

FSRT-Trial

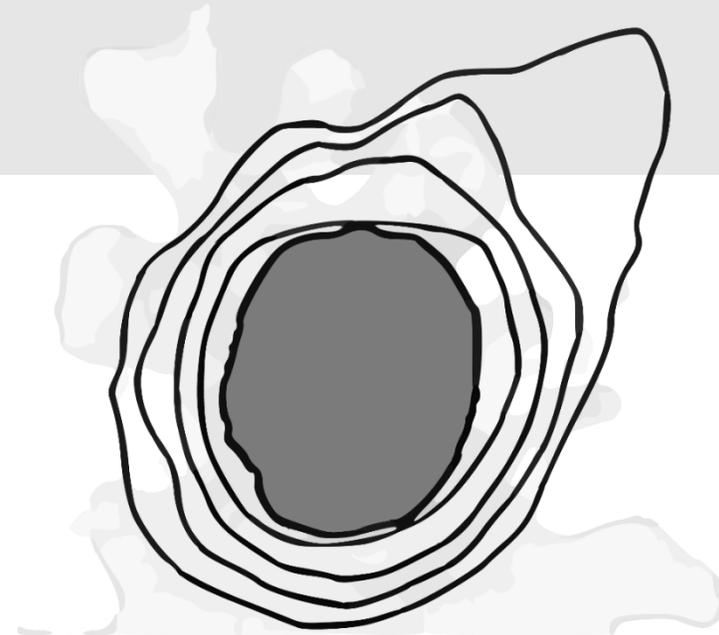
AG-NRO-05

AG Stereotaxie: 03.12.2021

Florian Putz



FRIEDRICH-ALEXANDER
UNIVERSITÄT
ERLANGEN-NÜRNBERG
MEDIZINISCHE FAKULTÄT



Universitätsklinikum
Erlangen

Strahlenklinik

Direktor: Prof. Dr. med. Rainer Fietkau



Hintergrund: SRS analog RTOG 9005 als Goldstandard

Tumor diameter	Treatment arm/dose/accrual			
≤ 20 mm	Arm 1—>	Arm 4—>	Arm 7	
	18 Gy	21 Gy	24 Gy	
	<i>n</i> = 12	<i>n</i> = 18	<i>n</i> = 10	
21–30 mm	Arm 2 —>	Arm 5 —>	Arm 8 —>	Arm II
	15 Gy	18 Gy	21 Gy	24 Gy
	<i>n</i> = 15	<i>n</i> = 15	<i>n</i> = 13	<i>n</i> = 12
31–40 mm	Arm 3 —>	Arm 6—>	Arm 9	
	12 Gy	15 Gy	18 Gy	
	<i>n</i> = 21	<i>n</i> = 22	<i>n</i> = 18	

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CLINICAL INVESTIGATION

Brain

SINGLE DOSE RADIOSURGICAL TREATMENT OF RECURRENT
 PREVIOUSLY IRRADIATED PRIMARY BRAIN TUMORS AND BRAIN
 METASTASES: FINAL REPORT OF RTOG PROTOCOL 90-05

Universitätsklinikum
 Erlangen

Shaw et al. IJRBP 2000

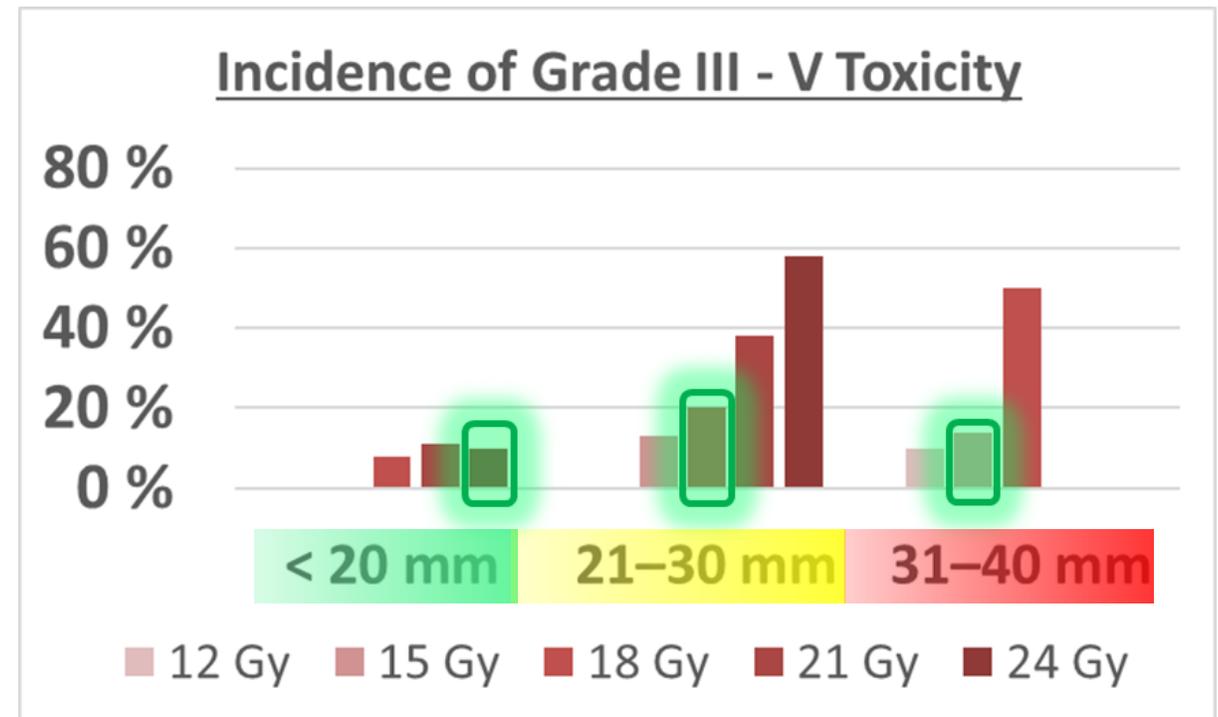


Hintergrund: SRS analog RTOG 9005 als Goldstandard

- **Goldstandard** nach wie vor **SRS analog RTOG 9005**

- < 2 cm: **SRS** mit **24 Gy**
- 2 – 3 cm: **SRS** mit **18 Gy**
- 3 – 4 cm: **SRS** mit **15 Gy**

- **Bei Hirnmetastasen > 2 cm**
muss die **Dosis reduziert**
werden um **Nebenwirkungen**
zu vermeiden



Fehlende Evidenz für den Vergleich SRS - FSRT

EANO Leitlinie Hirnmetastasen

with acceptable toxicity. However, randomized studies comparing stereotactic fractionated radiotherapy (SFRT) versus single dose SRS are lacking.

162

Neuro-Oncology

19(2), 162–174, 2017 | doi:10.1093/neuonc/now241

Diagnosis and treatment of brain metastases from solid tumors: guidelines from the European Association of Neuro-Oncology (EANO)

Riccardo Soffietti, Ufuk Abacioglu, Brigitta Baumert, Stephanie E. Combs, Sara Kinhult, Johan M. Kros, Christine Marosi, Philippe Metellus, Alexander Radbruch, Salvador S. Villa Freixa, Michael Brada, Carmine M. Carapella, Matthias Preusser, Emilie Le Rhun, Roberta Rudà, Joerg C. Tonn, Damien C. Weber, and Michael Weller



Fehlende Evidenz für den Vergleich SRS - FSRT

Key Question 2: What is the effectiveness of SRS/fractionated stereotactic radiation as initial treatment in patients with brain metastases on patient-relevant outcomes, such as overall survival and quality of life?

KQ2a. How does effectiveness vary by dose fractionation schedule and technique?

None of the identified studies compared the effects of fractionation schedules directly in a head-to-head comparison. Fractionation schedules varied in the 24 identified studies evaluating

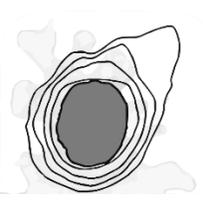
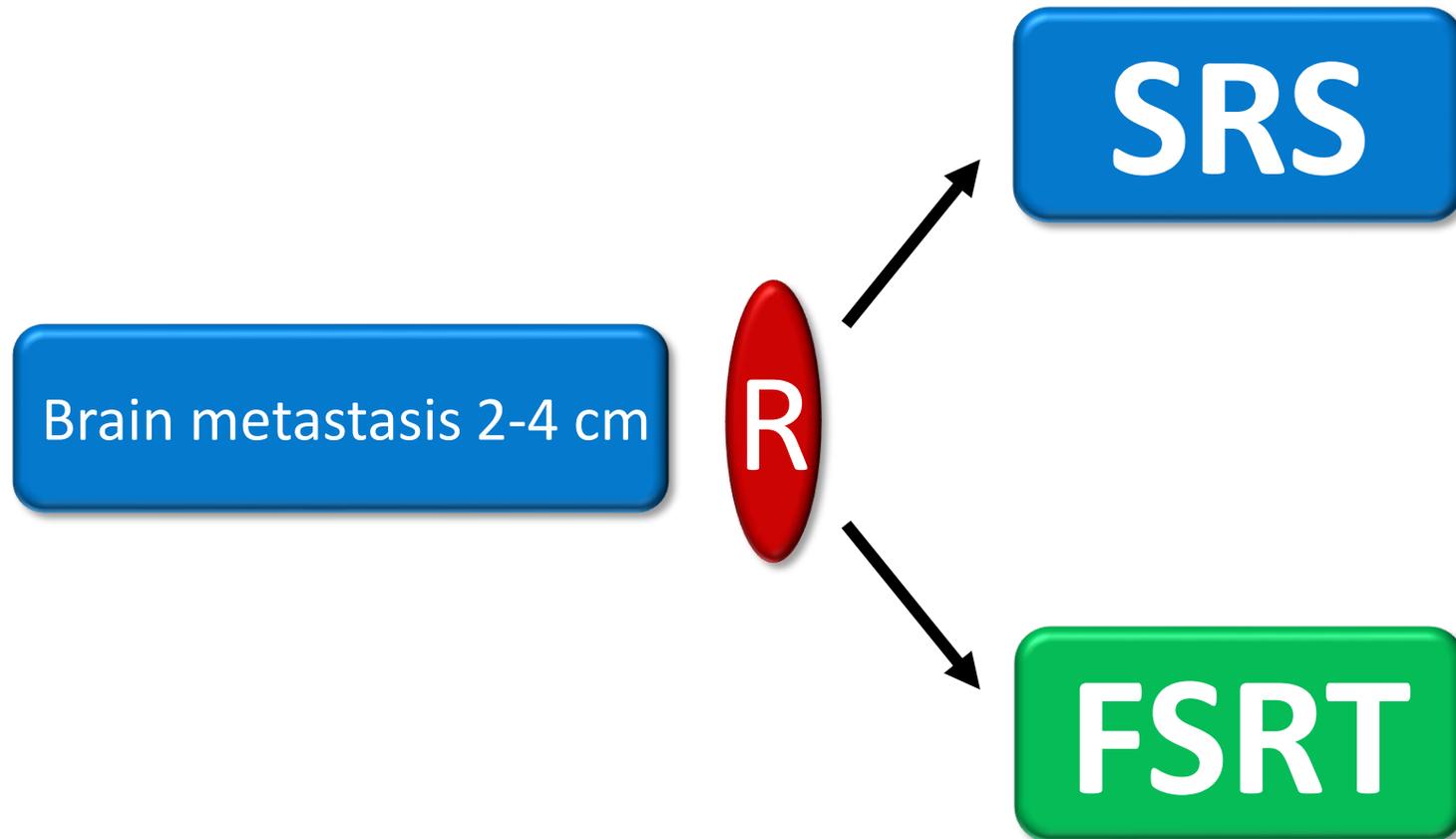
JUNE 2021

SYSTEMATIC REVIEW

Radiation Therapy for Brain Metastases

In Partnership with



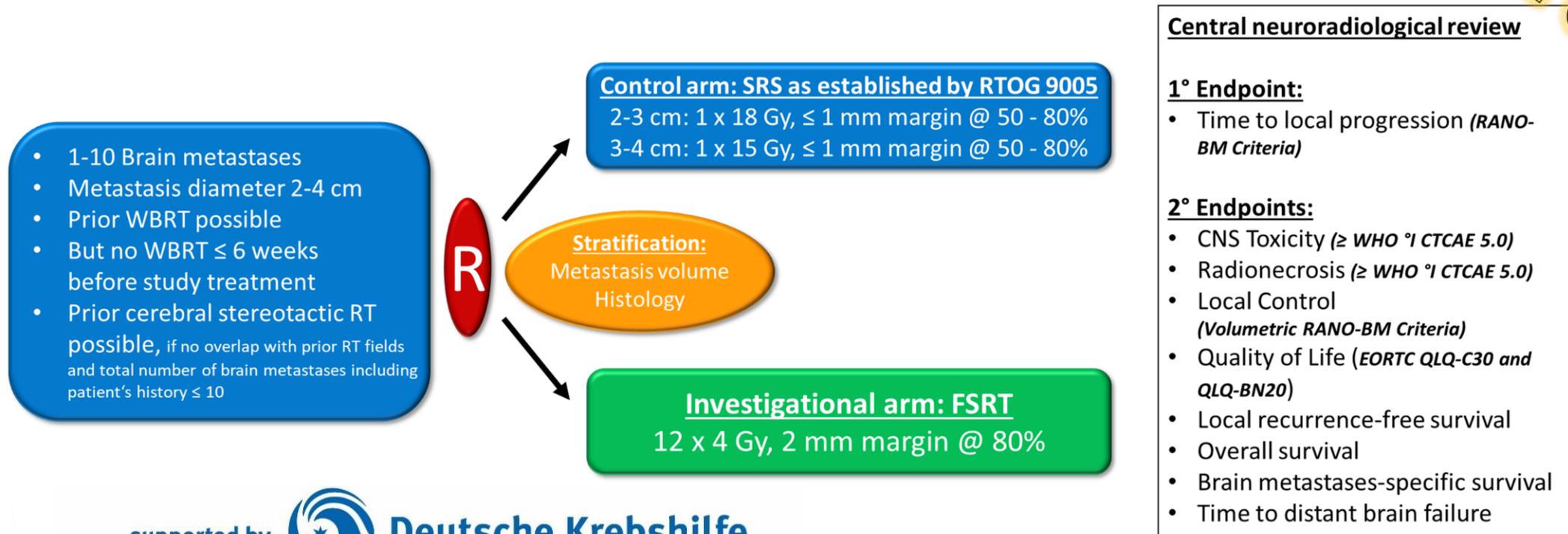
Studiendiagramm

Studiendiagramm (Protokoll 1.6)

FSRT Trial

Investigator-initiated, randomized, prospective multicenter study evaluating the superiority of fractionated stereotactic radiotherapy (FSRT) versus single-session radiosurgery (SRS) in larger brain metastases (2-4 cm).

Setzung des Goldstandards



- 1-10 Brain metastases
- Metastasis diameter 2-4 cm
- Prior WBRT possible
- But no WBRT ≤ 6 weeks before study treatment
- Prior cerebral stereotactic RT possible, if no overlap with prior RT fields and total number of brain metastases including patient's history ≤ 10



Table 1: Available studies on efficacy of **SRS for the treatment of large brain metastases**

Study	Observed local control (12 months)	Administered dose	Administered BED_{12-LQC}	Median diameter of the irradiated metastases
(Vogelbaum et al. 2006)	49.0%	1 x 18 Gy	36.00	> 2 cm
(Vogelbaum et al. 2006)	45.0%	1 x 15 Gy	28.54	> 3 cm
(Chao et al. 2008)	62.0%	1 x 18 Gy	36.00	> 2 cm
(Molenaar et al. 2009)	65.0%	1 x 18 Gy	36.00	> 2 cm
(Molenaar et al. 2009)	37.0%	1 x 15 Gy	28.54	> 3 cm
(Minniti et al. 2016)	77.0%	1 x 18 Gy	36.00	2.56 cm (calculated from volume)
Mean local control	55.8 %			

Table 2: Available studies on efficacy of FSRT for the treatment of large brain metastases

Study	Observed local control (12 months)	Administered dose	Administered BED_{12-LQC}	Median diameter of the irradiated metastases
(Ernst-Stecken et al. 2016)	76.0%	5 x 6 Gy	43.33	2.27 cm
(Narayan et al. 2012)				2.5 cm
(Higuchi et al. 2010)				2.5 cm
(Foka et al. 2010)				2.5 cm
(Matsuyama et al. 2010)				2.5 cm
(Kim et al. 2010)				2.5 cm
(Minniti et al. 2016)	91.0%	3 x 9 Gy	43.88	2.88 cm (calculated from volume)
Mean local control	77.0%	<i>SRS =</i>	55.8 %	

Größere Hirnmetastasen
 Um ~20% verbesserte
Lokale Kontrolle
 für
FSRT vs. SRS

Rationale für eine Überlegenheit der Einzeit-Radiochirurgie (SRS)

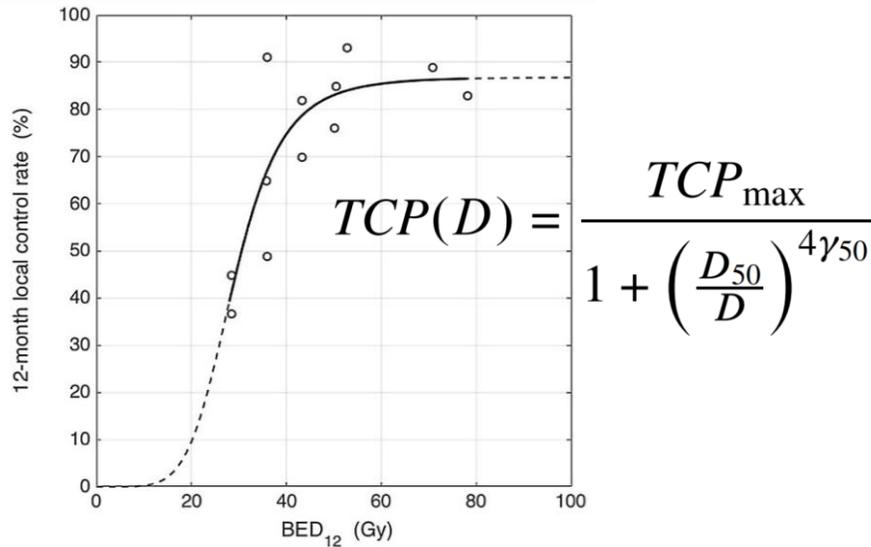
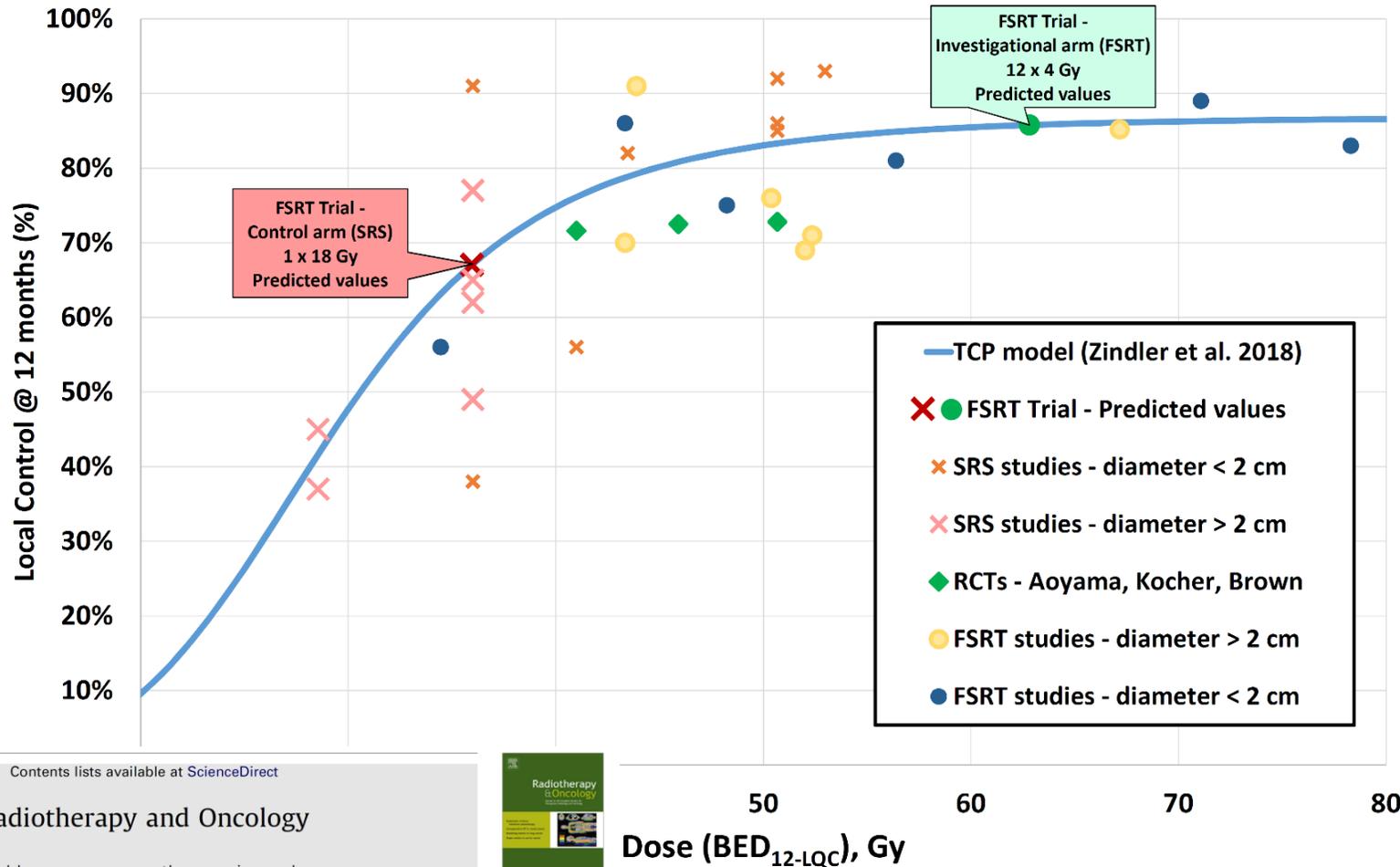


Fig. 5 A fitted dose-response curve based on data from Wiggenraad et al. [4]



- TCP model (Zindler et al. 2018)
- × ● FSRT Trial - Predicted values
- × SRS studies - diameter < 2 cm
- × SRS studies - diameter > 2 cm
- ◆ RCTs - Aoyama, Kocher, Brown
- FSRT studies - diameter > 2 cm
- FSRT studies - diameter < 2 cm

Strahlenther Onkol (2018) 194:560–569
<https://doi.org/10.1007/s00066-018-1262-x>

ORIGINAL ARTICLE



Improved effectiveness of stereotactic radiosurgery in large brain metastases by individualized isotoxic dose prescription: an *in silico* study

Jaap D. Zindler¹ · Jacqueline Schiffelers¹ · Philippe Lambin¹ · Aswin L. Hoffmann^{1,2,3}



Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



Systematic review

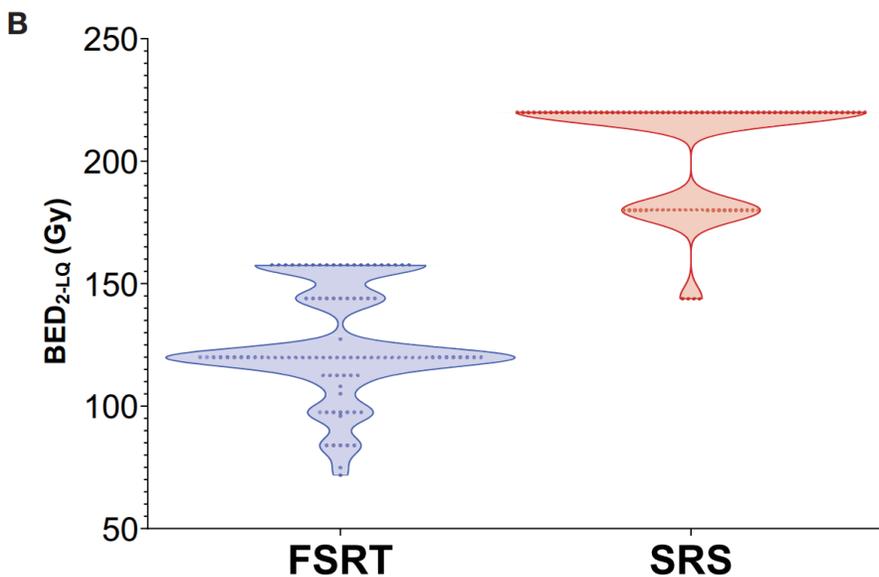
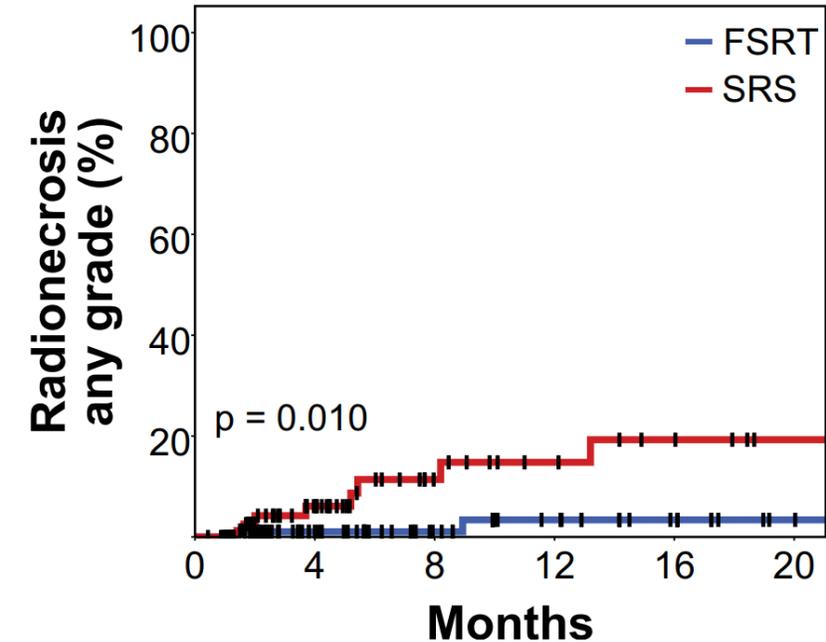
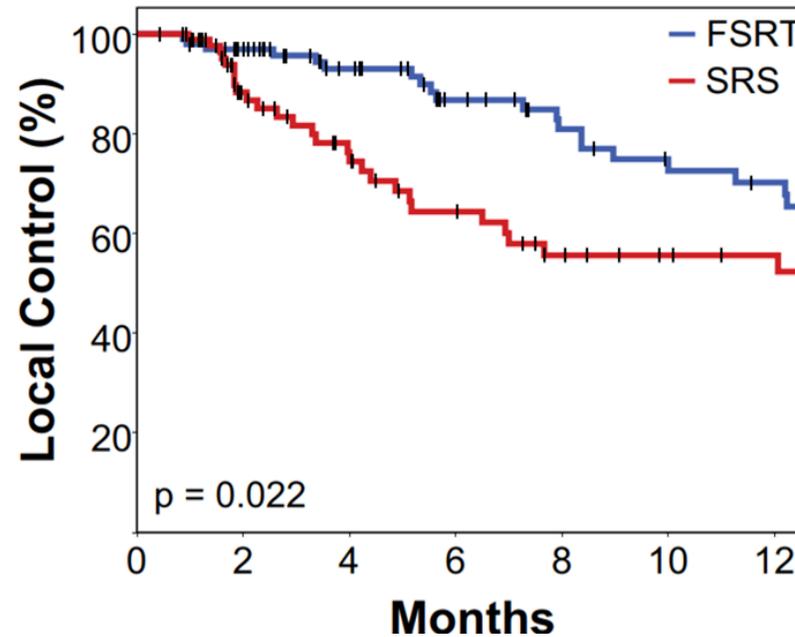
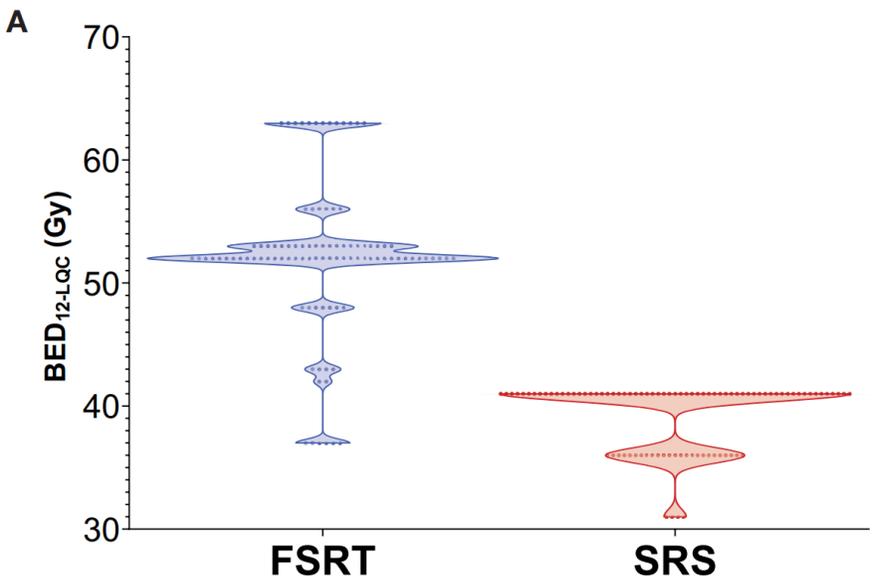
Dose-effect relation in stereotactic radiotherapy for brain metastases.

A systematic review

Ruud Wiggenraad^{a,*}, Antoinette Verbeek-de Kanter^a, Henk B. Kal^b, Martin Taphoorn^{c,e}, Thomas Vissers^d, Henk Struikmans^a

Universitätsklinikum
Erlangen

Rationale für eine Überlegenheit der FSRT bei Hirnmetastasen > 2 cm



ORIGINAL RESEARCH
published: 30 September 2020
doi: 10.3389/fonc.2020.559193

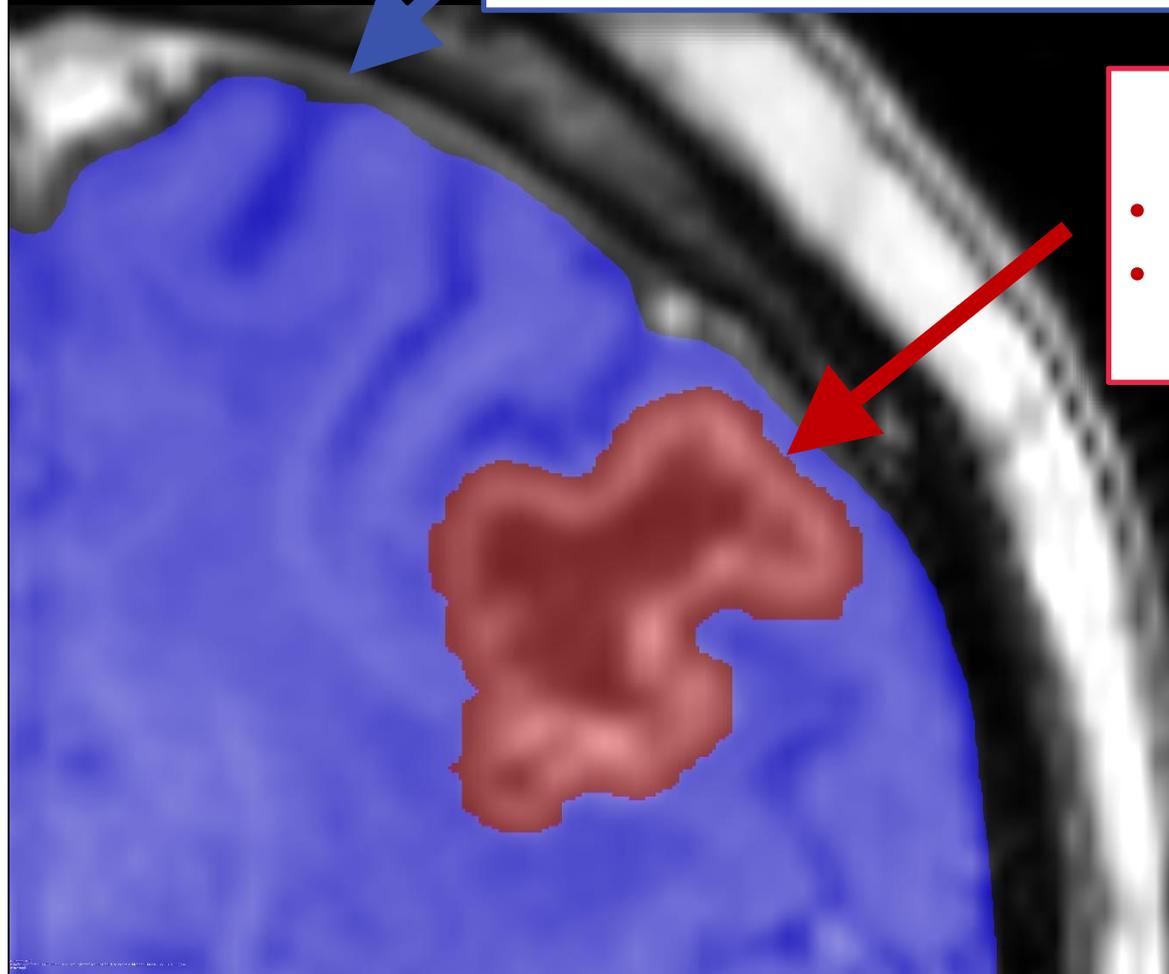
FSRT vs. SRS in Brain Metastases – Differences in Local Control and Radiation Necrosis – A Volumetric Study

Hirngewebe:

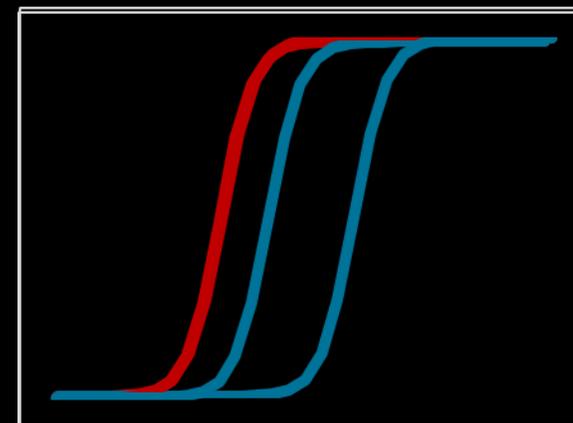
- Klassisch spät reagierendes Gewebe
- Niedriges α/β
- Verbesserte Toleranz ggü. niedrigen Einzeldosen

Hirnmetastase:

- Sehr hohes α/β von 12
- Kein Nachteil durch niedrige Einzeldosen

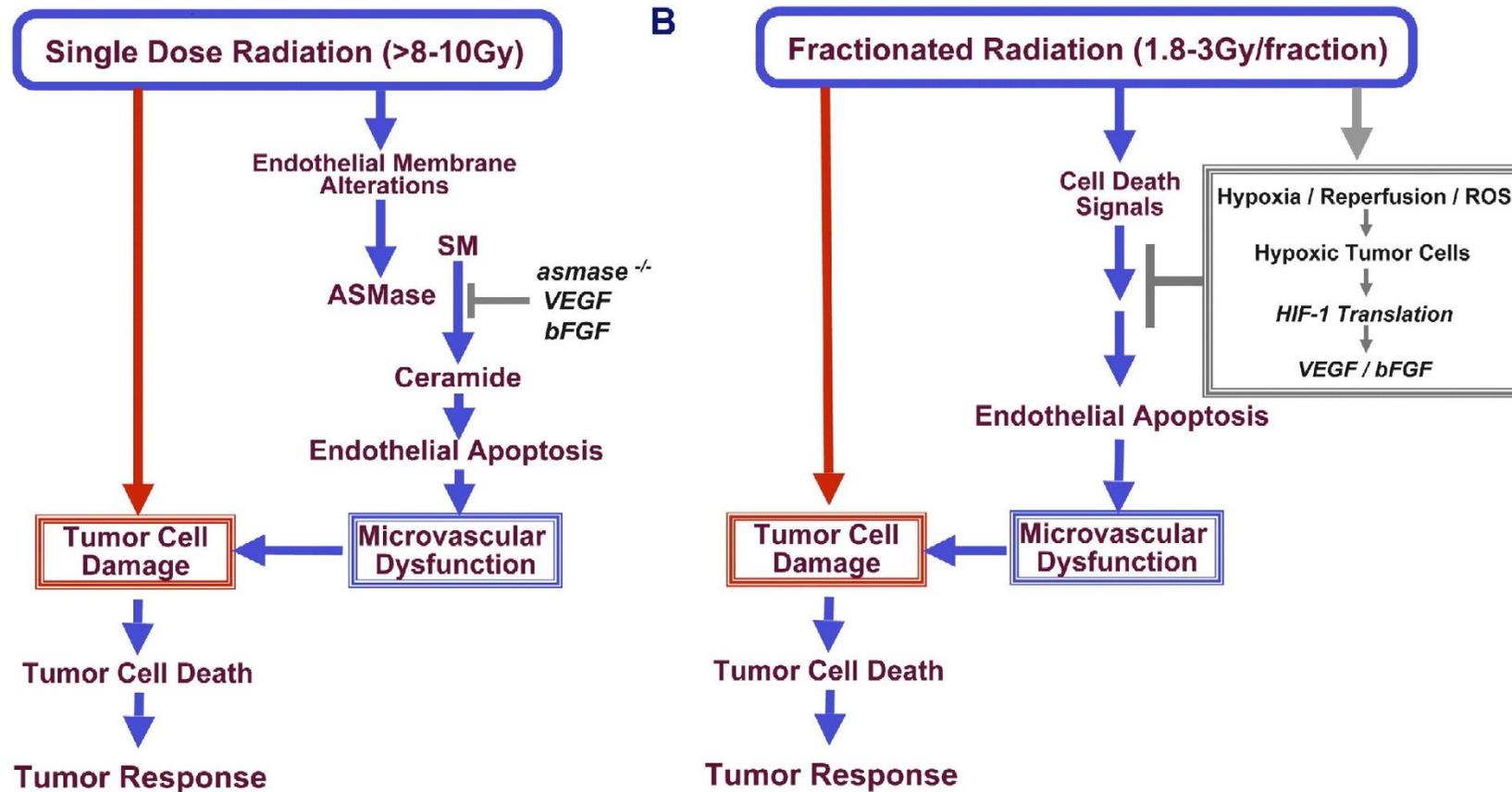


Niedrige Einzeldosis
Hohe Einzeldosis



Rationale für eine Überlegenheit der Einzeit-Radiochirurgie (SRS)

- **Veränderte Radiobiologie bei hohen Einzeldosen**
- **Endothelzell Apoptose durch den Sphingomyelinase Pathway**



FSRT-Trial: Protokoll 1.6 (Amendment)

FSRT Trial Study Protocol



***Efficacy and Safety of Fractionated
Stereotactic Radiation Therapy versus
Single Fraction Stereotactic Radiosurgery
for Large Brain Metastases (2 – 4 cm)***

Principal Investigator: Prof. Dr. med. Rainer Fietkau,
Strahlenklinik, Universitätsklinikum Erlangen

Scientific Study Director: Dr. med. Florian Putz
Strahlenklinik, Universitätsklinikum Erlangen

Study coordination: Studiensekretariat
Strahlenklinik, Universitätsklinikum Erlangen

Biometrics: Dr. Axel Hinke
CCRC, Düsseldorf

Translational Research: Prof. Dr. Udo Gajpl
Strahlenklinik, Universitätsklinikum Erlangen

Protocol code: FSRT Trial

Protocol version: Protocol version 1.6, 24.09.2021

Confidentiality Notice:

The contents of this study protocol are to be treated confidentially and must not be disclosed orally or in writing to any third party not involved in this trial without the approval of the study director.

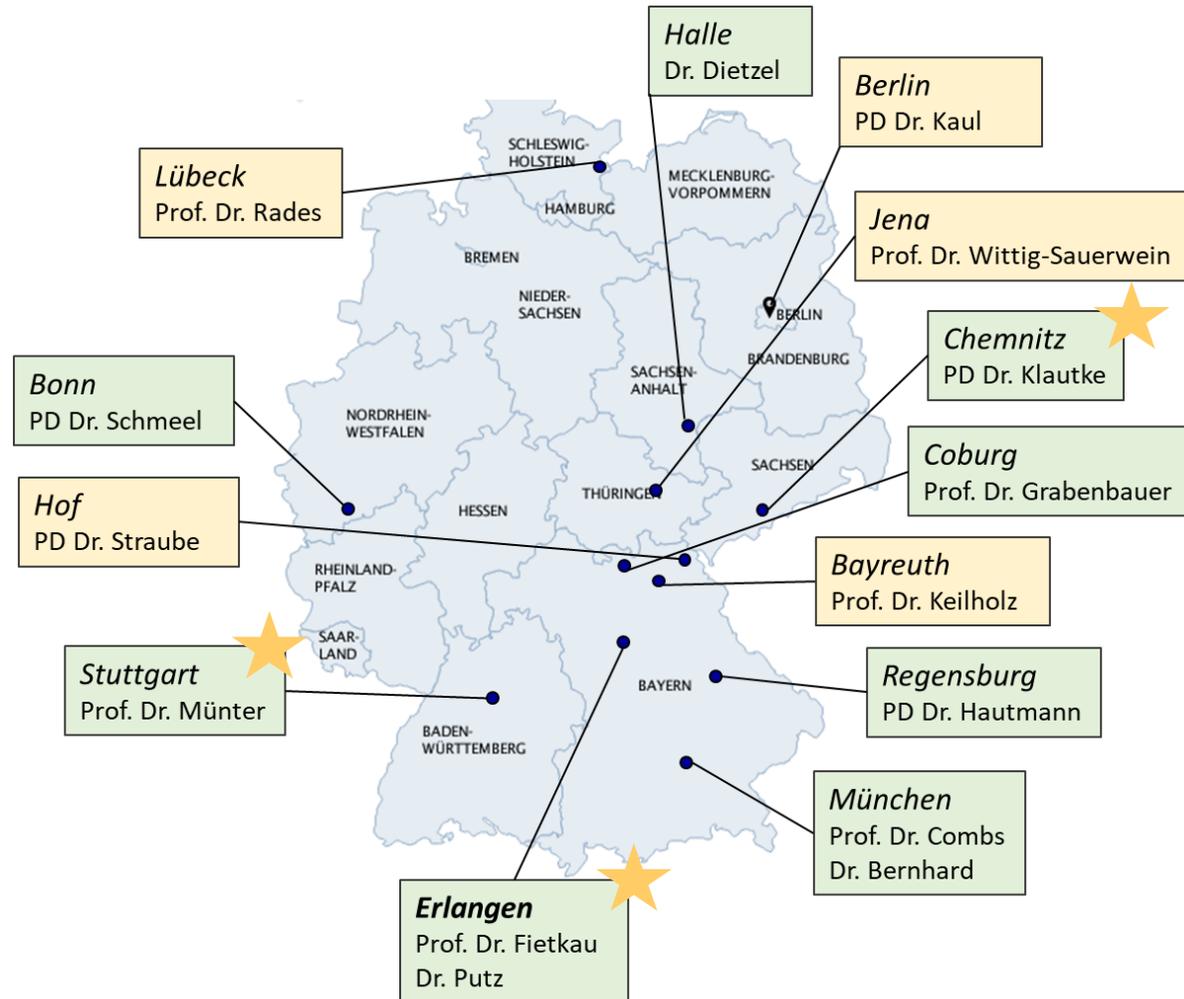
supported by  **Deutsche Krebshilfe**
HELLEN. FORSCHEN. INFORMIEREN.

- Einschluss bei **bis zu 10 Hirnmetastasen** möglich
- **Sicherheitssaum** von **bis zu 1 mm** im SRS-Arm
- **Dokumentation** harmonisiert mit **ICRU 91**
- Weitere **Konkretisierungen** und **Detailanpassungen** der Radiotherapie **entsprechend Feedback der Zentren**

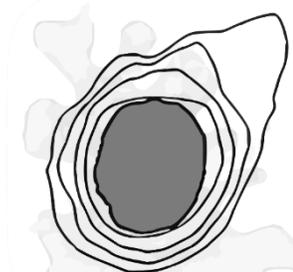
Aktueller Stand: Positives Votum vom 02.12.2021



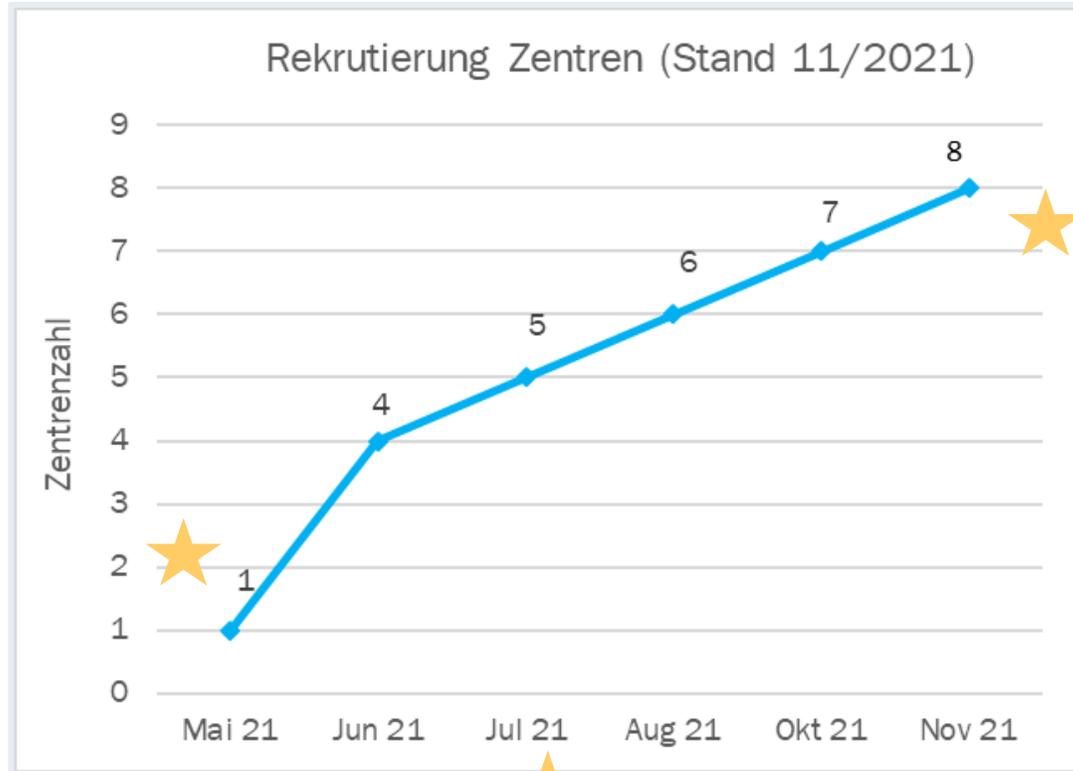
FSRT-Trial: Aktueller Stand Zentren



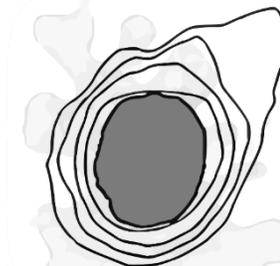
- **15 Zentren** vorgesehen
- **13 Zentren** zugesagt
- **8 Zentren** initiiert
- **5 Zentren** warten auf Ethik oder andere administrative Voraussetzungen für Initiierung
- **3 Zentren** Beginn **Patientenrekrutierung**



FSRT-Trial: Aktueller Stand Zentren

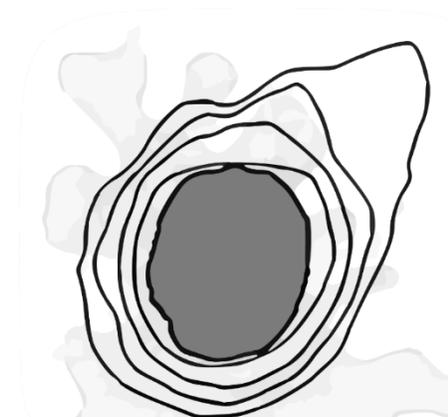


- **15 Zentren** vorgesehen
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- **8 Zentren** initiiert
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- **3 Zentren** Beginn **Patientenrekrutierung**



Schlussfolgerung:

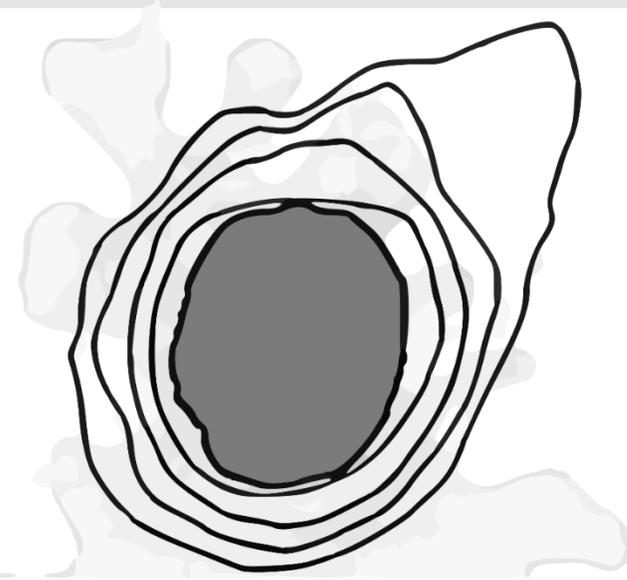
- **Schaffung prospektiv-randomisierter Evidenz sehr wichtig für zukünftigen Stellenwert der Neuroradioonkologie (IQWiG)**
- **Phase III FSRT-Trial** vergleicht erstmals **Einzeit-SRS** und **FSRT** bei **Hirnmetastasen > 2 cm** in **prospektiv randomisierter Weise** (Potential Veränderung Goldstandard)
- **Neues Amendment** ermöglicht **Einschluss von Patienten mit bis zu 10 Hirnmetastasen** und enthält **Konkretisierungen** und **Detailanpassungen** zur RT entsprechend der **Rückmeldung der Zentren**
- Werbung für **Teilnahme** und **Patienteneinschluss**



FSRT-Trial

Fragen zur Studie

FSRT



Trial

ST-FSRT@UK-Erlangen.de



FSRT-Trial.de

09131 85-33968

Universitätsklinikum
Erlangen

