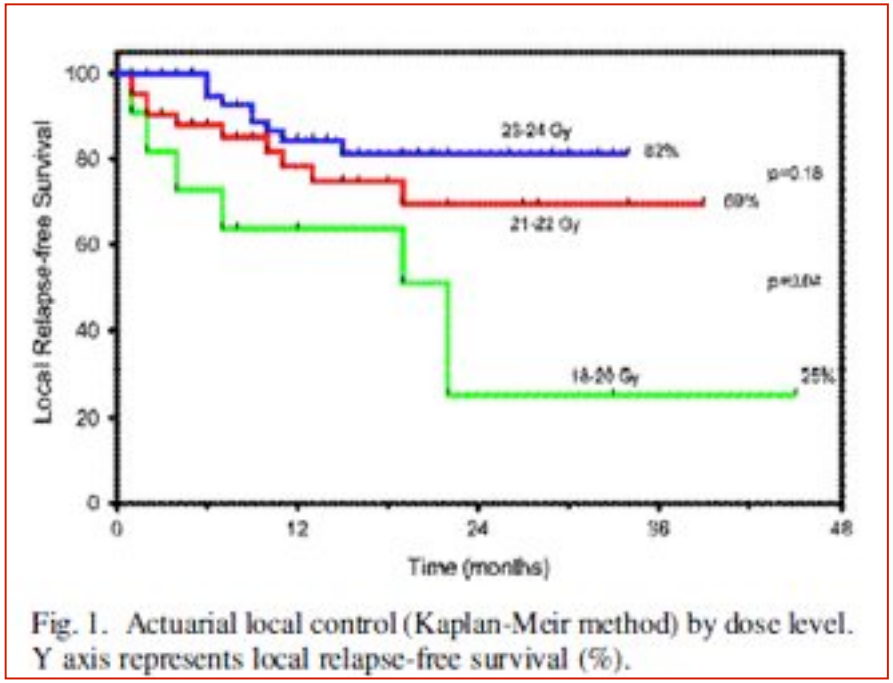

Fig. 1. Actuarial local control (Kaplan-Meir method) by dose level. Y axis represents local relapse-free survival (%).

Effetto dose

High dose **23-24 Gy**
Intermediate dose **21-22 Gy**
Low dose **18-20 Gy**

2 y-LRFS

High dose 82% vs Low dose 25% (*p*<0.0001)
Intermediate 69% vs low dose 25% (*p*=0.04)

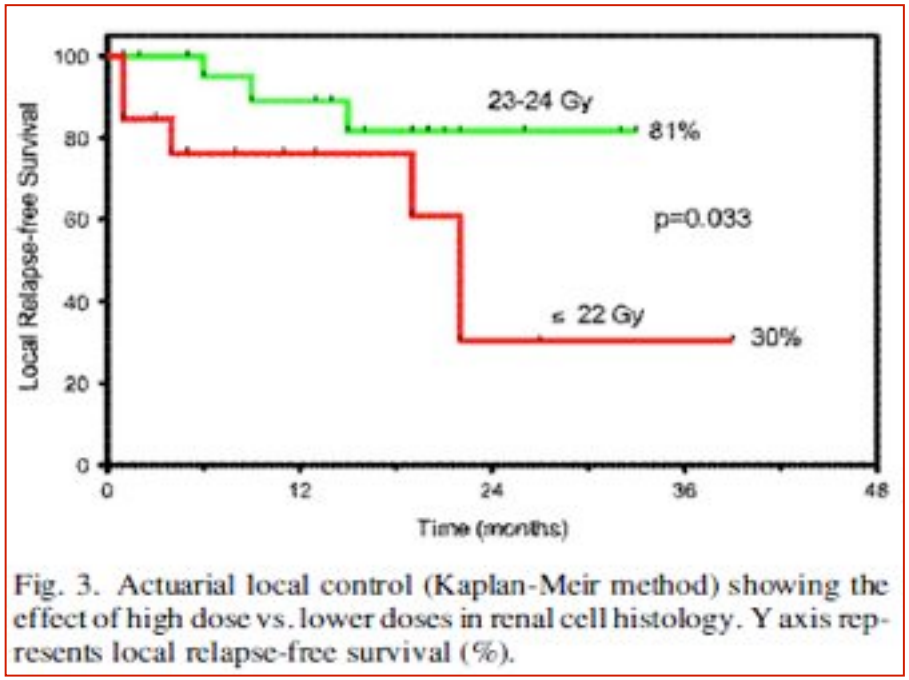

Fig. 3. Actuarial local control (Kaplan-Meir method) showing the effect of high dose vs. lower doses in renal cell histology. Y axis represents local relapse-free survival (%).

Istologia

Local control Renal cell histology

80 % high dose vs 37% low dose (p=0.04)

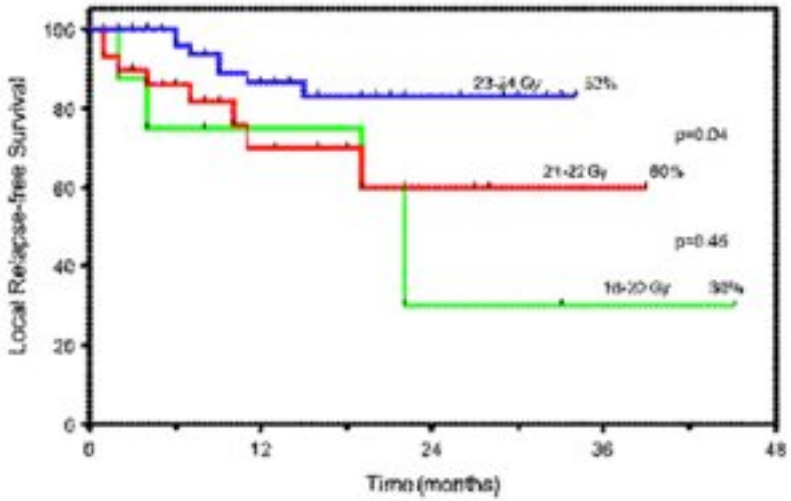

Fig. 6. Actuarial local control (Kaplan-Meir method) of bone lesions as a function of dose. Y axis represents local relapse-free survival (%).

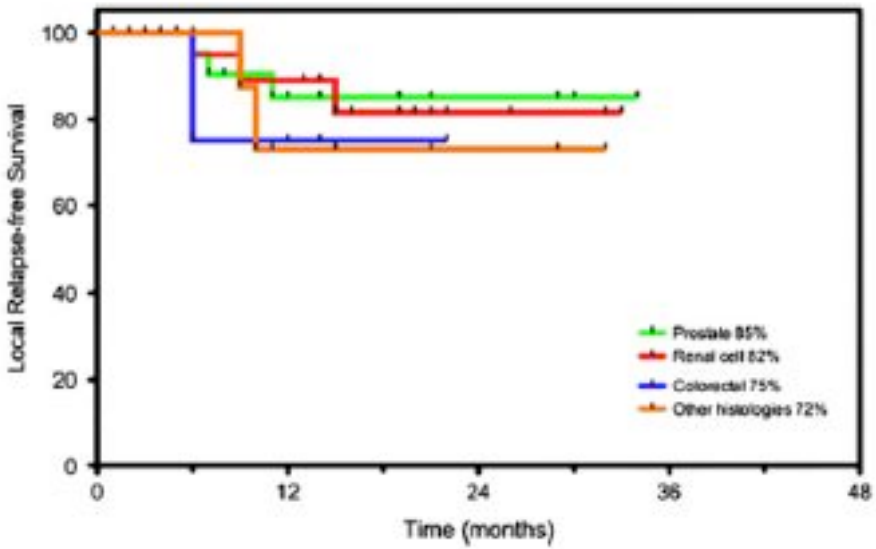

Fig. 4. Actuarial local control (Kaplan-Meir method) at the high dose level for all histologies. Y axis represents local relapse-free survival (%; $p = 0.90$).

94 pz con mts ossee

The relatively large number of bone lesions allowed further analysis of the effect of dose and histology in this site. A positive association (Fig. 6) between dose and actuarial LRFS was observed in bone metastases ($p = 0.019$). Moreover, the difference between high dose (83%) vs. intermediate dose (60%) was also significant ($p = 0.04$). At the high dose level, 2-year actuarial LRFS probabilities of osseous metastases were 86% for prostate, 80% for renal cell, 75% for colorectal, and 83% for all other histologies combined ($p = 0.89$).

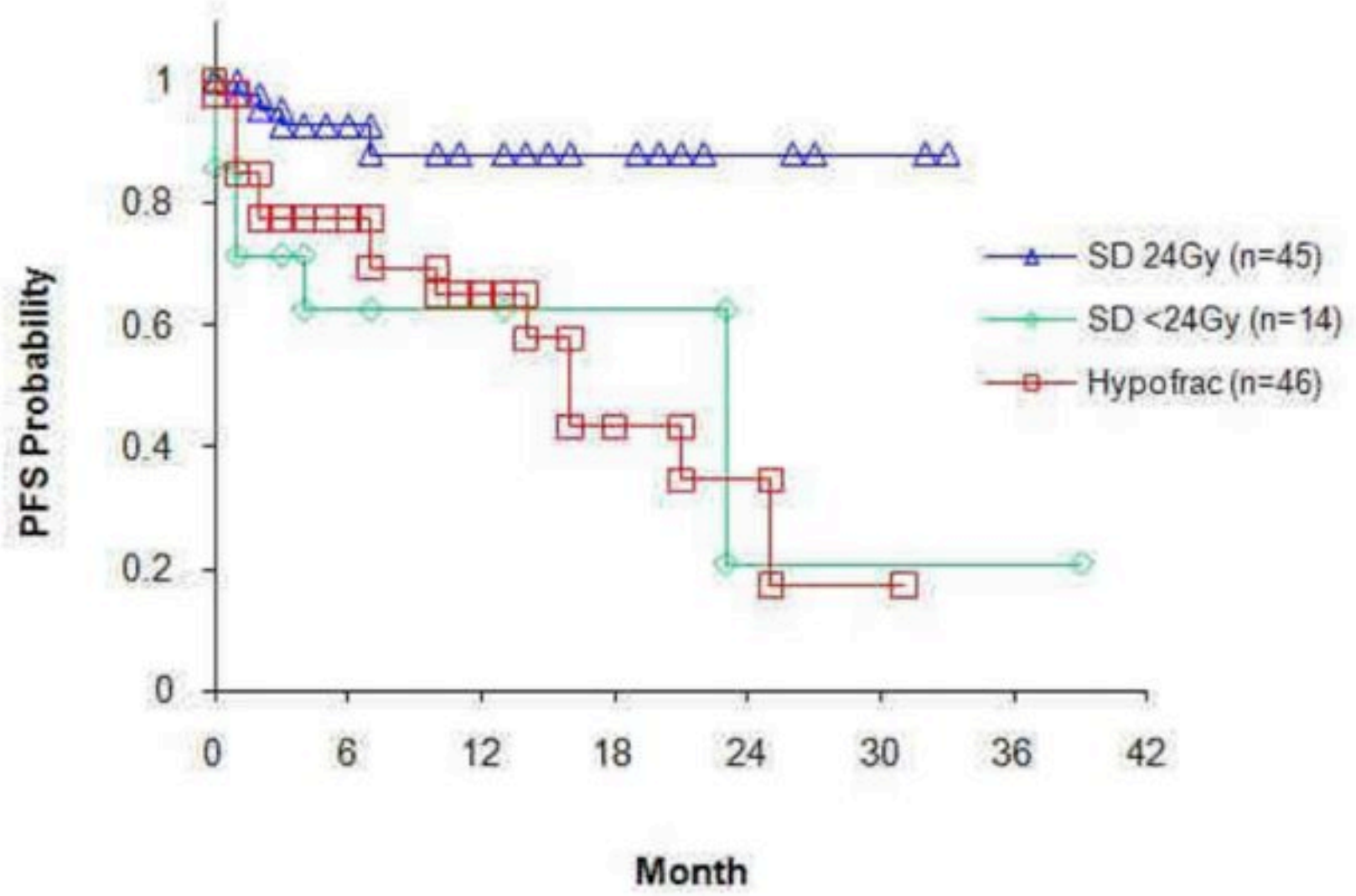

Fig 2.

Actuarial local control (Kaplan-Meir method) as a function of prescription regimen for renal cell cancer ($p = 0.001$). Y axis represents local relapse-free survival (%).

DISCUSSION

In this study, the excellent long-term LRFS rates (≥ 80%) observed with high SDIGRT for renal cell histologies defy standard linear-quadratic model predictions. In fact, it has been disputed that the linear-quadratic model overestimates cell killing at high single doses.(12) Experimental models and emerging clinical data consistently show that significantly lower single exposures can achieve high local control rates, leading to the hypothesis that the underlying mechanisms of tumor-cell killing may be different from fractionated radiotherapy.(13, 14)

Recent studies have suggested that tumor stem cells reside in niches where specific micro-environmental conditions, including hypoxia, provide critical signals to support and maintain their undifferentiated phenotype.(18) Large radiation doses may be potentially more effective in overcoming the inherent radioresistance of stem cells found in metastases. Consistent with this notion, traditional linear-quadratic formalism indicates that radioresistant tumor histologies with low alpha-beta ratios may respond more favorably to large fraction sizes, where irreparable lethal damage associated with the linked endothelial-stem cell mechanism of tissue damage may be the predominant method of tumor stem cell kill. Therefore, following high-dose irradiation, similar clinical outcomes are to be expected

of this response, this pathway does not appear to be engaged in fractionated regimens where individual doses are too low to invoke this apoptotic stimulus on endothelial cells. While the mechanism by which endothelial damage and microvascular dysfunction confer tumor stem cell clonogen lethality is currently being investigated, these observations support the notion that the mechanisms of tumor cure by single high-dose are distinct, and raises the question whether hypofractionation is necessary when excellent control can be achieved with stereotactic SD-IGRT.

Engaging the vascular component of the tumor response

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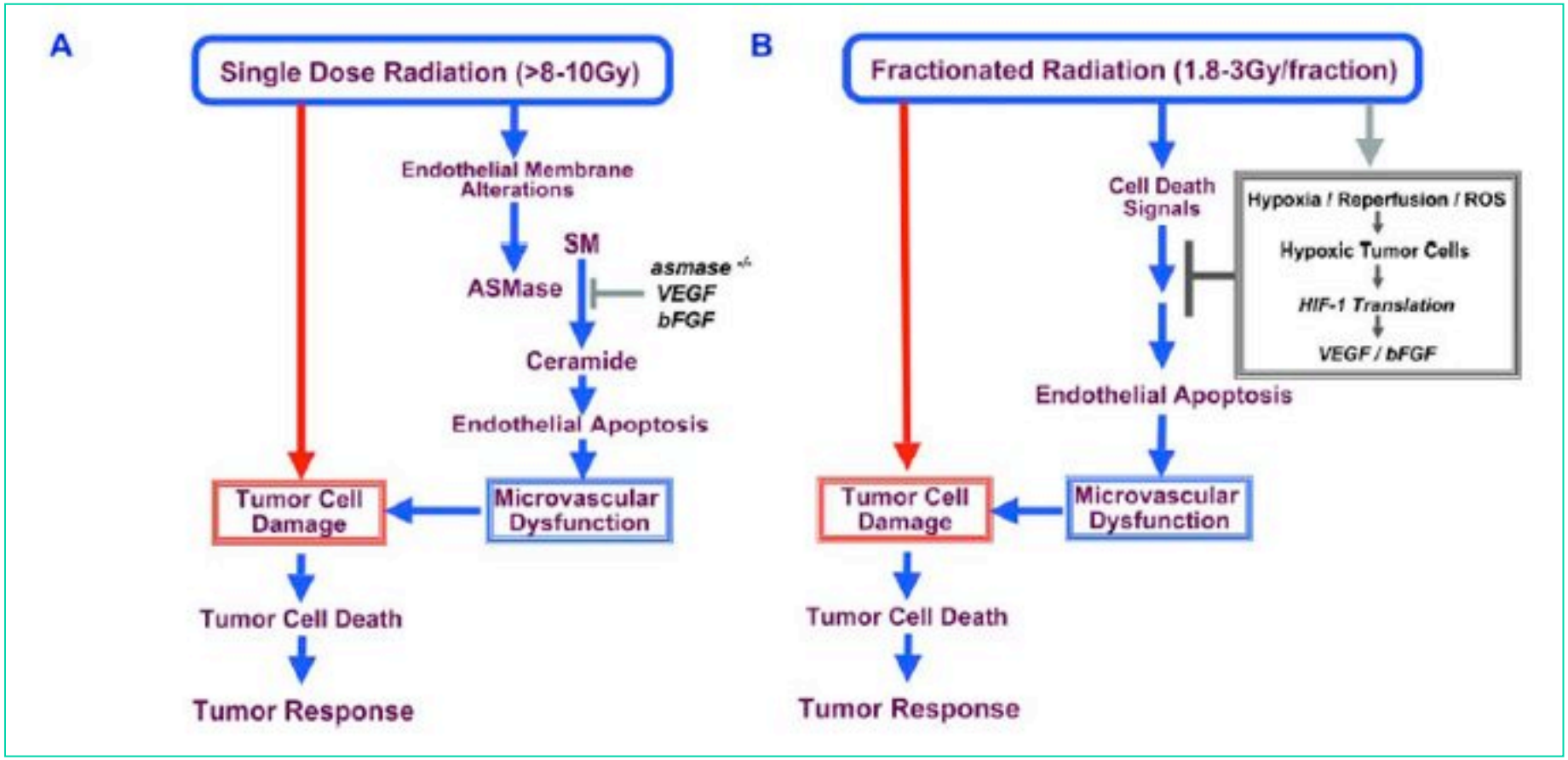

VOLUMI

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Clinical Investigation: Central Nervous System Tumor

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

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Int J Radiation Oncol Biol Phys, Vol. 83, No. 5, pp. e597–e605, 2012
0360-3016/$ - see front matter
doi:10.1016/j.ijrobp.2012.03.009

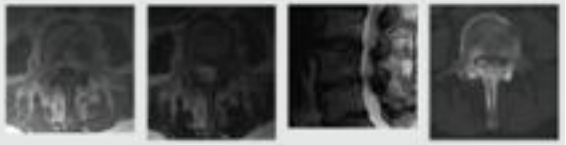
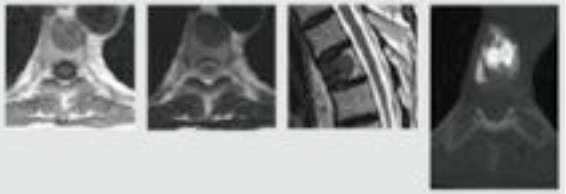
Summary

Ten physician members of the International Spine Radiosurgery Consortium independently contoured 10 cases representing common scenarios in spinal radiosurgery for metastases.

Estimation. Consensus guidelines for target volume definition in spinal stereotactic radiosurgery for metastatic disease were generated. This report serves as a foundation for refining radiosurgery target volume delineation. We advocate using consensus target definitions in future spine radiosurgery protocols.

10 cases

Table 1 Summar

Anatomic description	MRI axial T1 post	MRI axial T2	MRI sagittal	CT
Case 1: L5 lesion limited to the anterior VB with no epidural extension				
Case 2: T8 lesion involving left pedicle, posterolateral VB, and neural foramen. Involvement of the ventral and left lateral epidural space, mild spinal canal compromise, and abutment of the spinal cord				
Case 3: T6-8 lesion with T8 collapse deformity, ventral epidural disease, moderate spinal canal compromise, mild spinal cord displacement, extension to the bilateral neural foramina, and paraspinal extension				
Case 4: T11 lesion involving pedicle and posterior elements, mild ventral and right lateral epidural disease, narrowing of the right T10/11 and T11/12 neural foramina				
Case 5: L5 lesion centered in the spinous process and extending to the bilateral lamina, bilateral posterior paraspinal musculature, and bilateral dorsal epidural space extension with mild spinal canal compromise				
Case 6: L2-3 expansile mass in right-sided VB and right posterior elements with mild right ventral, lateral, and dorsal epidural disease. Involvement of the right L2/3 and L3/4 neural foramina				
Case 7: T3 posterior VB lesion extending into the left neural foramen with mild spinal canal compromise and left ventral and lateral epidural extension				
Case 8: T10 lesion in posterior VB				
Case 9: L4 diffuse marrow replacement including left pedicle and articular facets, ventral epidural extension, left lateral recess extension, and left L4/5 neural foramen involvement				
Case 10: T5 lesion with mild superior and inferior endplate infractions resulting in mild loss of VB height. Mild anterior paraspinal extension. Patient underwent T5 kyphoplasty				

Abbreviations: CT = computed tomography; MRI = magnetic resonance imaging; VB = vertebral body.

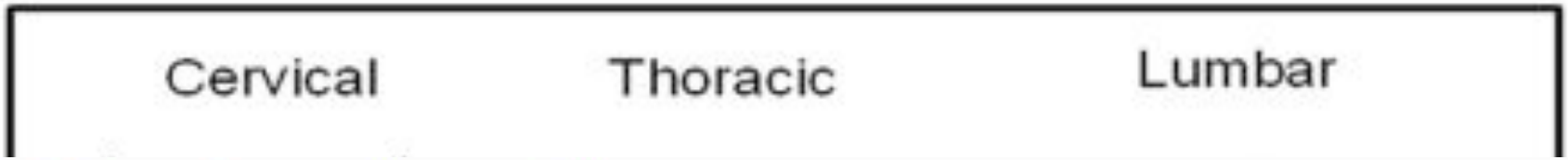
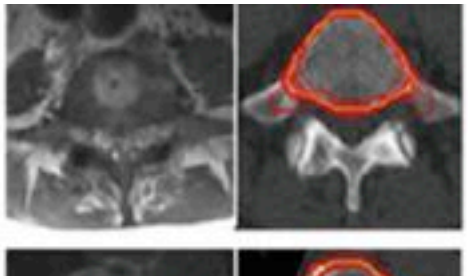
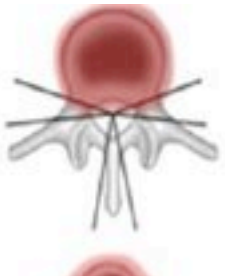


Table 3 Guidelines for spinal SRS bony CTV delineation

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

Abbreviations: CTV = clinical target volume; GTV = gross tumor volume; ISRC = International Spine Radiosurgery Consortium.





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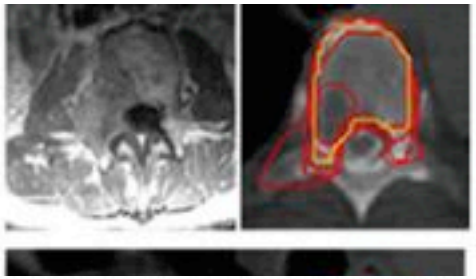

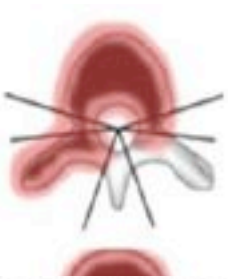

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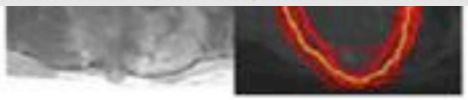
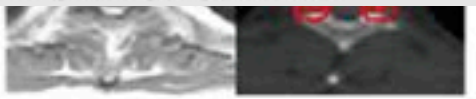
Table 4 Summary of contouring guidelines for GTV, CTV, and PTV in spinal stereotactic radiosurgery

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.





Individual contours

consensus contours

Tossicità

ACUTA

Effect of Dexamethasone Rescue

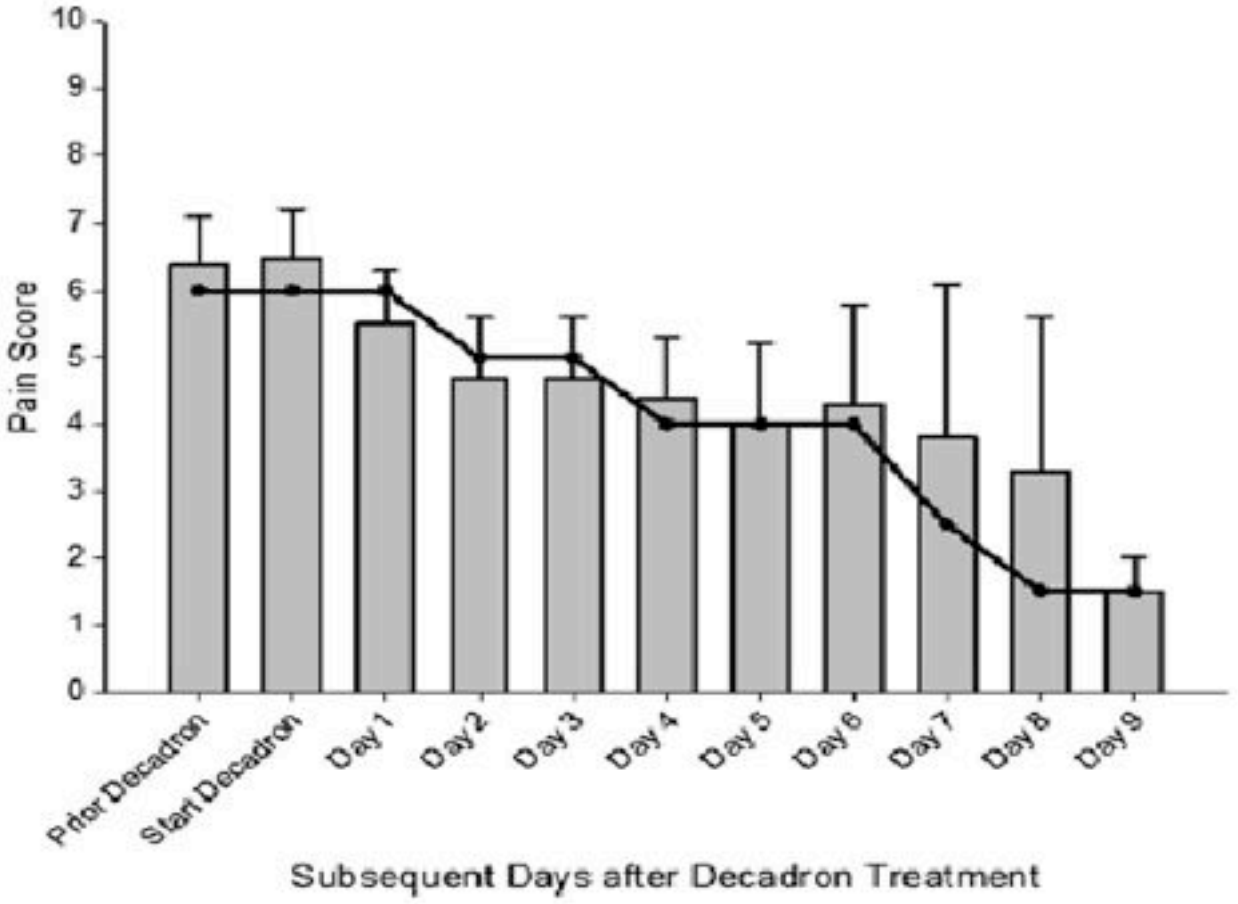
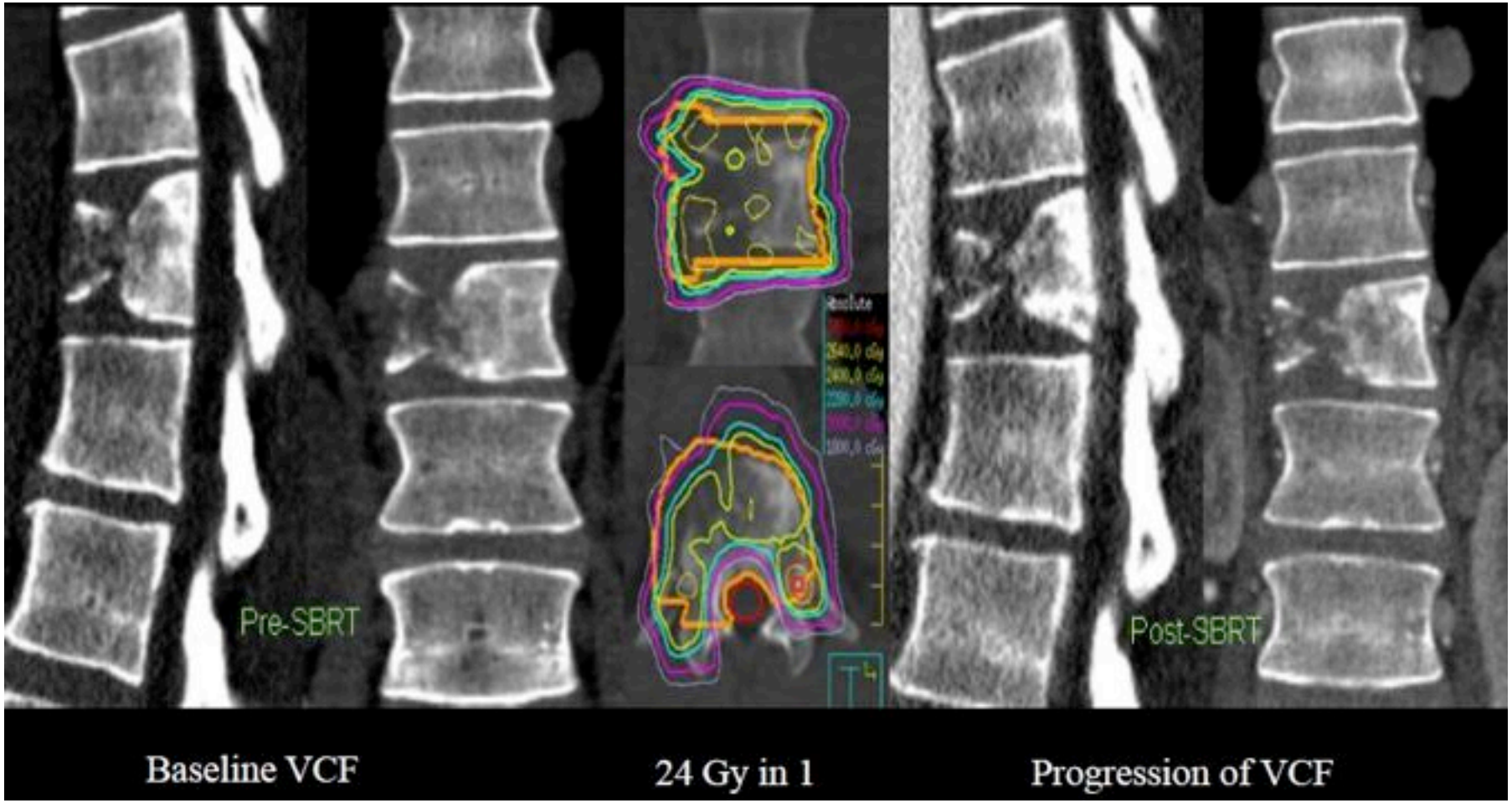


Fig. 2. Change in pain scores after initiation of dexamethasone (n = 11 patients). The bars highlight change in mean worst pain scores (standard error) over time, whereas the dotted line represents the change in median worst pain scores over time.

TARDIVA

Vertebral compression fracture (VCF) post -SBRT



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Clinical Investigation: Metastases

Vertebral Compression Fracture (VCF) After Spine Stereotactic Body Radiation Therapy (SBRT): Analysis of Predictive Factors

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Spine Oncology Study Group (SOSG)
Spinal Instability Neoplastic Score (SINS) not clinical validate

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A Novel Classification System for Spinal Instability in Neoplastic Disease

Element of SINS	Score
Location	
Junctional (occiput-C2, C7–T2, T11–L1, L5–S1)	3
Mobile spine (C3–C6, L2–L4)	
Semi-rigid (T3–T10)	
Rigid (S2–S5)	
Pain relief with recumbency and/or pain with movement/loading of the spine	
Yes	
No (occasional pain but not mecha	
Pain free lesion	
Bone lesion	
Lytic	
Mixed (lytic/blas	
Blastic	0
Radiogra	
Sublux	4
De novo	2
Normal ali	0
Vertebral body	
>50% collapse	3
<50% collapse	2
No collapse with > body involved	1
None of the above	0
Posterolateral involvement of the spinal elements (facet, pedicle or CV joint fracture or replacement with tumor)	
Bilatoral	3
Unilateral	1
None of the above	0

system has not been clinically validated. The purpose of this study was to report the rate of VCF in spine SBRT patients and determine which of the SINS components in addition to specific clinical and dosimetric factors relevant to spine SBRT were predictive of VCF.

ble	0-6 pts 7-12 pts
e	>12 pts

Charles Fisher et al. 2011, Spine

• **Singole fraction 20-24 Gy SBRT if no history of prior RT e no epidural disease otherwisethey fractionate**

Results: The median follow-up was 7.4 months. We identified 19 fractures (11%): 12 de novo fractures (63%) and 7 cases of fracture progression (37%). The mean time to fracture after SBRT was 3.3 months (range, 0.5-21.6 months). The 1-year fracture-free probability was 87.3%. Multivariate analysis confirmed that alignment ($P = .0003$), lytic lesions ($P = .007$), lung ($P = .03$) and hepatocellular ($P < .0001$) primary histologies, and dose per fraction of 20 Gy or greater ($P = .004$) were significant predictors of VCF.

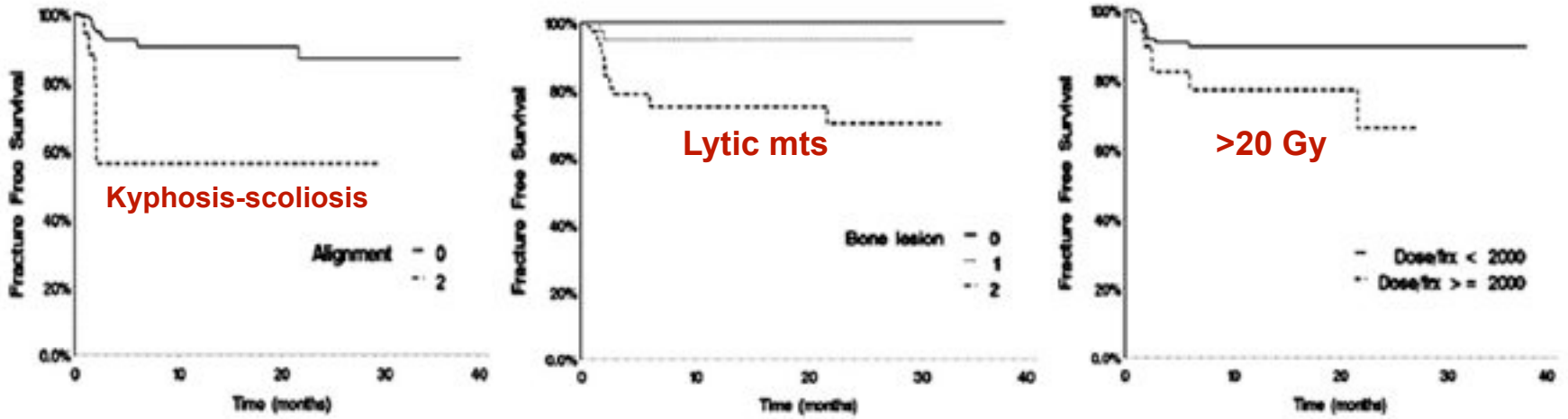


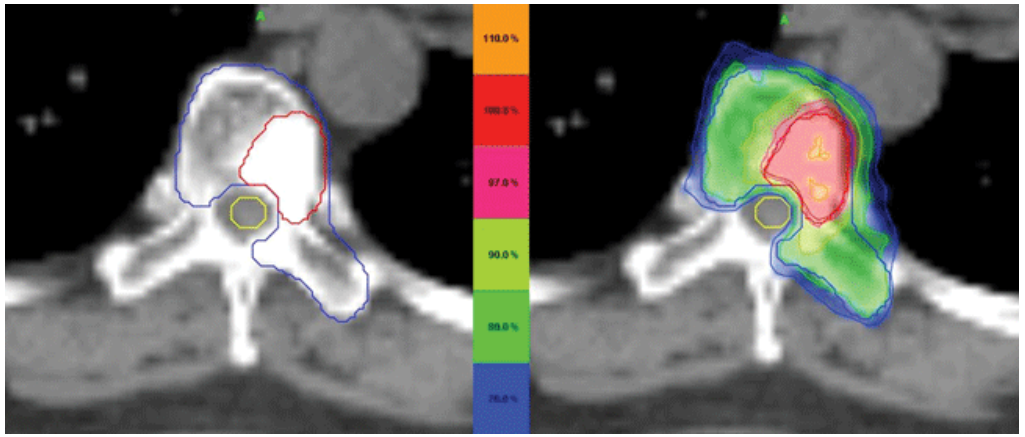
Fig. 2. Kaplan-Meier freedom-from-fracture analysis for Spinal Instability Neoplastic Score (SINS) component (6) based on spinal alignment stratified according to the presence of a SINS score of 2 signifying a de novo kyphosis/scoliosis (n = 19) and a SINS score of 0 signifying normal alignment (n = 148) (left); based on type of lesion stratified according to the presence of a SINS score of 2 signifying lytic metastases (n = 80), a SINS score of 1 signifying mixed (lytic/blastic) metastases (n = 44), and a SINS score of 0 signifying blastic metastases (n = 43) (middle); and based on dose per fraction (frx) of 20 Gy or greater (n = 31) and less than 20 Gy (n = 136) (right).

Age, pre-existing fracture or prior RT not increased th risk of VCF

	Toronto University	MSKCC Rose et al	MDACC
Num lesions	167	71	123
Fracture	11%	39%	20%
Median time to fracture	3.3 months	25 months	3 months
fraction	1-3-5 fract	Single f. 18-24 Gy	1-3-5 frac
Previous RT	yes	no	yes
		Lytic disease, increasing involvement of the vertebral body or lumbar region	

Tossicità al midollo

La tolleranza del midollo è un fattore dose limitante in RT.
Il rischio di danni aumenta all'aumentare della dose totale e della dose/fr.



La dose di tolleranza stimata del midollo alle singole dosi che deriva da modelli sperimentali ed estrapolazioni di dati clinici
sarebbe nel range di 10 Gy

- Partial volume tolerance of spinal cord and complications of single dose SRS

(Ryu, Cancer 07)

- **8-18 Gy ; 230 treated metastatic lesions**

- 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

volume

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

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Clinical Investigation: Central Nervous System Tumor

Probabilities of Radiation Myelopathy Specific to Stereotactic Body Radiation Therapy to Guide Safe Practice

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radiation exposure. Through a multi-institutional collaboration, we analyzed the actual DVH data for each RM case, and compared them to a cohort of patients treated with spine SBRT who had not developed RM. The data were modeled using logistic regression to generate a probability profile for RM specific to SBRT to guide safe practice.

Table 3 Comparison of median and mean nBED between the radiation myelopathy (RM) and no-RM cohorts

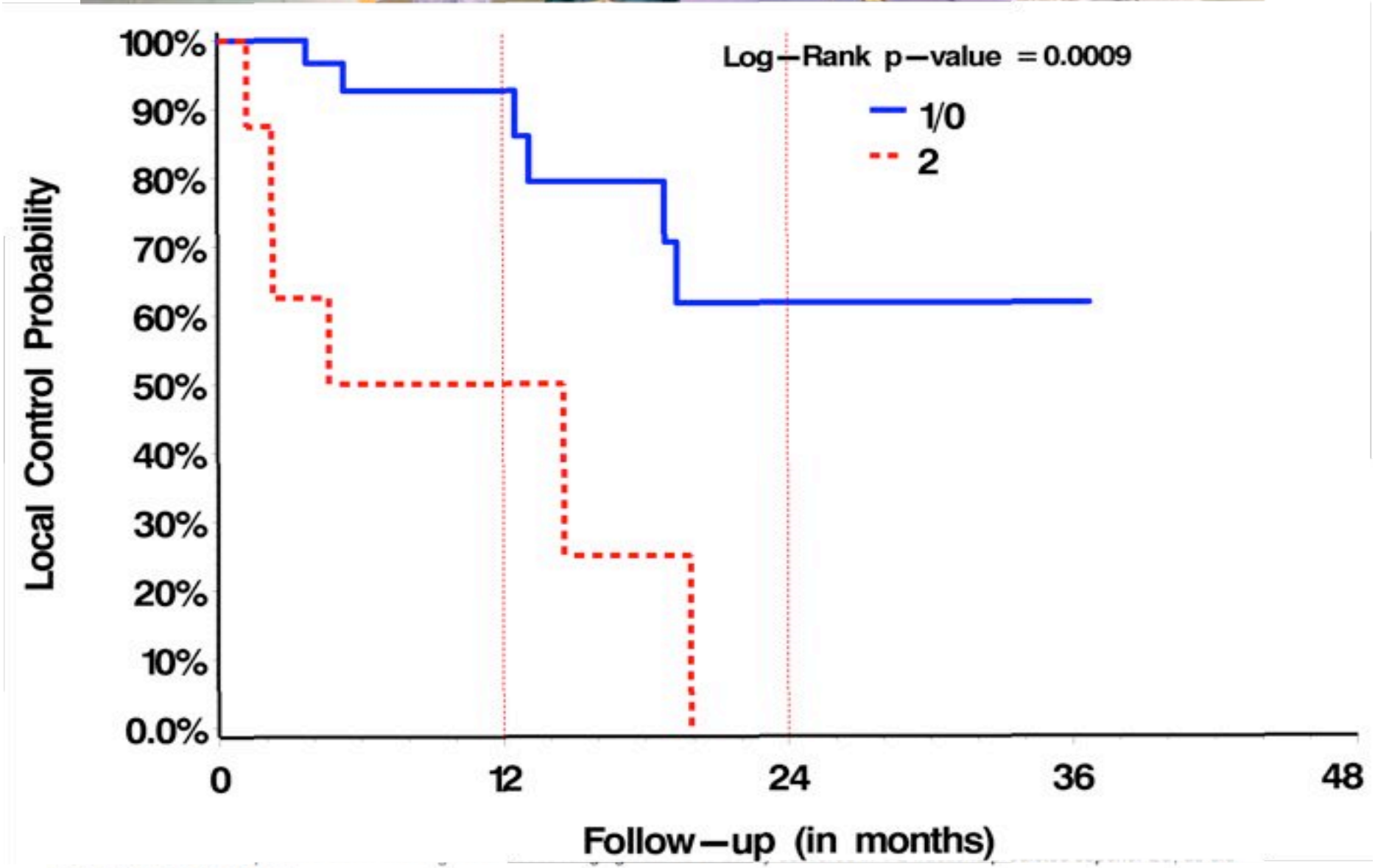
	No-RM cohort (n = 66) ($Gy_{2/2}$)	RM cohort (n = 9) ($Gy_{2/2}$)	Mann-Whitney/ *t* test (*P* value)
Median/mean Pmax volume nBED	35.69/38.82	73.69/70.60	.0003/.0006
Median/mean 0.1 cc nBED	28.32/29.28	56.20/56.63	.001/.006
Median/mean 0.2 cc nBED	27.65/26.89	54.08/52.53	.003/.008
Median/mean 0.3 cc nBED	26.34/25.10	52.46/49.32	.005/.01
Median/mean 0.4 cc nBED	24.36/23.87	49.85/46.69	.006/.01
Median/mean 0.5 cc nBED	20.35/22.64	47.45/44.30	.01/.02
Median/mean 0.6 cc nBED	21.20/22.08	41.86/41.75	.01/.02
Median/mean 0.7 cc nBED	20.54/21.32	39.75/39.44	.02/.03
Median/mean 0.8 cc nBED	19.91/20.69	38.30/37.24	.03/.04
Median/mean 0.9 cc nBED	19.13/20.12	36.55/35.12	.04/.05
Median/mean 1 cc nBED	17.63/19.51	35.05/33.68	.08/.05
Median/mean 2 cc nBED	13.48/16.07	22.15/23.44	.35/.14

Table 5 Predicted Pmax volume absolute doses in Gy for 1 to 5 SBRT that result in 1%-5% probability of radiation myelopathy (RM)

	1 fraction Pmax limit (Gy)	2 fractions Pmax limit (Gy)	3 fractions Pmax limit (Gy)	4 fractions Pmax limit (Gy)	5 fractions Pmax limit (Gy)
1% probability	9.2	12.5	14.8	16.7	18.2
2% probability	10.7	14.6	17.4	19.6	21.5
3% probability	11.5	15.7	18.8	21.2	23.1
4% probability	12.0	16.4	19.6	22.2	24.4
5% probability	12.4	17.0	20.3	23.0	25.3

Conclusion

We report logistic estimates for the probability of RM specific to 1- to 5-fraction SBRT based on the thecal sac contour and delivery using a dedicated SBRT unit. Dose within small volumes of spinal cord predicts the likelihood of RM post-SBRT, and we report doses that yield 1%-5% risks of RM. For a risk of RM of less than 5%, we recommend limiting the thecal sac Pmax volume dose to 12.4 Gy in a single fraction, 17.0 Gy in 2 fractions, 20.3 Gy in 3 fractions, 23.0 Gy in 4 fractions, and 25.3 Gy in 5 fractions. We recognize that these limits are based on a limited number of cases and are subject to change as we obtain more data and have additional follow-up, and as our ability to model the biologic effect of hypofractionated SBRT within normal tissues matures.



postoperative epidural grade.

Minimal Access Spine Surgery (MASS) for Decompression and Stabilization Performed as an Out-Patient Procedure for Metastatic Spinal Tumours Followed by Spine Stereotactic Body Radiotherapy (SBRT): First Report of Technique and Preliminary Outcomes

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Valutazione risposta

- **Risposta clinica:** criteri di risposta antalgica e sintomi Neurologici che ci permettono di determinare l'efficacia degli agenti terapeutici nei trials clinici

- **Controllo locale:** criteri radiografici

Journal of Cancer
2010; 1:80-92

Review

Cancer Response Criteria and Bone Metastases: RECIST 1.1, MDA and PERCIST

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Published: 2010.06.28

Because bone metastases are typically located in irregularly shaped bones and are difficult to measure with rulers, they have been previously considered unmeasurable disease

RECIST

Response Evaluation Criteria in Solid Tumors

..... updated to **RECIST 1.1** (in 2009)

One of the differences between RECIST and RECIST 1.1 is that **bone metastases with soft tissue masses measuring ≥ 10 mm are now accepted as target lesions.**
The soft tissue component is to be measured in an identical manner to that used for other target lesions

RECIST 1.1 specifies contrast administration for both MRI and CT scans.

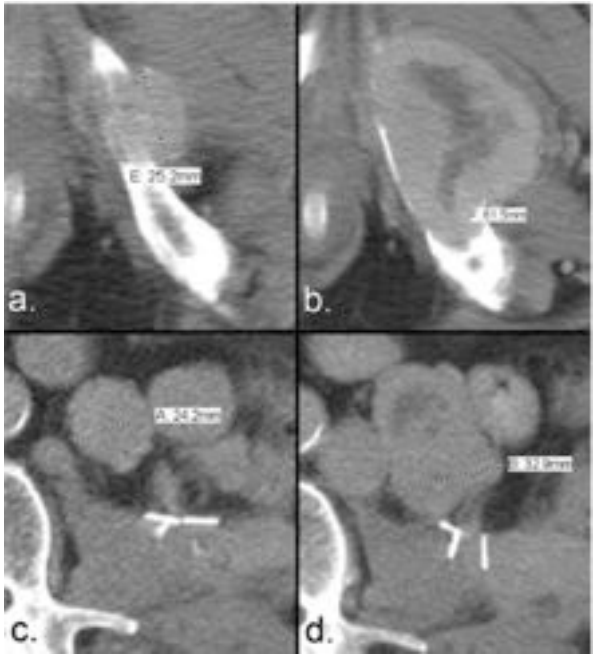

Table 1 Response Evaluation Criteria in Solid Tumors (RECIST 1.1)*

Response category	Criteria
Complete response	Disappearance of all target lesions
	Reduction in short axis of target lymph nodes to < 10 mm
Partial response	Decrease in target lesion diameter sum ≥ 30%†
Progressive disease	Increase in target lesion diameter sum ≥ 20%‡
	≥ 5 mm increase in target lesion diameter sum
	New, malignant FDG uptake in the absence of other indications of progressive disease or an anatomically stable lesion, and confirmed on contemporaneous or follow-up CT
	Unequivocal progression of nontarget lesions
Stable disease	Does not meet other criteria‡

Texas MD Anderson Cancer Center in 2004 (18). The MDA criteria updated the UICC and WHO bone re-

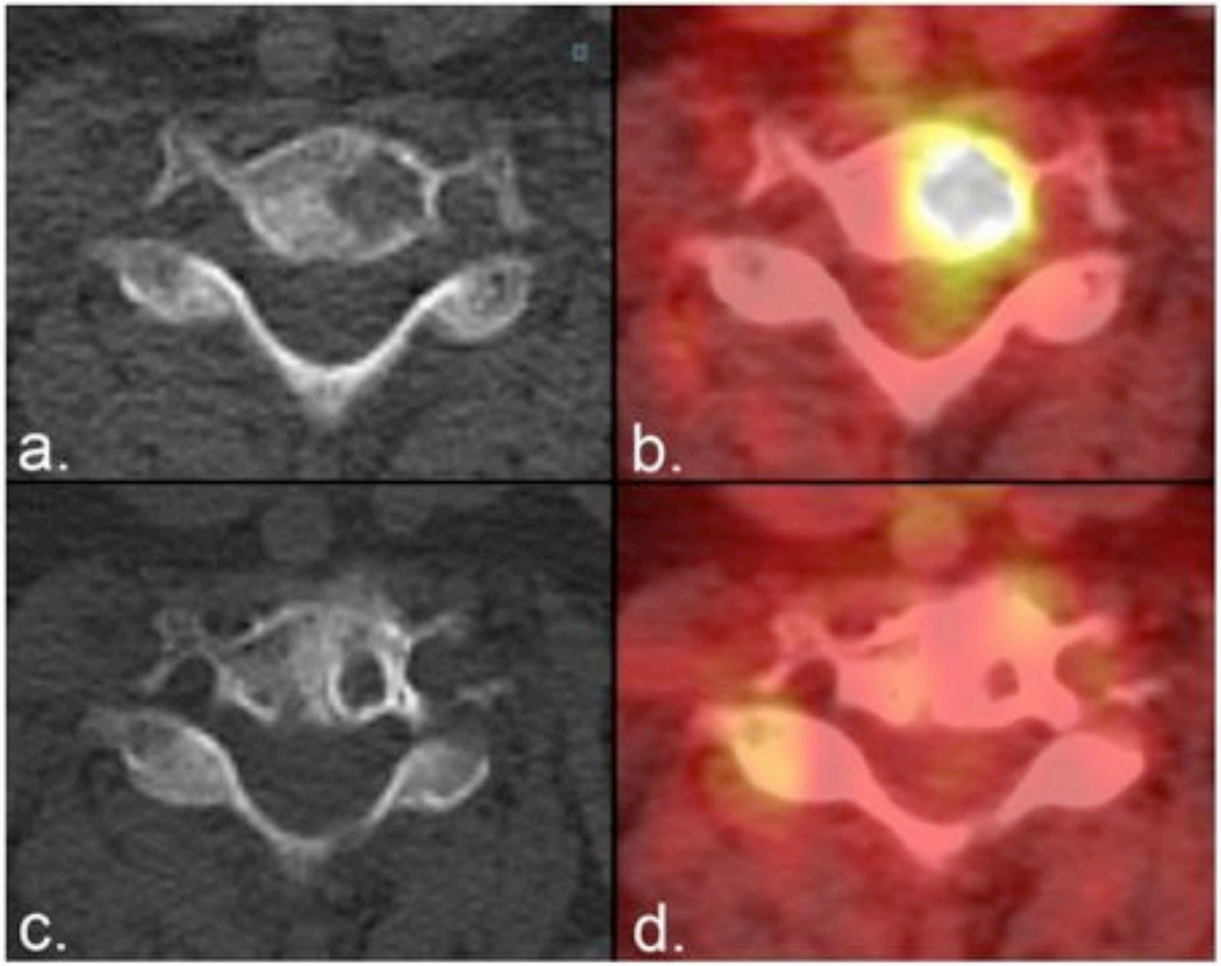

Figure 5. Partial response on radiographs according to the MDA criteria. **(a)** A lytic metastasis is seen in the C7 vertebral body on CT in a patient with breast cancer. **(b)** Fused PET/CT image from the same examination demonstrates FDG uptake representing active tumor. **(c)** Five weeks later, the lesion developed a sclerotic rim that resulted in a reduction in the size of the lytic area. **(d)** Fused PET/CT image from the same examination as **(c)** shows resolution of FDG activity, confirming the positive anatomic response.

PERC
Pet E

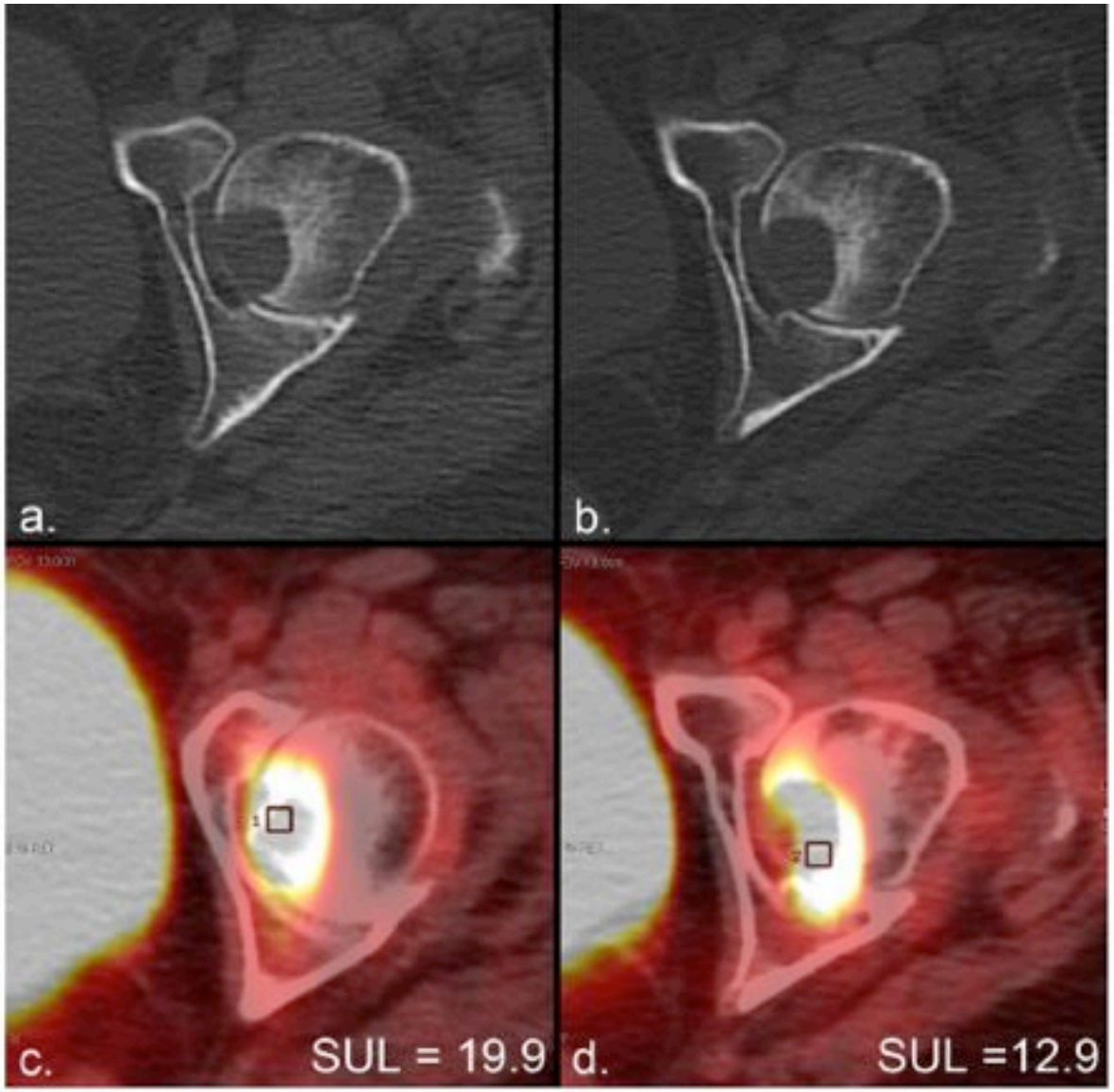

Figure 10. Metabolic response according to the PERCIST criteria in the absence of anatomic response. **(a)** The CT portion of an FDG PET/CT scan in a patient with lung cancer demonstrates a lytic metastasis in the left femoral head. **(b)** The CT from a PET/CT scan 2 months later demonstrates no anatomic change. **(c, d)** The standardized uptake value corrected for lean body mass (SUL) peak (average SUL in a 1-cm^3 region of interest centered at the most active part of each tumor) changes from **(c)** 19.8 to **(d)** 12.9, representing a 35% decrease that satisfies the minimal requirements for partial response (> 30%) according to PERCIST. Assessment of tumor metabolism allowed therapeutic response to be measured in the absence of any other indication of change.

Table 4. Comparison of RECIST, MDA and PERCIST

	RECIST	MDA criteria	PERCIST
Characteristics	Anatomic response criteria for soft tissue metastases	Anatomic response criteria for bone metastases	Functional response criteria reflecting tumor metabolism
Advantages	Common use allows direct comparison of the results of different studies	- Allows the response of the majority of bone metastases to be factored into therapeutic response	Allows response determination regardless of the location of the metastasis
		- Provides response criteria for patients with bone-only disease	
Disadvantages	- Limited to "measurable" soft tissue metastases or unequivocal progression of unmeasurable disease	Limited to bone metastases	Limited to FDG avid metastases

All criteria are subject to minimum lesion size limitations and PERCIST is also subject to minimum FDG uptake limitations.

CONCLUSIONI

Perché fare SBRT vertebrale ?

- Dose ablativa e non palliazione (malattia non diffusa)
- Metastasi da primitivo radioresistente
- Malattia confinata ad una parte della vertebra
- Reirradiazione

Alto impiego di risorse

- economiche (alta tecnologia, IGRT, planning) per la corretta esecuzione del trattamento

- Umane (team multidisciplinare dedicato, neurologo, neurochirurgo, oncologo, radio-oncologo, neuroradiologo)

Gioco di squadra

Grazie per l’attenzione