



# Spinal Metastases

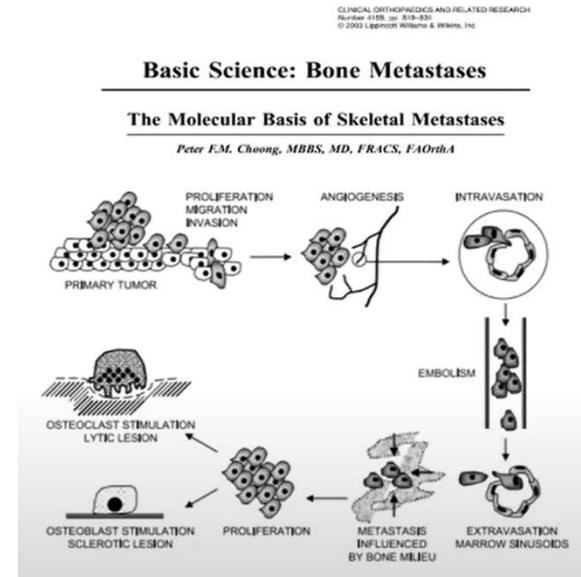
## Kypho-IORT

Assoc. Prof. Dr. med. Frederic Bludau  
Head of Spine Surgery Department  
Deputy clinic director

Orthopaedic and Trauma Surgery Centre  
University Medical Centre Mannheim  
Medical Faculty Mannheim Heidelberg University

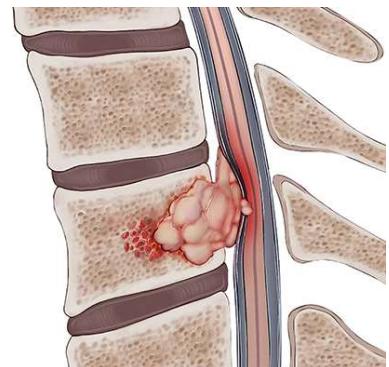
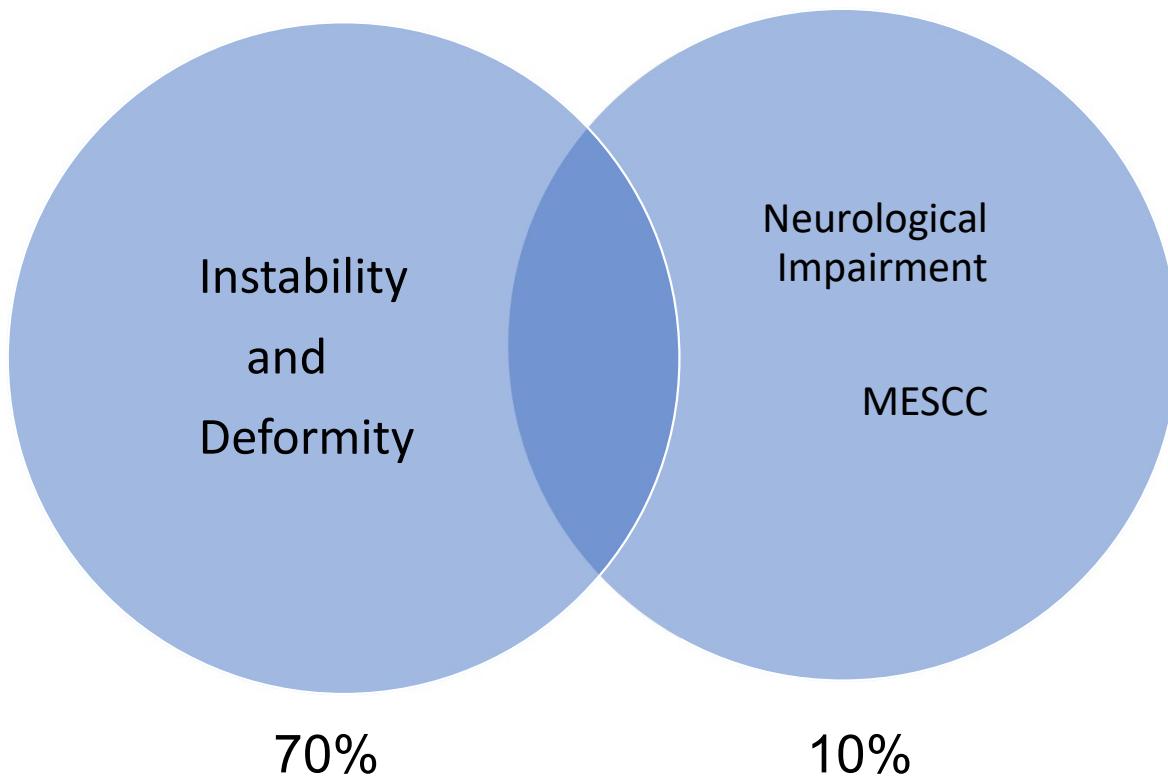
# Background

- 10-15 % of newly dx'd cancer pts have spinal mets
  - Synchronous metastasis
- **30-40% of pts with systemic cancer will have sympt. spinal metastases during life-span**
  - 10% of these will have neurological deficits
- ~70% of all mets are limited to the vertebral body, less than 10% with intradural/intramedullary portions
- **pain control** is considered to be the most relevant outcome parameter for patients treated with palliative intent



Ecker, Mayo Clin Proc 2005  
Wong, Spine 1990  
Gomez, International Orthopaedics, 1995  
Schaser, Unfallchirurg 2007  
Georgy, AJNR 2008

# Treatment Goals: Pain due to



# Heterogeneous Target-Groups Spine-Metastases

Oligometastatic Pat.,  
Limited Tumor Progress

- limited Pain
- excellent KPS

## Aims

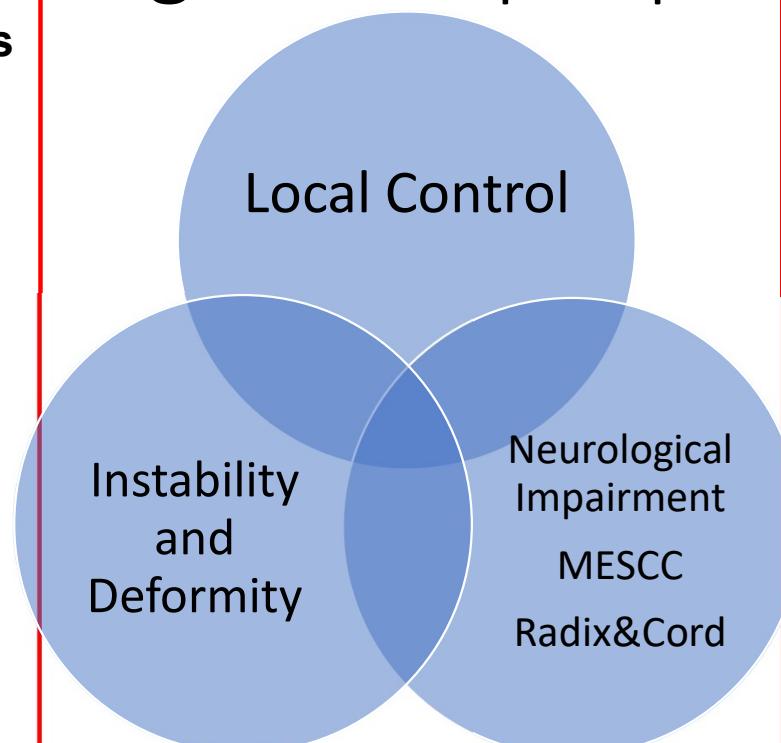
- **local Tumor-Control**
- Improvement of overall survival  
→pseudo-cure
- Low Morbidity

Palliative Pat.,  
Advanced Tumor Progress

- limited KPS
- Pain

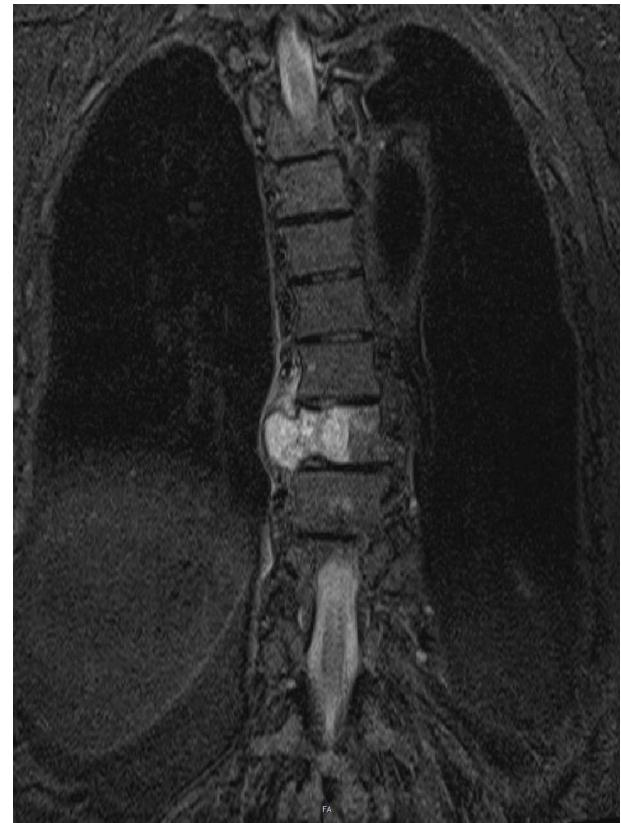
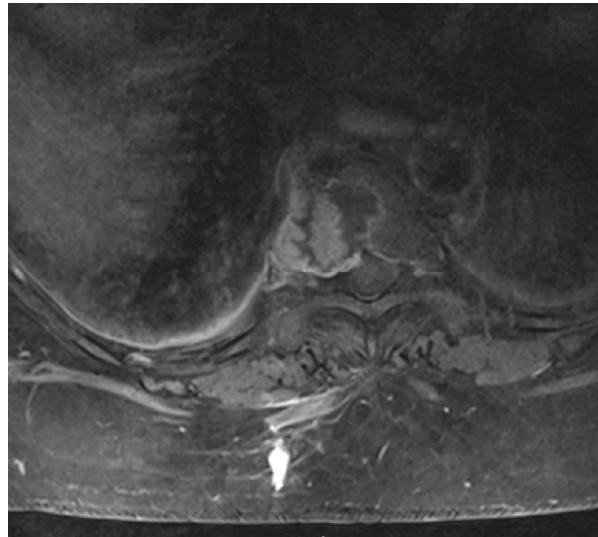
## Aims

- **effective Pain control**
- Spinal Stability
- short time in the hospital
- one-stop procedure
- local Tumor-Control

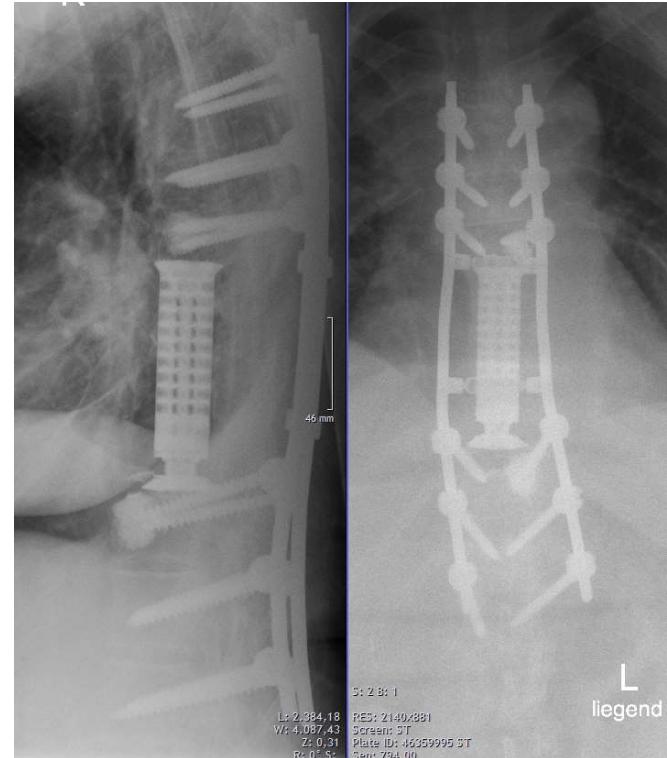
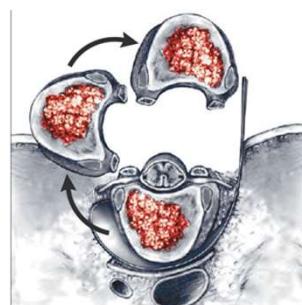
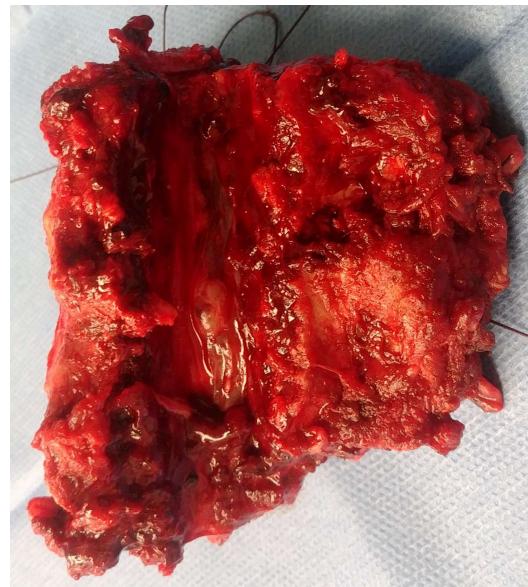
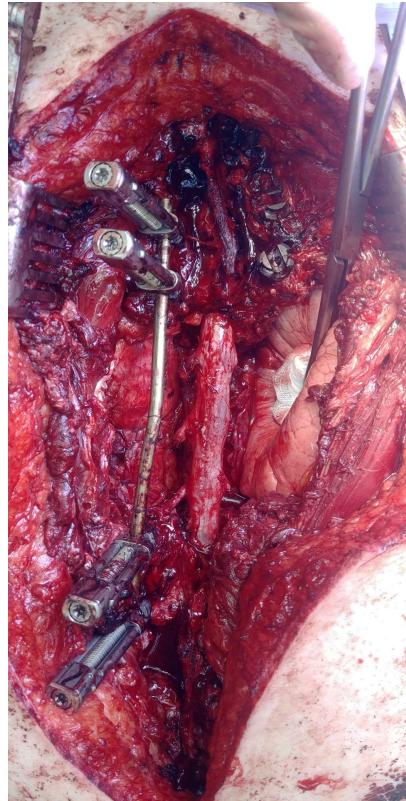


## Chondrosarcoma T8-T10

- WBB A-D, 5-10



## Multi-Level-Enbloc-Spondylectomy (R0-resection)

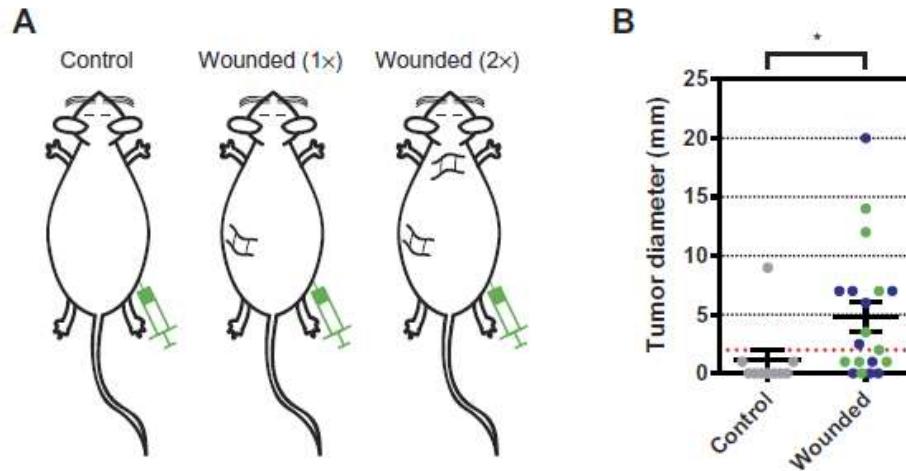


## CANCER

# The systemic response to surgery triggers the outgrowth of distant immune-controlled tumors in mouse models of dormancy

Jordan A. Krall,<sup>1</sup> Ferenc Reinhardt,<sup>1</sup> Oblaise A. Mercury,<sup>1</sup> Diwakar R. Pattabiraman,<sup>1</sup> Mary W. Brooks,<sup>1</sup> Michael Dougan,<sup>1,2</sup> Arthur W. Lambert,<sup>1</sup> Brian Bierie,<sup>1</sup> Hidde L. Ploegh,<sup>1,3\*</sup> Stephanie K. Dougan,<sup>1,4</sup> Robert A. Weinberg<sup>1,3,5†</sup>

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for the Advancement  
of Science. No claim  
to original U.S.  
Government Works





## HHS Public Access

Author manuscript

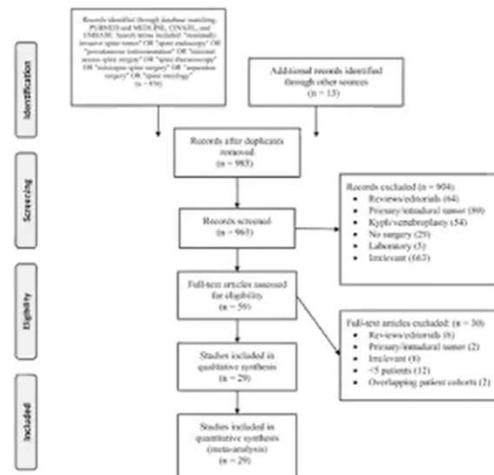
*Spine (Phila Pa 1976)*. Author manuscript; available in PMC 2017 October 15.

Published in final edited form as:  
*Spine (Phila Pa 1976)*. 2016 October 15; 41(Suppl 20): S246–S253. doi:10.1097/BRS.0000000000001824.

### When Less Is More:

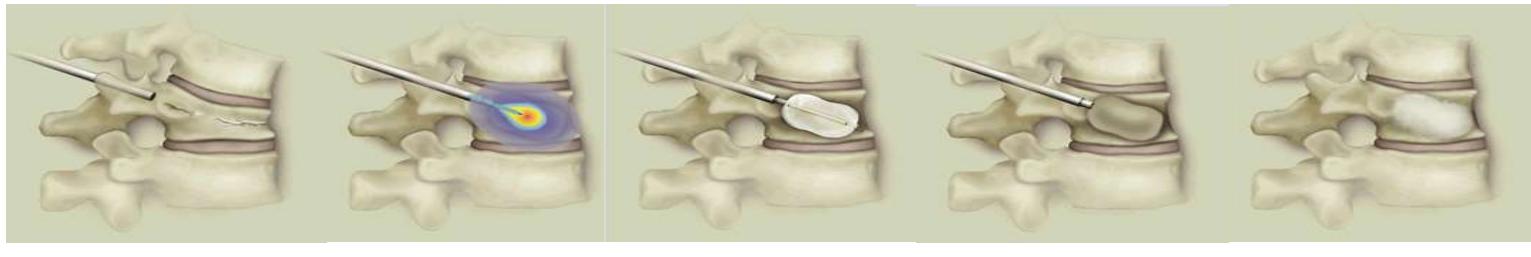
The indications for MIS Techniques and Separation Surgery in Metastatic Spine Disease

Scott L. Zuckerman, MD<sup>\*</sup>, Ilya Laufer, MD<sup>†</sup>, Arjun Sahgal, MD<sup>‡</sup>, Yoshiya J. Yamada, MD<sup>§</sup>, Meic H. Schmidt, MD, MBA, FAANS, FACS<sup>¶</sup>, Dean Chou, MD<sup>||</sup>, John H. Shin, MD<sup>||</sup>, Naresh Kumar, MD<sup>††</sup>, and Daniel M. Sciubba, MD<sup>‡‡</sup>



- Review the techniques, indications, and outcomes of minimally invasive surgery (MIS) and separation surgery with subsequent radiosurgery in the treatment of patients with metastatic spine disease
- 29 articles met inclusion criteria
- Indications were similar across all studies and included patients with instability, refractory pain, or neurologic compromise
- Intraoperative variables, outcomes, and complications were similar in MIS studies compared to traditional approaches, and some MIS studies showed a statistically significant improvement in outcomes
- Studies of mini-open techniques had the strongest evidence for superiority
- Low-quality evidence currently exists for MIS techniques and separation surgery in the treatment of metastatic spine disease

## Intraoperative treatment



Incision

Radiotherapy (~5 min)

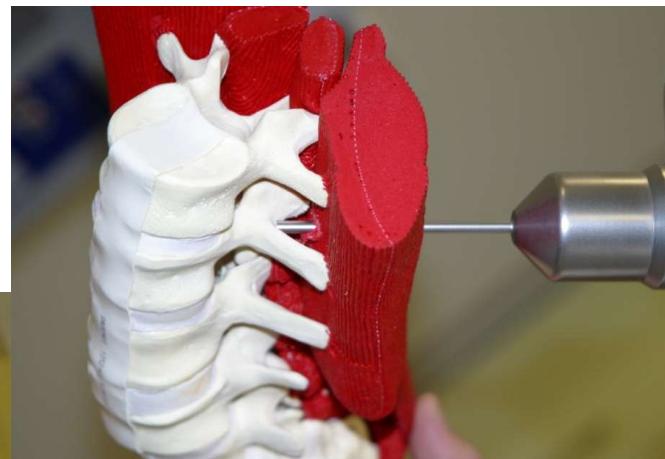
Entering/ inflating the balloon

Remove balloon

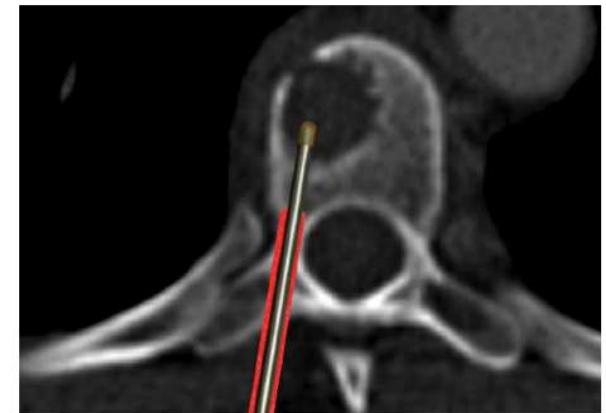
Inject PMMA

## Development of the model

11/2007

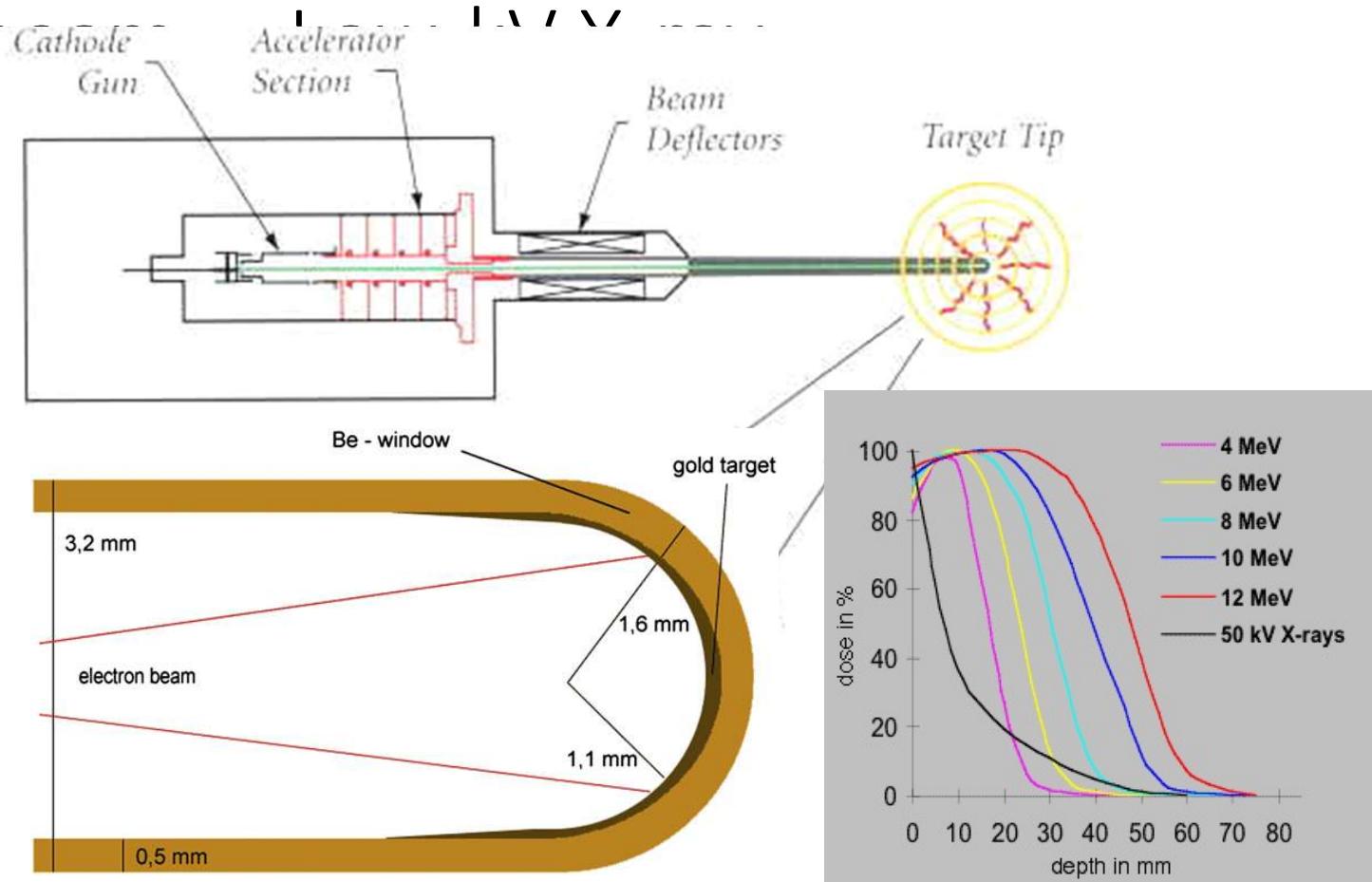


# New developed technical solutions I: Applicator



**Outer diameter 4,2mm  
Length 94 mm**

# Intra



Exper. Phantomstudy – Phase 0  
→ Procedure Safety

6/2008

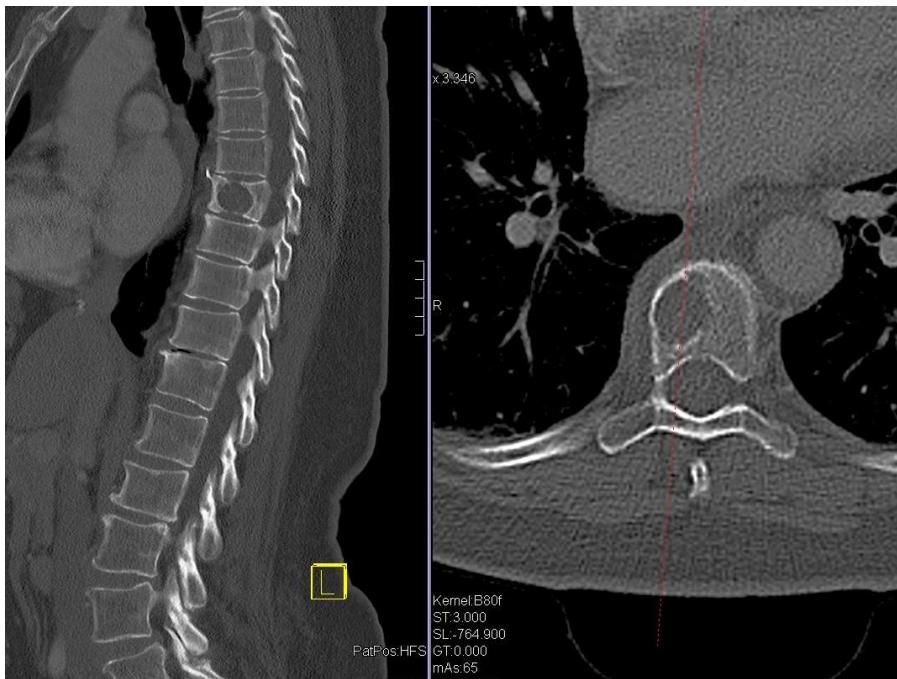


6/2008

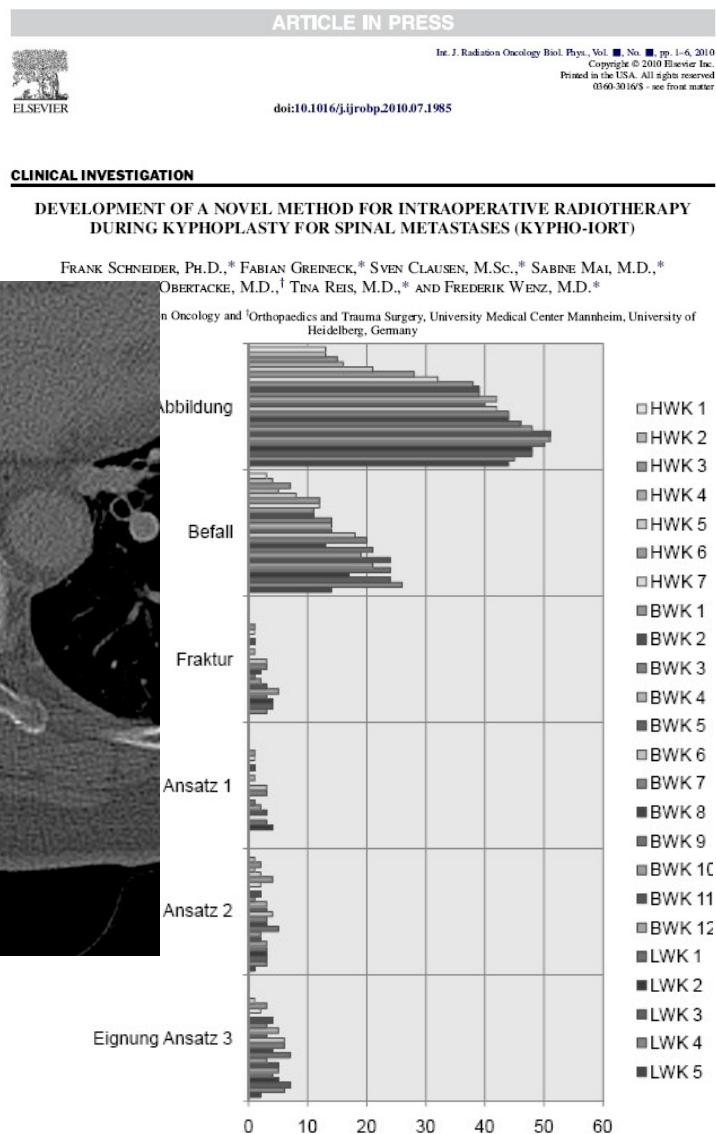


Schneider et al 2010  
Int J Radiat Oncol Biol Phys

# Kypho-IORT Studie – Eligible Patients Phase -1

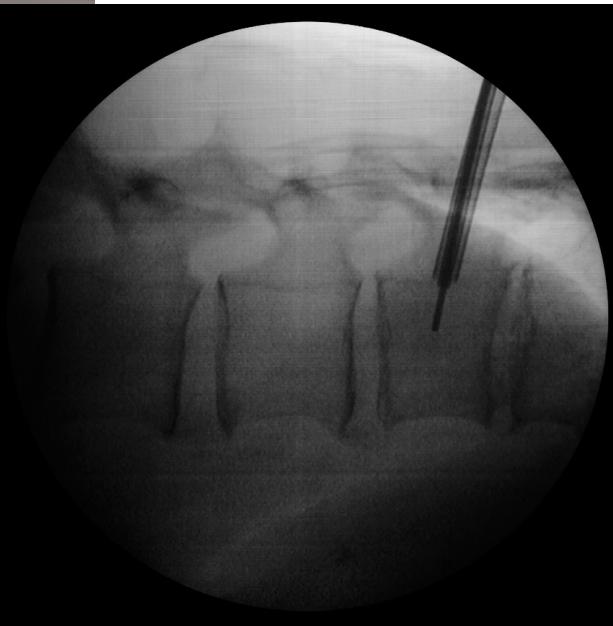


- 
- **→ ca. 30 – 35% der Pat**



First clinical application

07/2009

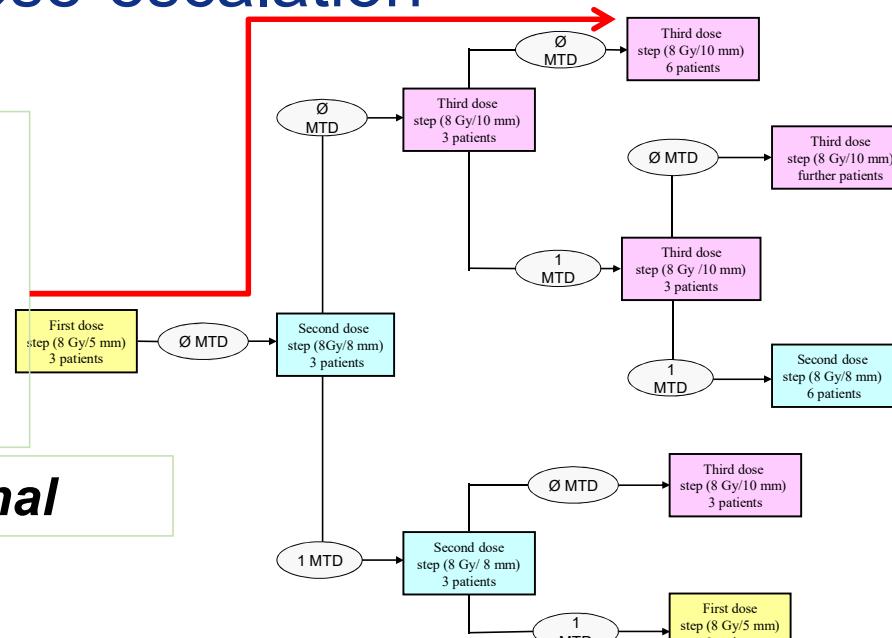
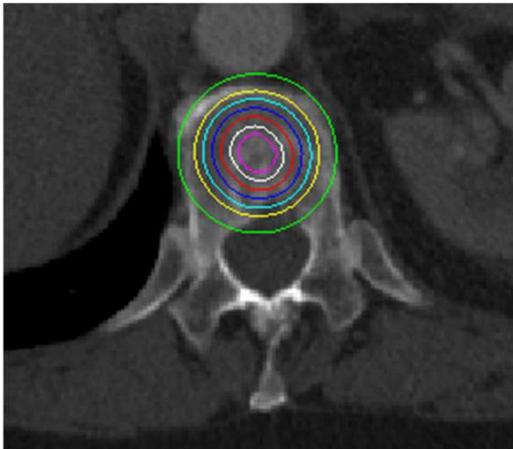


# Kypho-IORT – Dose-escalation Phase 1/2

## **Max. tolerable Dose (MTD)**

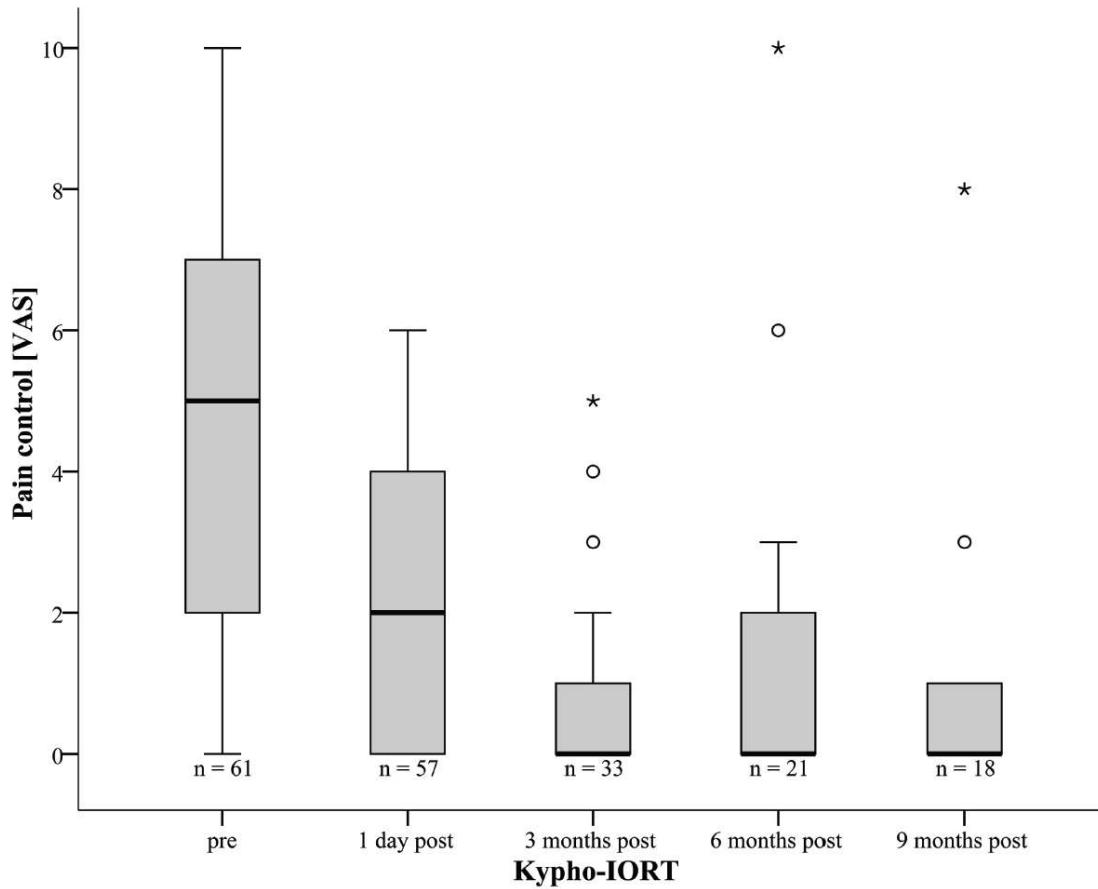
- **Osteoradionecrosis**
- **Myelon-toxicity**
- **Organ**

**max 8Gy @ spinal canal**



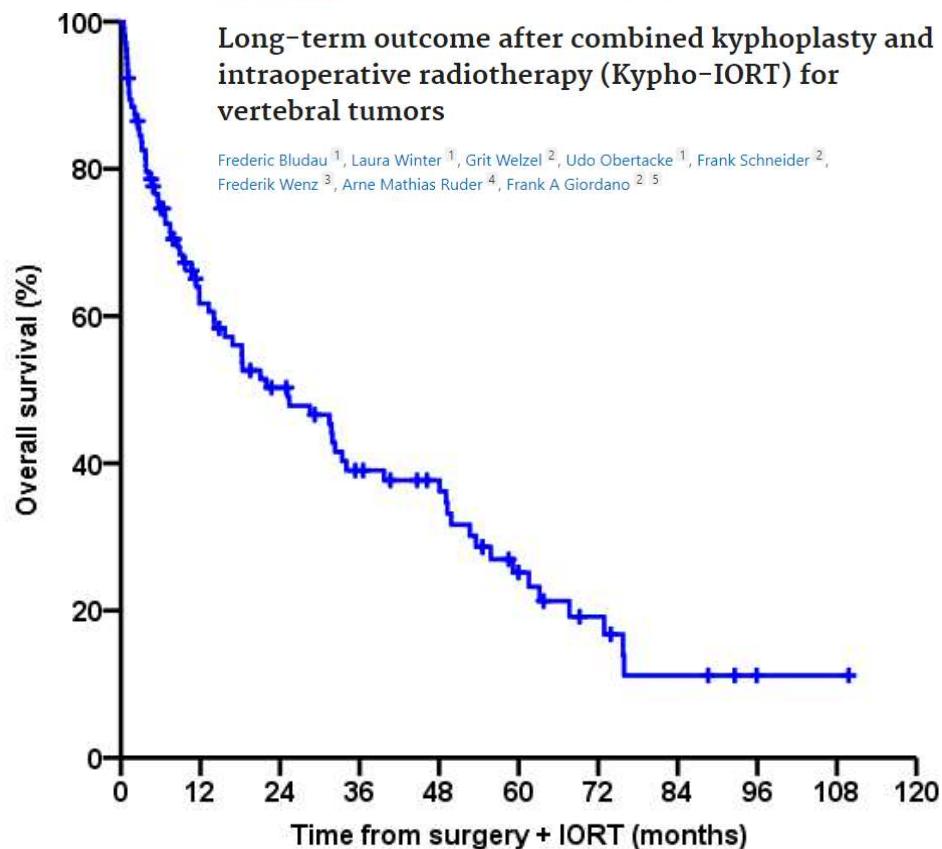
**Water model,  
Homogenous dose fall-off ( $r^2$ )**

## Results Pain control (n=61)



# Kypho-IORT -- Overall Survival

➤ Radiat Oncol. 2020 Nov 12;15(1):263. doi: 10.1186/s13014-020-01715-z.



The Spine Journal 18 (2018) 1804–1814

THE  
SPINE  
JOURNAL

Clinical Study

Predicting survival for metastatic spine disease: a comparison of nine scoring systems

A. Karim Ahmed, BS<sup>a</sup>, C. Rory Goodwin, MD, PhD<sup>a,b,\*</sup>, Amir Heravi, BS<sup>a</sup>, Rachel Kim, BS<sup>a</sup>,  
Nancy Abu-Bonsrah, MD<sup>a</sup>, Eric Sankey, MD<sup>b</sup>, Daniel Kerekes, BS<sup>a</sup>,  
Rafael De la Garza Ramos, MD<sup>c</sup>, Joseph Schwab, MD<sup>d</sup>, Daniel M. Sciubba, MD<sup>a</sup>

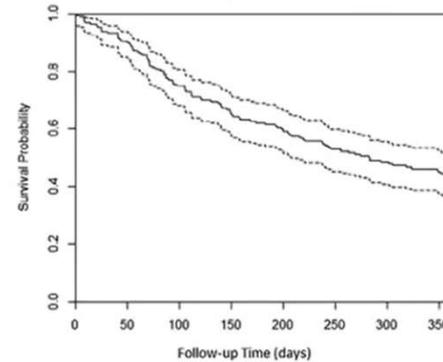


Fig. 1. Kaplan-Meier curve for patient survival within 1 year after surgery. After surgery, the median age of survival for the 176 patients included in the present study was 282 days (95% confidence interval [CI] 207–374).



n=679

# Clinical Results – Kypho-IORT

Phase I/II trial of combined kyphoplasty and intraoperative radiotherapy  
in spinal metastases

Frederic Bludau, MD<sup>a</sup>, Grit Welzel, MSc<sup>b</sup>, Tina Reis, MD<sup>b</sup>, Frank Schneider, PhD<sup>b</sup>,  
Elena Sperk, MD<sup>b</sup>, Christian Neumaier, MD<sup>b</sup>, Michael Ehmann, MD<sup>b</sup>, Sven Clausen, PhD<sup>b</sup>,  
Udo Obertacke, MD<sup>a</sup>, Frederik Wenz, MD<sup>b</sup>, Frank A. Giordano, MD<sup>b,\*</sup>

THE  
SPINE  
JOURNAL  
05/2018

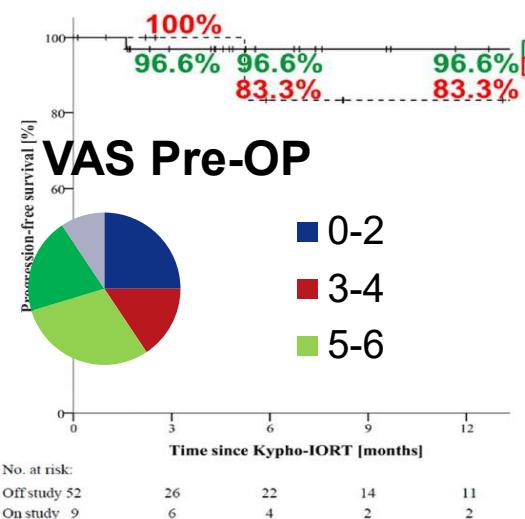
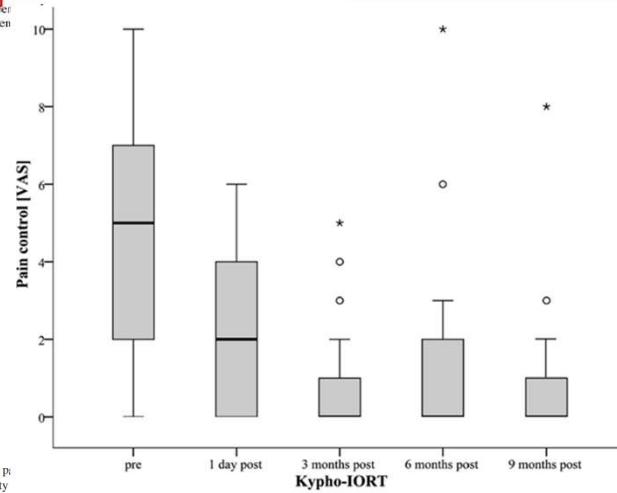


Fig. 2. Local progression-free survival. Shown are Kaplan-Meier plots for 52 patients in the (phase II) cohort expansion part of the trial. Kypho-IORT, kyphoplasty



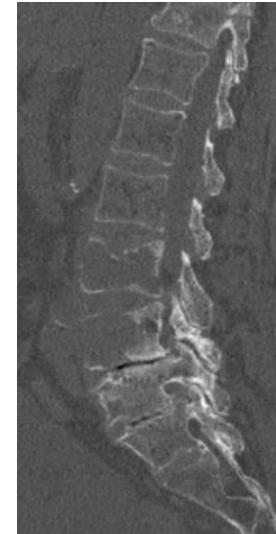
## Implications

Some of the study limitations are covered by the authors. Confounding factors (chemo, tumor type, kyphosis, many early deaths, etc.) and corporate sponsorship are concerning. Independent assessment of the technique and better delineation of indications is needed. That said, the findings are promising for palliation and serve as a nidus for further study.

## Indications - Contraindications

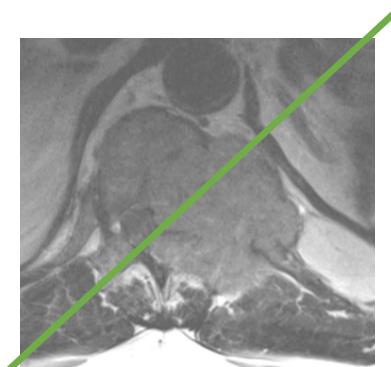
### Indications

- Local pain due to
  - Manifest vertebral fracture
  - Impending instability
- (Oligometastatic status)



### Contra-Indications

- Radicular- and spinal compression (MESCC)
- Diffuse bone metastasis



### Treatment-Goals

- Instant stability and pain reduction
- Local tumor control
- Reduce hospitalization of the palliative patient

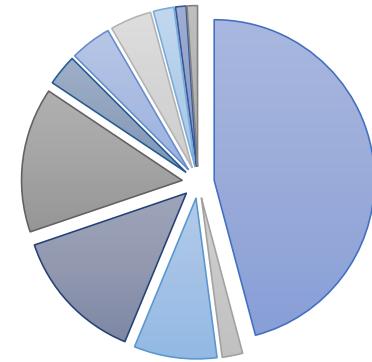
## Results

> Radiat Oncol. 2020 Nov 12;15(1):263. doi: 10.1186/s13014-020-01715-z.

### Long-term outcome after combined kyphoplasty and intraoperative radiotherapy (Kypho-IORT) for vertebral tumors

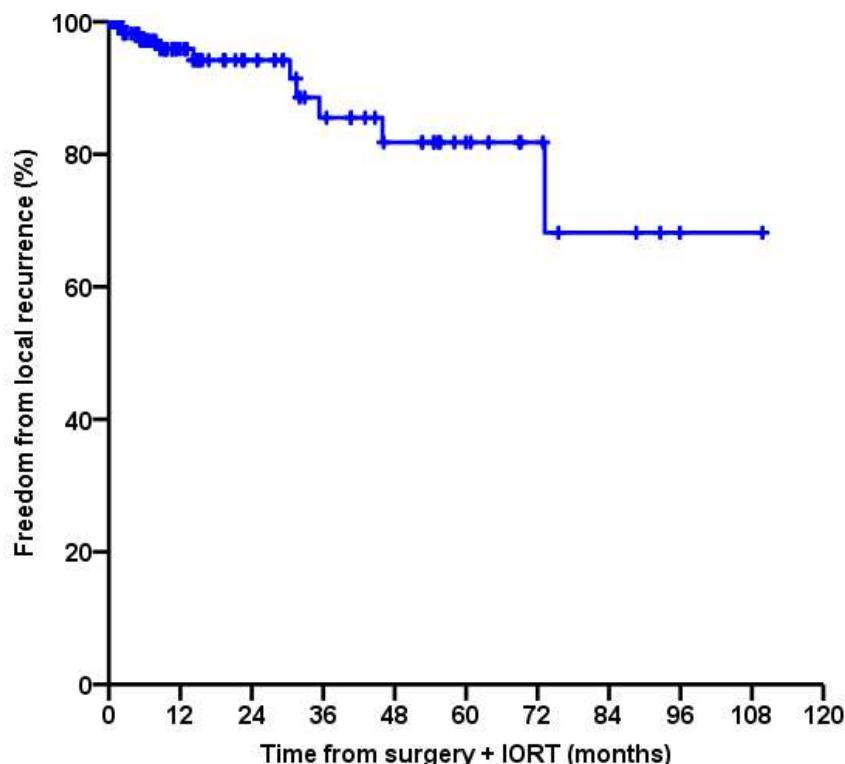
Frederic Bludau <sup>1</sup>, Laura Winter <sup>1</sup>, Grit Welzel <sup>2</sup>, Udo Obertacke <sup>1</sup>, Frank Schneider <sup>2</sup>,  
Frederik Wenz <sup>3</sup>, Arne Mathias Ruder <sup>4</sup>, Frank A Giordano <sup>2, 5</sup>

- 100 / 104 patients/relatives could be reached
- n=27 alive, n=73 died, n=4 lost to follow-up
- 143 therapied lesions
- 10 local failure (10/143 wk)
- Mean Overall-Survival 2,2 years, Median 1 year
- Karnofsky Performance Index, prä-OP (median): 80% (40% - 100%)
- Pain, prä-OP (median): VAS 5



Breast-CA	49%
Bronchial-CA	15%
Prostate-Ca	14%
Other (GIST;Sarcoma; Mult.Myelom, Melanoma)	14%
Gastro-Intestinal-Tumors	8%

## Kypho-IORT -- Local Controle



➤ Radiat Oncol. 2020 Nov 12;15(1):263. doi: 10.1186/s13014-020-01715-z.

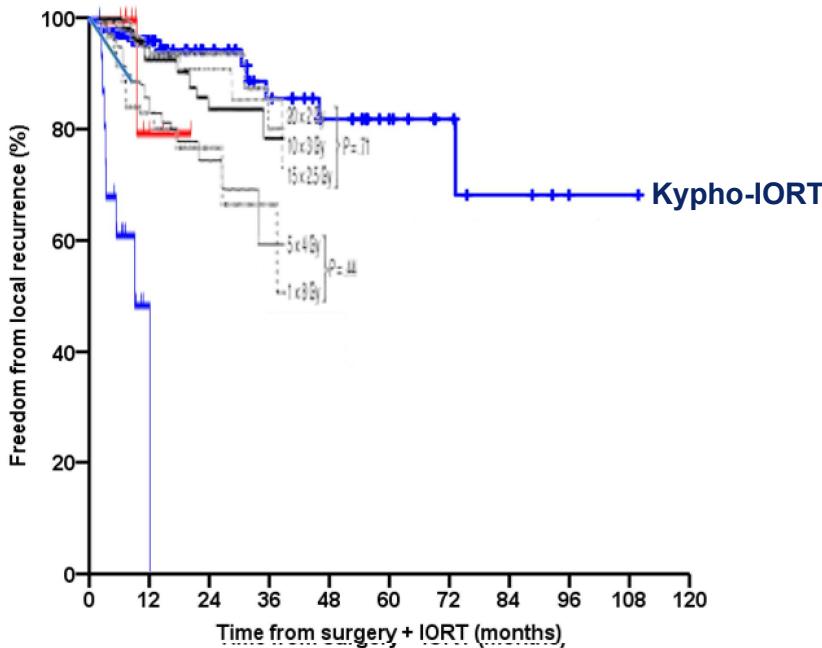
**Long-term outcome after combined kyphoplasty and intraoperative radiotherapy (Kypho-IORT) for vertebral tumors**

Frederic Bludau <sup>1</sup>, Laura Winter <sup>1</sup>, Grit Welzel <sup>2</sup>, Udo Obertacke <sup>1</sup>, Frank Schneider <sup>2</sup>,  
Frederik Wenz <sup>3</sup>, Arne Mathias Ruder <sup>4</sup>, Frank A Giordano <sup>2, 5</sup>

At risk	Time (Month)							
	0	12	24	36	48	60	72	84
N	143	60	40	28	21	12	7	4
L-PFS (%)	100	95.9	94.2	85.5	81.8	81.8	81.8	68.2

Died Pat. censored

# Diskussion – Kypho-IORT vs. RFA / EBRT / SBRT



**Radiofrequency Ablation and Radiation Therapy Improve Local Control in Spinal Metastases Compared to Radiofrequency Ablation Alone**

Kavitha M. Prezzano, MD<sup>1</sup>\*, Dheerendra Prasad, MD<sup>1</sup>, Gregory M. Hermann, MD, MPH<sup>1</sup>\*, Ahmed N. Belal, MD<sup>2</sup>, and Ronald A. Alberico, MD<sup>2</sup>

n = 28

J Clin Oncol. 2005 May 20;23(15):3366-75.

Evaluation of five radiation schedules and prognostic factors for metastatic spinal cord compression.

Rades D<sup>1</sup>, Stalroers LJ, Veninga T, Schulte R, Hoskin PJ, Obradic N, Bejrovic A, Rudat V, Schwarz R, Hulshof MC, Poortmans P, Schild SE.

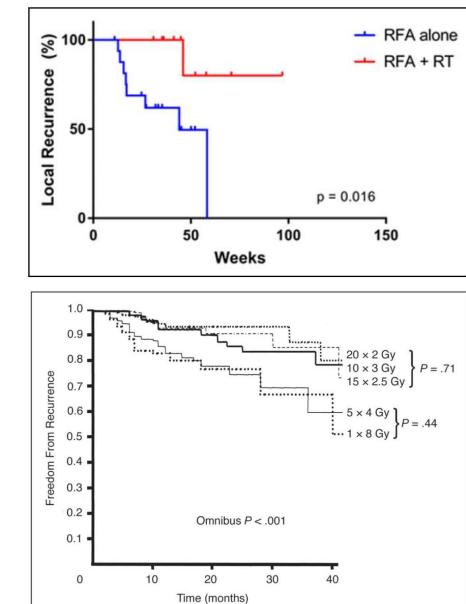
n = 1304 (5 x 250)

**JNS SPINE** LITERATURE REVIEW  
J Neurosurg Spine 27:295-302, 2017

## Stereotactic body radiotherapy for de novo spinal metastases: systematic review

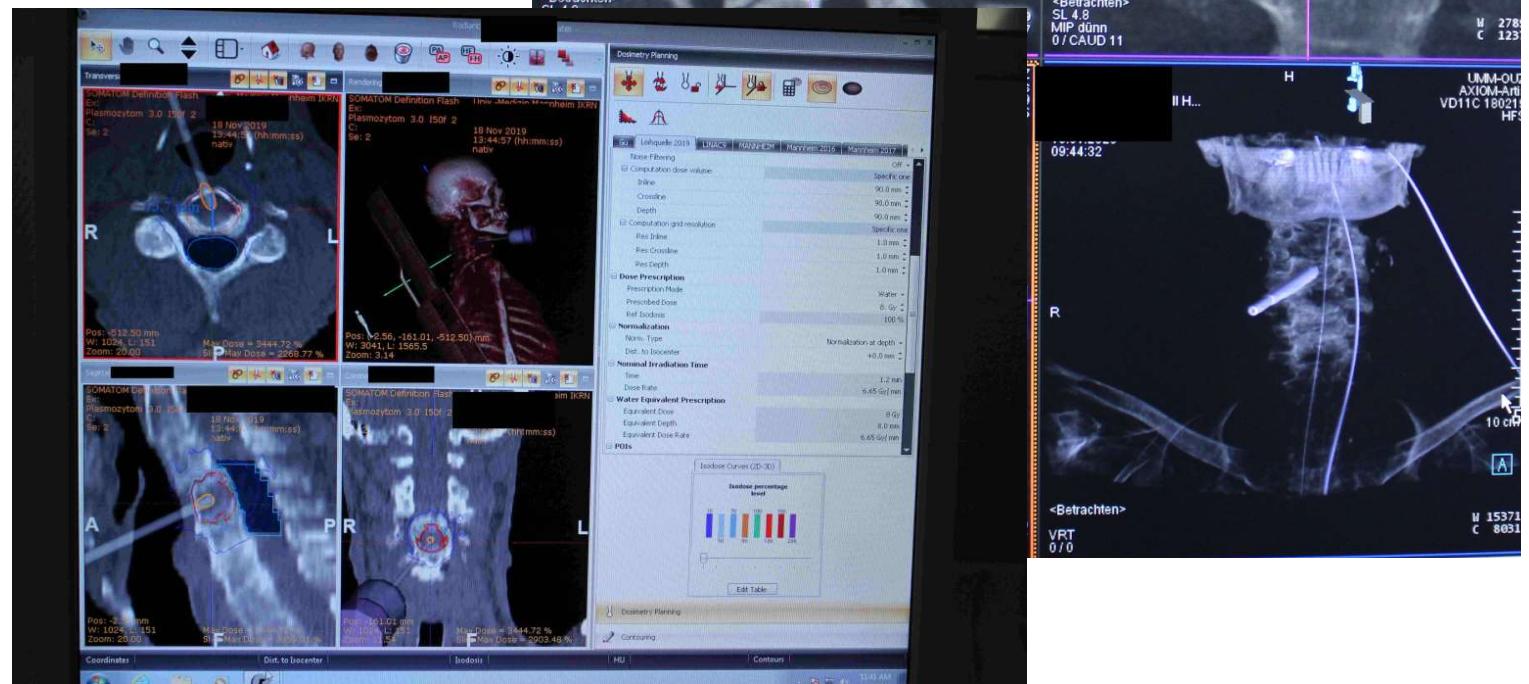
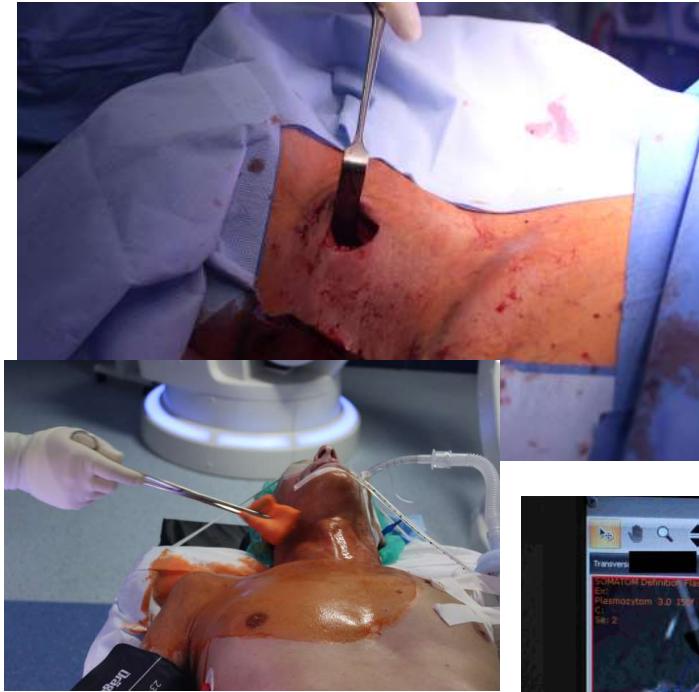
International Stereotactic Radiosurgery Society practice guidelines

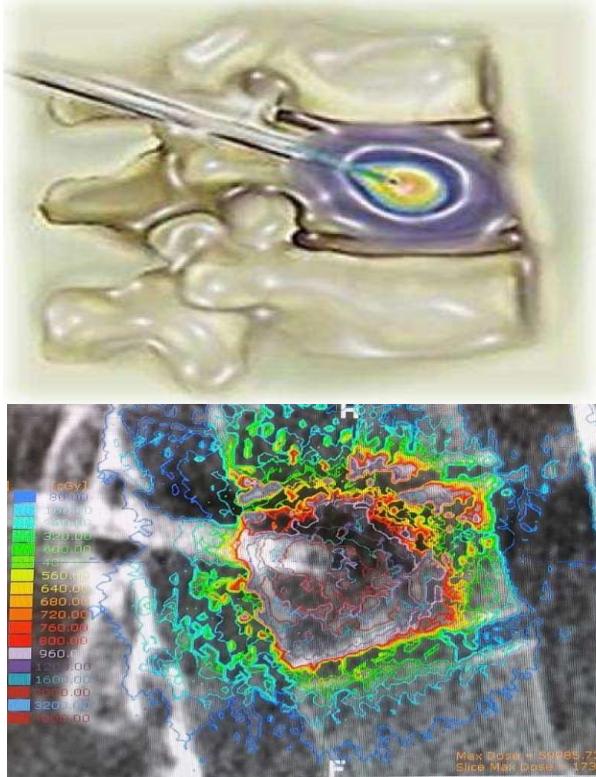
Zain A, Husain, MD;<sup>1</sup> Arjun Sahgal, MD;<sup>2</sup> Antonio De Salles, MD;<sup>3</sup> Melissa Funaro, MS, MLS;<sup>4</sup> Janis Glover, MLS;<sup>5</sup> Motohiro Hayashi;<sup>6</sup> Masahiro Hiraoka, MD;<sup>7</sup> Marc Levitt, MD;<sup>8</sup> Lijun Ma, PhD;<sup>9</sup> Roberto Martinez-Alvarez, MD;<sup>10</sup> J. Ian Paddick, MSc;<sup>11</sup> Jean Régis, MD;<sup>11</sup> Ben J. Slotman, MD, PhD;<sup>12</sup> and Samuel Ryu, MD.<sup>13</sup>



## Local Tumor Control

Data on local control were available for all studies except for 1 of them. All studies for which local control data were reported used follow-up imaging as the basis for reporting outcomes. One study, however, also used symptomatic findings of worsened pain as a marker of progression.<sup>20</sup> Reporting of local control differed; some studies reported crude rates, and others reported actuarial rates. For studies that reported crude values, 346 (85%) of 407 lesions remained controlled. For studies that reported actuarial values, the weighted average result revealed a 90% 1-year local control rate.





3

Hitting two birds with one stone:

**Kypho-IORT:**

**Pain and  
Tumor Control  
and  
Histology-Samples**

# Post-<sup>a</sup> e-beam CT



Physica Medica



Technical note

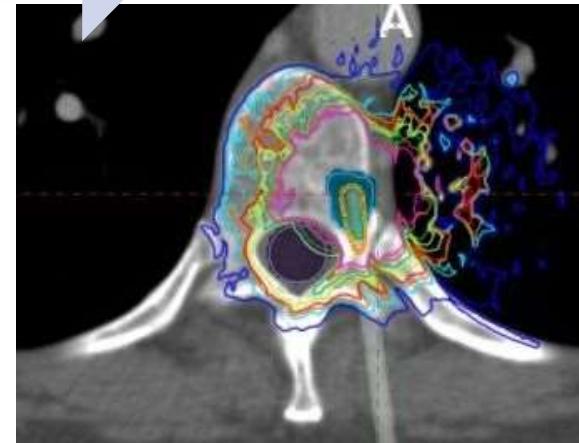
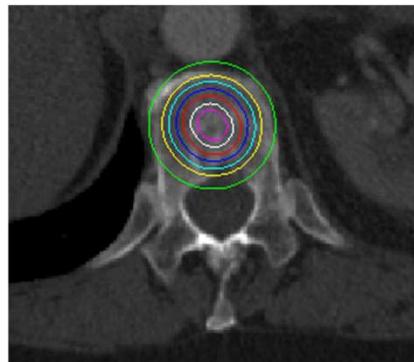
Precision IGRT  
therapy (igIGRT)  
including tissue heterogeneity correction ☆

„Basic“  
Patient  
Planning

Individual  
Post-  
planning

„On the fly“  
Intra-Op-  
Planning

Frank Schneider <sup>a</sup> , Frederic Bludau <sup>b</sup>, Sven Clausen <sup>a</sup>, Jens Fleckenstein <sup>a</sup>, Udo Obertacke <sup>b</sup>, Frederik Wenz <sup>a</sup>

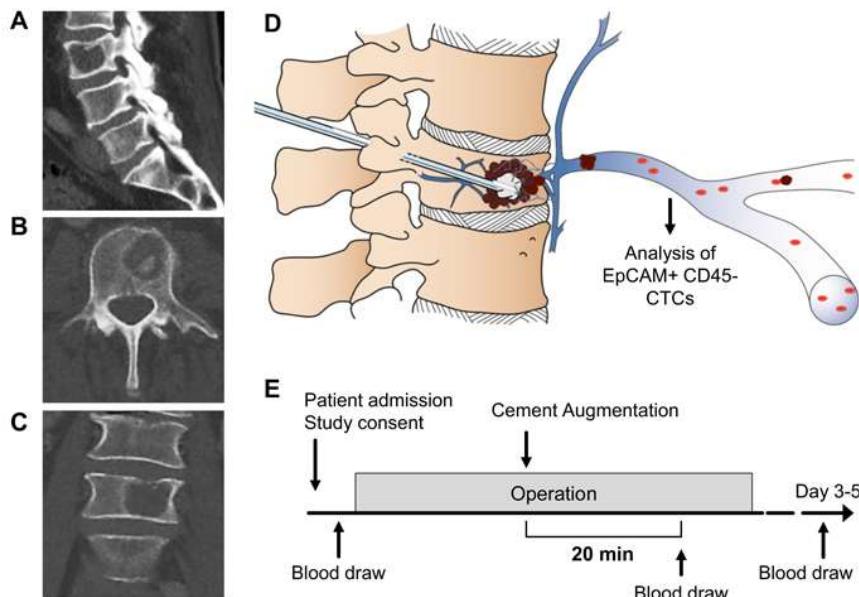


# CTCs due to surgical interventions

Sci Rep. 2017 Aug 3;7(1):7196. doi: 10.1038/s41598-017-07649-z.

## Circulating Tumour Cell Release after Cement Augmentation of Vertebral Metastases.

- Study: Mohme M<sup>1</sup>, Riethdorf S<sup>2</sup>, Dreimann M<sup>3</sup>, Werner S<sup>2</sup>, Maire CL<sup>4</sup>, Joosse SA<sup>2</sup>, Bludau F<sup>5</sup>, Mueller V<sup>6</sup>, Neves RPL<sup>7</sup>, Stoecklein NH<sup>7</sup>, Lamszus K<sup>4</sup>, Westphal M<sup>4</sup>, Pantel K<sup>2</sup>, Wikman H<sup>2</sup>, Eicker SO<sup>4</sup>.



# German S2k-Guide Spinalmetastases

DGOU Leitlinie 187-003 - Wirbeläulenmetastasen



Empfehlung 53

Neu (2024)

Für Fälle mit tumorbedingter Myelonkompression Bilsky/MESCC  $\geq 2$  und einem wenig strahlensensiblen Tumor sollte das Konzept der Separation Surgery mit nachfolgender Stereotactic Body Radiotherapy (SBRT) überprüft werden.

Konsensstärke: 100%; starker Konsens

## 10.4.5 Intraoperative Bestrahlung

In einer retrospektiven Studie von 2008 erhielten 96 nicht gefährlicher Patientinnen und Patienten mit MESCC im Rahmen einer operativen Dekompression plus Stabilisierung eine intraoperative Strahlentherapie (IORT) mit Elektronen (20-30 Gy) [302]. Dies führte bei 60 % der Betroffenen zu einer Schmerzlinderung. Eine Verbesserung der neurologischen Funktion von mindestens einem Grad der Klassifikation nach Frankel [303] war in 85 % der Fälle zu verzeichnen und 80 % der Patientinnen und Patienten waren nach der Therapie wieder gefähig. Ein Patient entwickelte eine radiogene Myelopathie nach fast drei Jahren. Darüber hinaus benötigten vier Patientinnen und Patienten im Verlauf eine operative Revision aufgrund einer Wirbelkörperfraktur mit zum Teil signifikanten motorischen Ausfällen (N=3). Im Jahr 2010 wurde ein neues Verfahren, bestehend aus Kyphoplastie und IORT (1 x 8 Gy mit 50 kV Röntgenstrahlen), präsentiert [304]/[305]/[306]. In einer ersten klinischen Studie mit 18 Patientinnen und Patienten war der mediane Schmerz-Score (visuelle Analogskala, VAS) bereits am ersten Tag signifikant niedriger als vor der Therapie (5/10 vs. 2,5/10, p<0,001); nach sechs Wochen lag der mediane Score bei 0/10 (p=0,001) [306]. In einer Phase-II-Studie betrug die Ansprechrate (Schmerzreduktion um  $\geq 3$  Punkte) 69,8 %, im weiteren Verlauf 79,1 % [307]. Die Rate für das lokale progressionsfreie Überleben nach einem Jahr war 93,8 %. Eine retrospektive Studie mit Langzeitergebnissen (104 Patientinnen und Patienten mit 143 behandelten Wirbelkörpern) wurde 2020 publiziert [308]. Die Raten für die lokale Kontrolle nach einem und zwei Jahren betrugen 95,9 % und 94,2 %. Aktuell läuft eine randomisierte Phase-III-Studie, die die Kombination von Kyphoplastie und IORT (1 x 8 Gy) mit einer konventionellen Bestrahlung (1 x 8 Gy oder 10 x 3 Gy) vergleicht [309]. In einer prospektiven Beobachtungsstudie von 2021 wurden eine operative Dekompression, eine IORT (1 x 20 Gy mit Elektronen) und eine postoperative konventionelle Strahlentherapie (10 x 3 Gy) kombiniert [310]. Zwei der insgesamt 20 Patientinnen und Patienten hatten keine postoperative Strahlentherapie erhalten. Die Raten der Schmerzlinderung betragen 82 % nach drei Monaten und 100 % nach sechs Monaten. Nach einem Jahr war die Gefährtlichkeit gegenüber der Baseline vor Therapie bei 25 % der Patientinnen und Patienten verbessert und bei 75 % stabil. Eine radiogene Myelopathie wurde nicht beobachtet. Wirbelkörperfrakturen in 10 % der Fälle. Insgesamt ist die Datenlage hinsichtlich der IORT noch nicht ausreichend, um dieses Verfahren für die klinische Routine zu empfehlen. Die Ergebnisse der laufenden Phase-III-Studie können möglicherweise trotz der geplant geringen Fallzahl (N=54) zu einer weiteren Klärung beitragen [309].

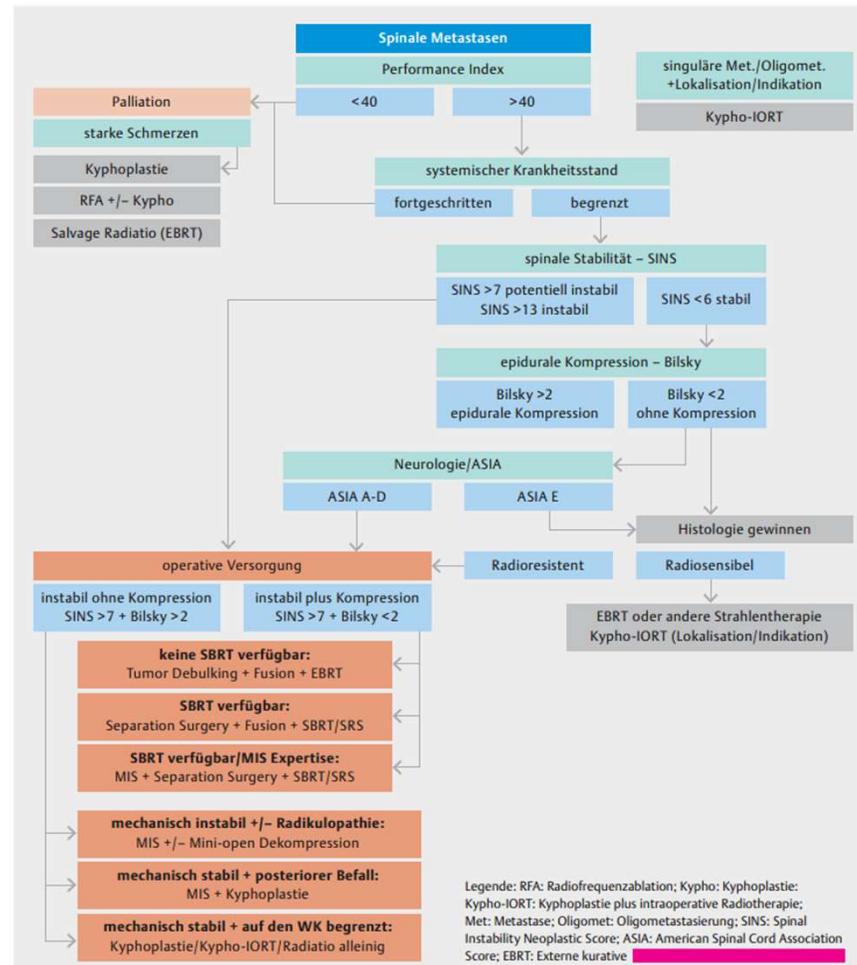
Empfehlung 54

Neu (2024)

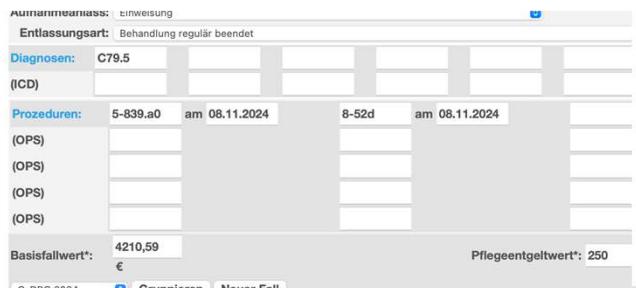
Aufgrund der noch unzureichenden Datenlage sollte die intraoperative Strahlentherapie bei der Behandlung vertebraler Metastasen erfahrenen Zentren vorbehalten bleiben und vorzugsweise in Studien eingesetzt werden.

Konsensstärke: 100%; starker Konsens

# Therapeutisches Management



# Reimbursements



Gruppierungsergebnis (G-DRG 2024)

MDC	08
DRG	I06B Komplexe Eingriffe an Wirbelsäule, Kopf und Hals mit sehr komplexem Eingriff bei schw. am Knochen oder Alter < 19 Jahre
PCCL	0 Status: normales Grouping (GetDRG-Grouper 2024) (GetDRG V23.2.5.0)
Verweildauer	aktuelle VWD: 5 1. Tag Abschlag: 3 1. Tag Abschlag: 3 mittl. VWD (arith.): 12,5 untere GWVD: 4 obere GWVD: 12,5
Bewertungsrelation (DRG)	Katalog-BWR (DRG): 4,631 eff. DRG-Bewertungsrelation: 4,631 (Zus.
DRG-Entgelt	Basisentgelt: 19499,24 € eff. DRG-Entgelt: 19499,24 € (Zus.
Pflege-Entgelt	Pflege BWR/Tag: 1,1102 eff. Pflege-BWR (VWD=5): 5,551 eff.
Summe Entgelte:	20886,99 €

