IORT for Brain Metastases

Impact on Time to Systemic Treatment Onset and Other Patient-Relevant Outcomes

Cas S. Dejonckheere MD

Department of Radiation Oncology
University Hospital Bonn, Germany

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Conflict of Interest

- none

Context

- relative diagnostic **incidence** of brain metastases (BMs) ↑
- large/symptomatic BMs: maximal **surgical resection** + **adjuvant stereotactic radiotherapy** (SRT) to ↑ local control

⟶ prevent neurological decline

⟶ avoid additional interventions

⟶ overall BM treatment time ↑

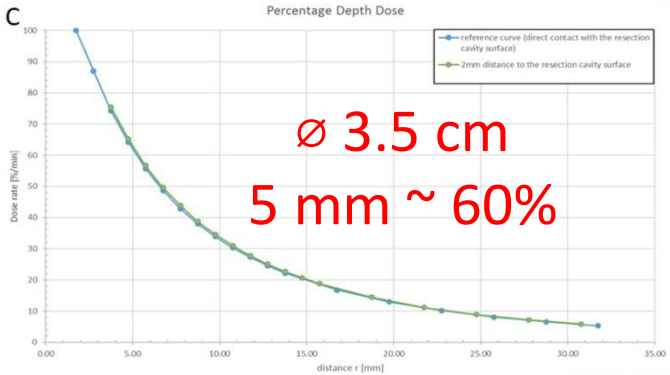
⟶ delayed onset of (systemic) treatment (survival ↓ ?)

IORT

- high rates of local tumor control
- prevent early repopulation of residual microscopic tumor
- steep dose gradient, sparing of organs at risk (OARs)

- **solitary BM**: omission of SRT
- **multiple BMs**: 1 fewer target volume

  ⟶ reduced total number of treatment days



Grimmer *et al.* Adv Radiat Oncol 2024

Objective

- data on local control, distant brain control, overall survival, radiation necrosis etc. are maturing
- here: meaningful **secondary** endpoints
  - **time to next treatment** (TTNT) = number of days between BM resection and start of the next **extracranial** oncological intervention (systemic treatment, extracranial surgery, or radiotherapy)
  - duration of postoperative **corticosteroid** treatment
  - **in-hospital times** (both as in- and out-patient)

⟶ compared to SRT

Methods

- University Hospital Bonn, Germany

- November 2020 till June 2023

  - prospective BM-IORT registry
  - all patients receiving SRT within the same timeframe (institutional database)

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Methods -- IORT arm

- spherical applicator 1.5–5 cm
- 50 kV photons
- 16–30 Gy with INTRABEAM 600 (Carl Zeiss Meditec, Germany)
- OAR distance/dose measured intraoperatively (neuronavigation)
  - optic chiasm < 12 Gy
  - brainstem < 12.5 Gy

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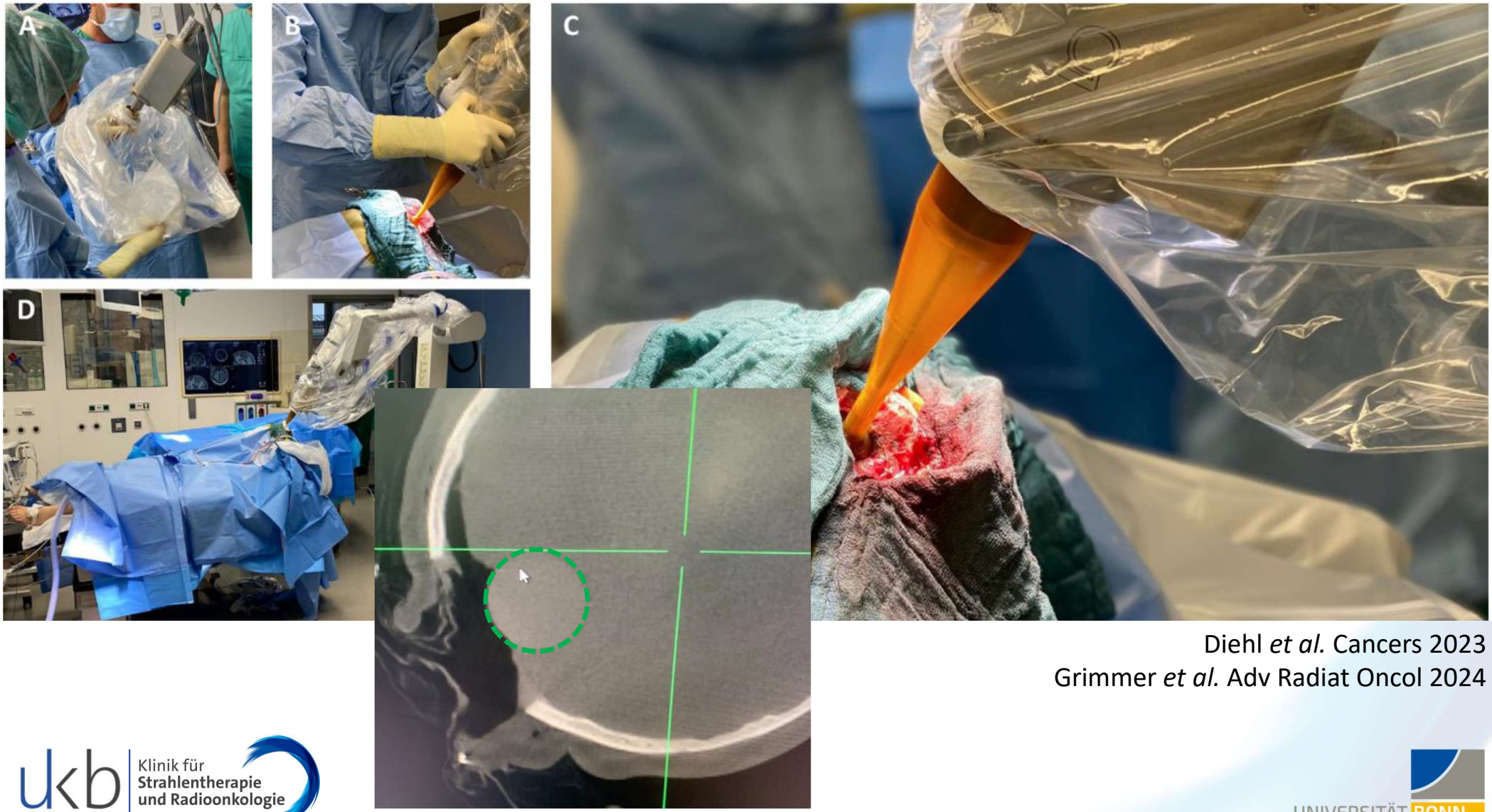

Diehl *et al.* Cancers 2023
Grimmer *et al.* Adv Radiat Oncol 2024

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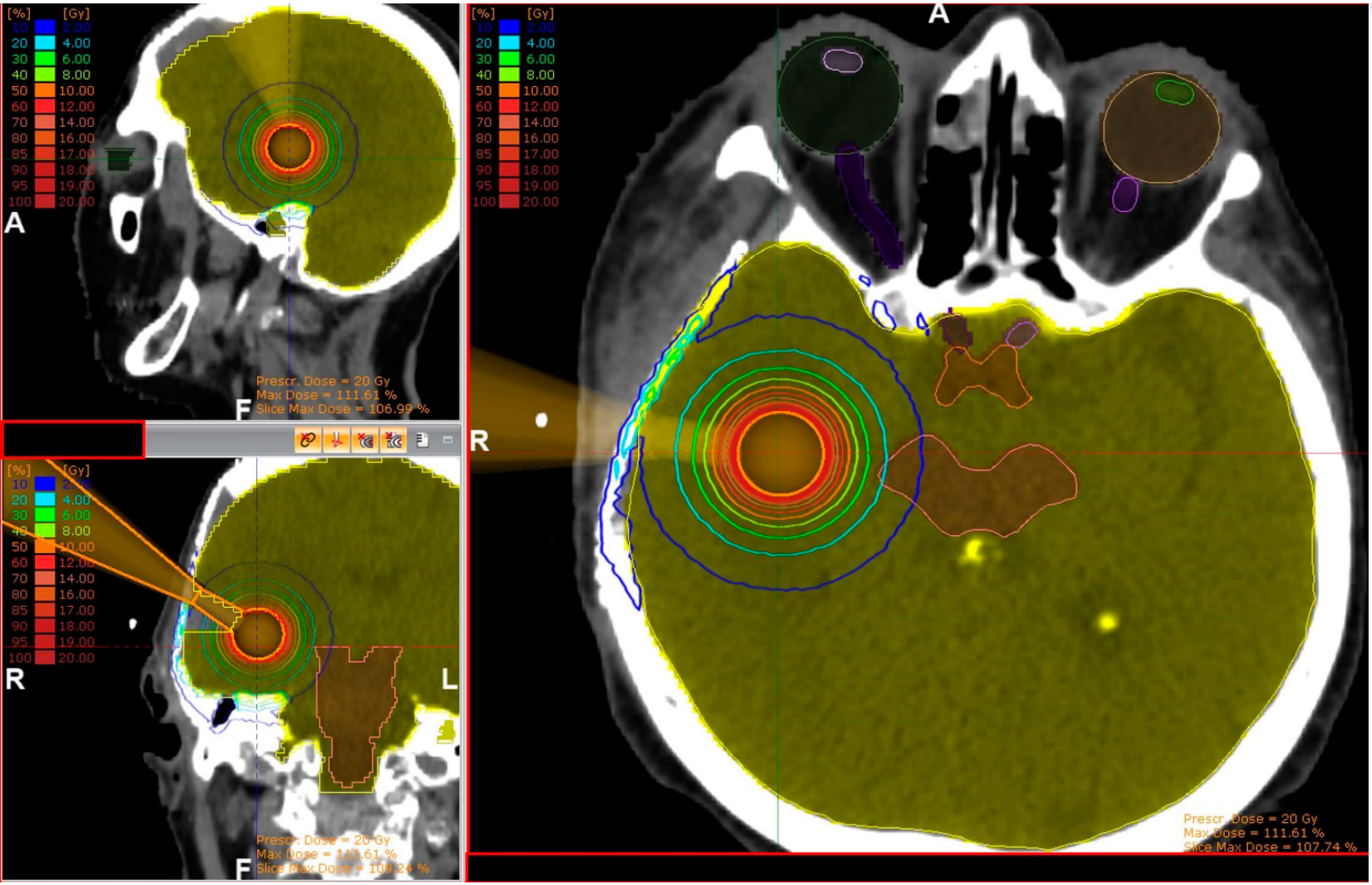


Sarria *et al.* Front Oncol 2021

Methods -- SRT arm

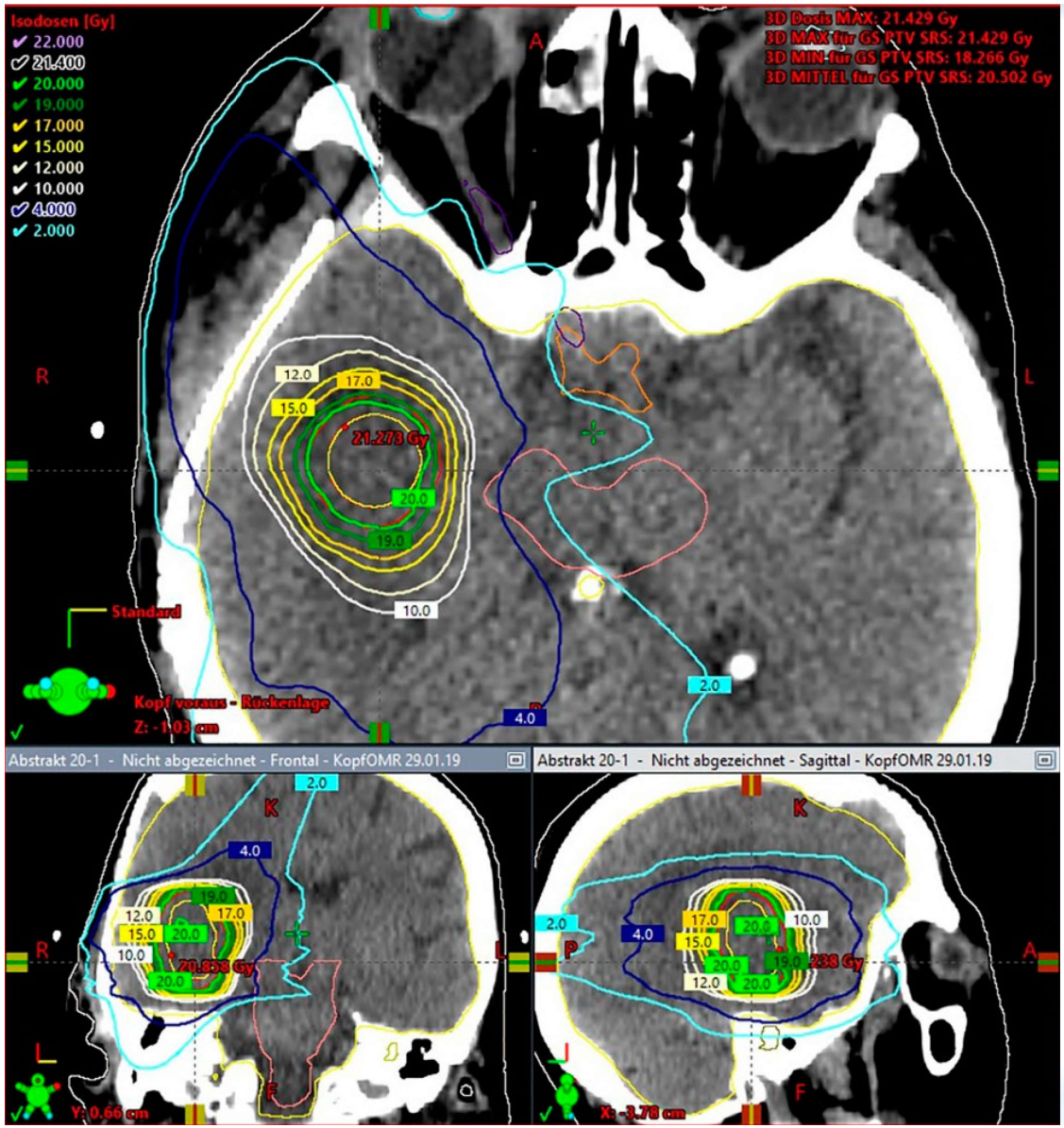
- initially screened for IORT but not carried out **or** upfront planned SRT
- 1–10 BMs at time of surgery, solid tumor histology
- SRS or fSRT, after **interval**

> Patients who underwent RT >22 days after surgical resection had a decreased risk for all-cause mortality of 47.2% (95% CI: 8.60, 69.5%). Additionally, waiting >40 days for RT after surgical resection more than doubled the risk of tumor progression; adjusted hazard ratio 2.02 (95% CI: 1.12, 3.64).

Yaghi *et al.* Neuro Oncol Pract 2022

- thermoplastic mask + simulation CT + planning MRI
- IMRT (TrueBeam STx, Varian Medical Systems, USA) and IGRT (ExacTrac, Brainlab, Germany)

Sarria *et al.* Front Oncol 2021



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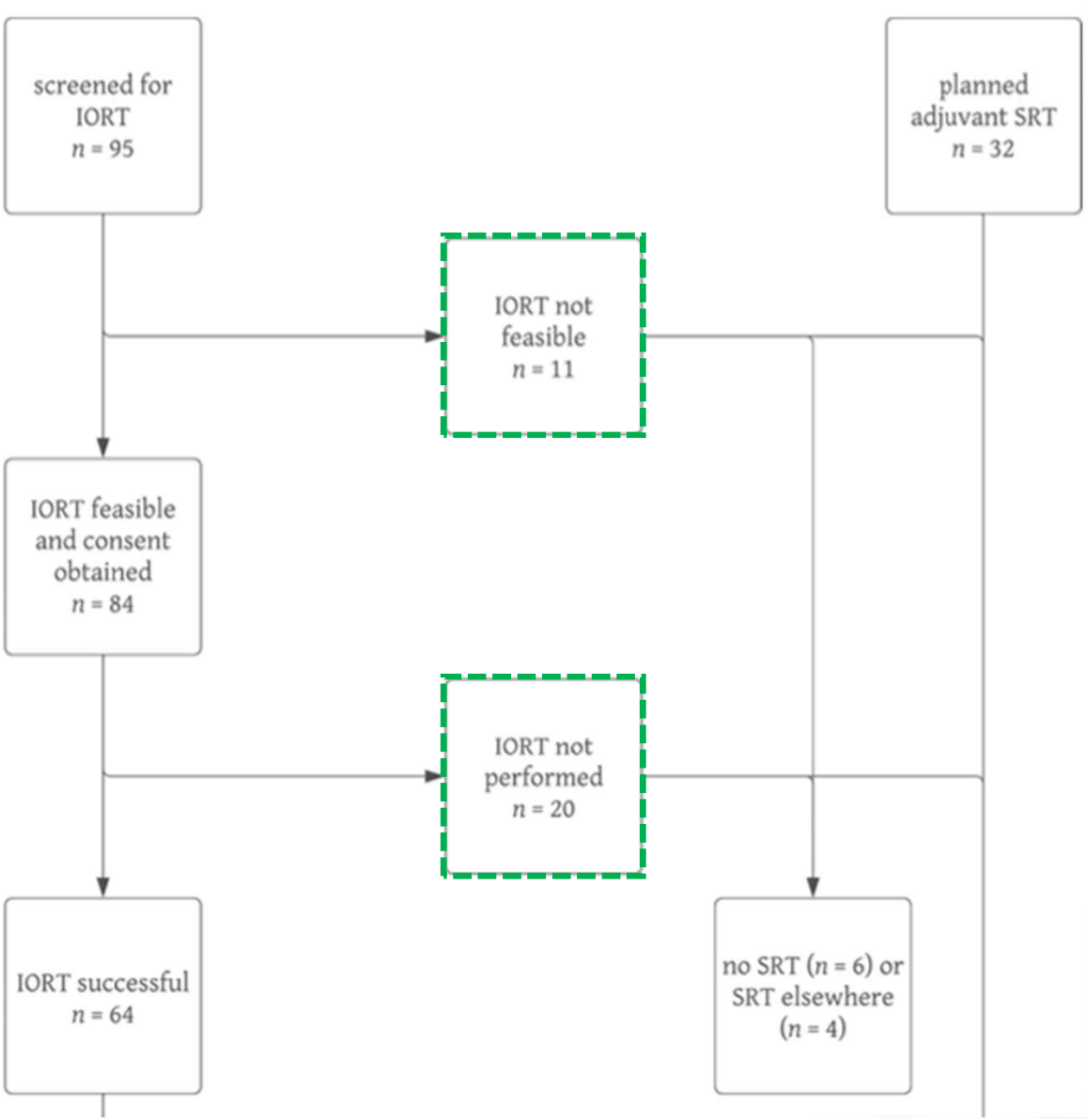
screened for
IORT
$n = 95$

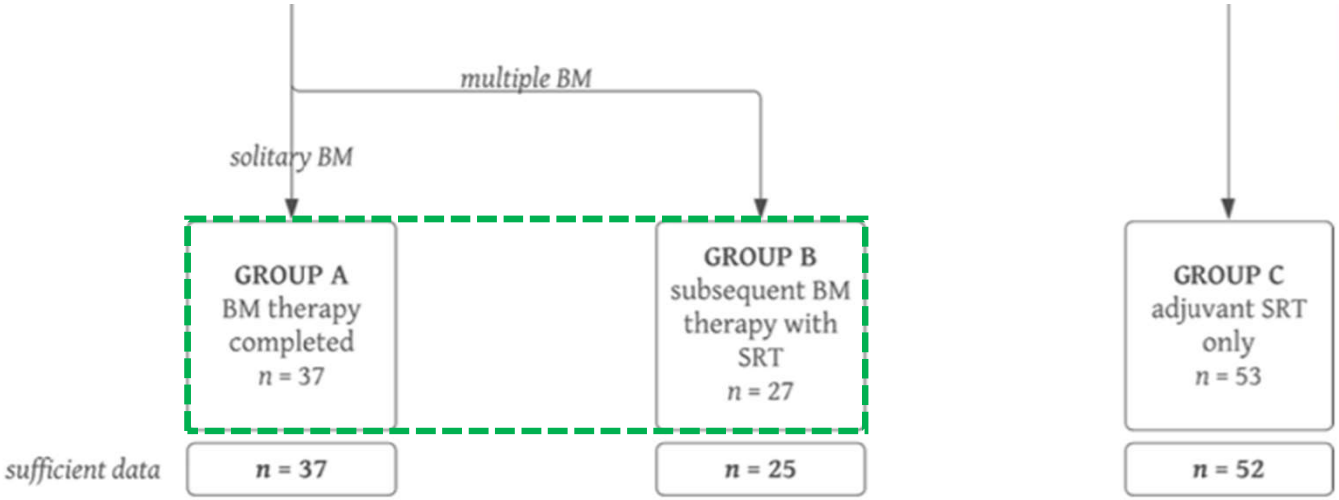
Table 1 Reasons for not receiving IORT for resectable brain metastasis. IORT = intraoperative radiotherapy; OAR = organ at risk

IORT not possible or feasible ($n = 11$)
logistics ($n = 6$)
expected violation of OAR constraint ($n = 3$)
patient declining surgery ($n = 2$)
IORT possible and feasible, but not performed ($n = 20$)
frozen section unclear ($n = 7$)
resection cavity not spherical ($n = 5$)
technical reasons ($n = 4$)
logistics ($n = 2$)
measured violation of OAR constraint ($n = 1$)
patient declining surgery ($n = 1$)

Selection


screened for IORT n = 95
planned adjuvant SRT n = 32
IORT not feasible n = 11
IORT feasible and consent obtained n = 84
IORT not performed n = 20
IORT successful n = 64
no SRT (n = 6) or SRT elsewhere (n = 4)

Selection


multiple BM
solitary BM
GROUP A
BM therapy
completed
n = 37
GROUP B
subsequent BM
therapy with
SRT
n = 27
GROUP C
adjuvant SRT
only
n = 53
sufficient data
n = 37
n = 25
n = 52

Results

	IORT	SRT	*p*
n	62	52	
female sex, *n* (%)	31 (50)	25 (48)	0.85
median age at surgery (range) in years	63 (35 – 91)	64 (34 – 87)	0.86
KPS at surgery, *n* (%)	49 (79)	43 (83)	0.77
≥ 70	13 (21)	9 (17)	
< 70			
median DS-GPA at surgery (range)	2 (0 – 4)	2 (0 – 4)	0.39
extracranial metastases at surgery, *n* (%)	52 (84)	27 (68)	0.09
median radiation dose (range) in Gy *	30 (16 – 30)	35 (20 – 45)	
primary lobe, *n* (%)			
frontal	24 (39)	17 (33)	0.07
parietal	2 (3)	10 (19)	
occipital	16 (26)	8 (15)	
temporal	8 (13)	8 (15)	
cerebellum	12 (19)	9 (17)	
primary tumour, *n* (%)			
lung	37 (60)	25 (48)	0.26
melanoma	10 (16)	9 (17)	
GI	5 (8)	7 (13)	
GU	6 (10)	3 (6)	
breast	3 (5)	3 (6)	
gynaecological	1 (2)	1 (2)	
other	0 (0)	4 (8)	
number of BMs at surgery, *n* (%)			
solitary	36 (58)	31 (60)	0.49
multiple	26 (42)	21 (40)	
(range of multiple BMs)	(2 – 10)	(2 – 10)	
median time (range) to			
SRT onset in days		25 (11 – 173)	
SRT completion in days		34 (11 – 187)	

Patients who underwent RT >22 days after surgical resection had a decreased risk for all-cause mortality of 47.2% (95% CI: 8.60, 69.5%). Additionally, waiting >40 days for RT after surgical resection more than doubled the risk of tumor progression; adjusted hazard ratio 2.02 (95% CI: 1.12, 3.64).

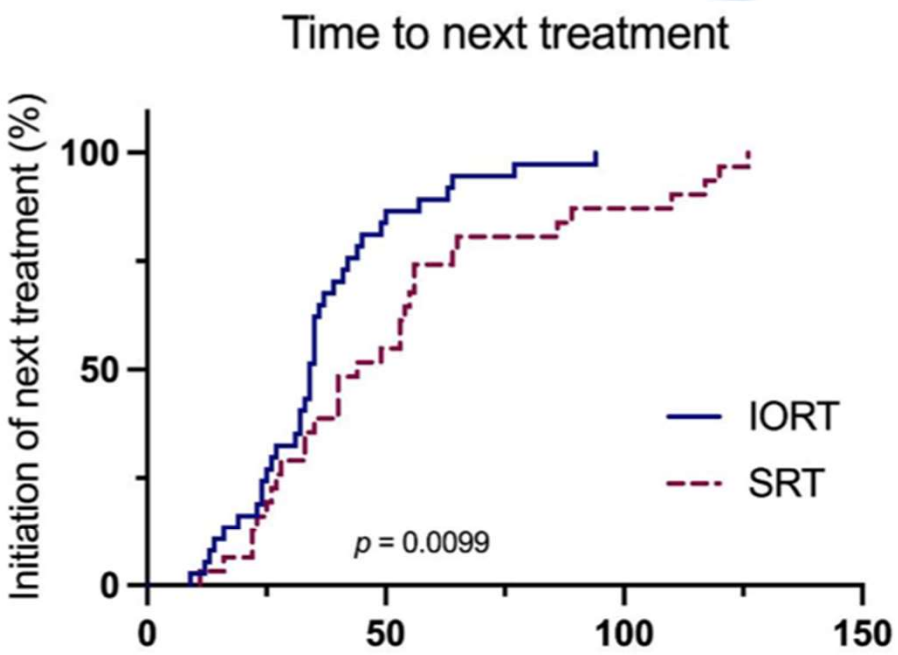
Yaghi *et al.* Neuro Oncol Pract 2022

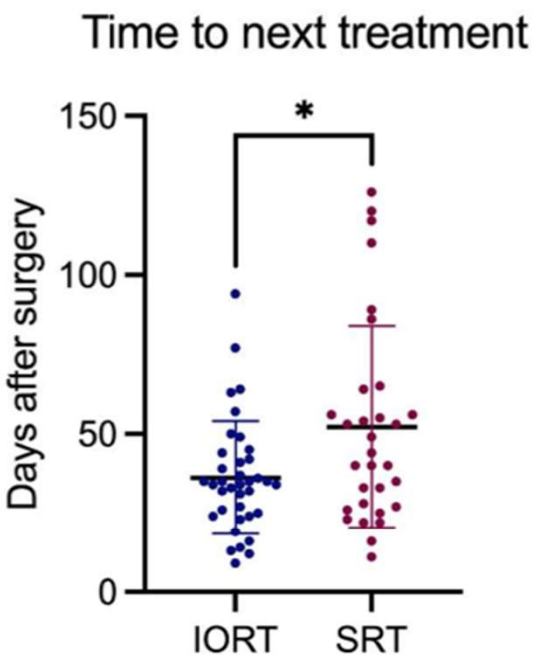
Table 3 Time to next treatment, duration of postoperative corticosteroid treatment, and in-hospital time. IORT = intraoperative radiotherapy; SRT = stereotactic radiotherapy; SD = standard deviation

	IORT	SRT	*p*
received postoperative extracranial treatment, *n* (%)			
yes	39 (63) *	31 (60)	0.99
no	18 (29) **	15 (29)	
unknown	5 (8)	6 (11)	
type of additional treatment, *n* (%)			
chemotherapy	6 (16)	12 (39)	0.11
immunotherapy	20 (54)	12 (39)	
chemoimmunotherapy	4 (11)	6 (19)	
antihormone therapy	1 (3)	0 (0)	
extracranial surgery	3 (8)	1 (3)	
extracranial radiotherapy	3 (8)	0 (0)	
location of postoperative extracranial treatment, *n* (%)			
same center	21 (54)	23 (74)	0.08
different center	18 (46)	8 (26)	
time to next treatment			
median (range) in days	34 (9 – 94)	44 (11 – 126)	**0.01**
mean ± SD in days	36 ± 18	52 ± 32	
postoperative corticosteroid treatment			
median (range) in days	7 (0 – 30)	7 (0 – 14)	0.83
mean ± SD in days	8 ± 5	8 ± 3	
postoperative in-hospital time (in-patient)			
median (range) in days	8 (2 – 29)	8 (2 – 42)	0.97
mean ± SD in days	11 ± 6	12 ± 8	
total in-hospital time (in- and out-patient)			
median (range) in days	8 (2 – 29)	15 (7 – 48)	**< 0.001**
mean ± SD in days	11 ± 6	19 ± 9	

* Extracranial surgery had to be postponed in one patient suffering COVID pneumonia and another patient initially declined immunotherapy. Both patients were excluded from the analysis

** Two patients had already started systemic therapy prior to surgery and were also excluded from the analysis


Time to next treatment
Initiation of next treatment (%)
100
50
0
0
50
100
150
IORT
SRT
p = 0.0099


Time to next treatment
Days after surgery
150
100
50
0
*
IORT
SRT

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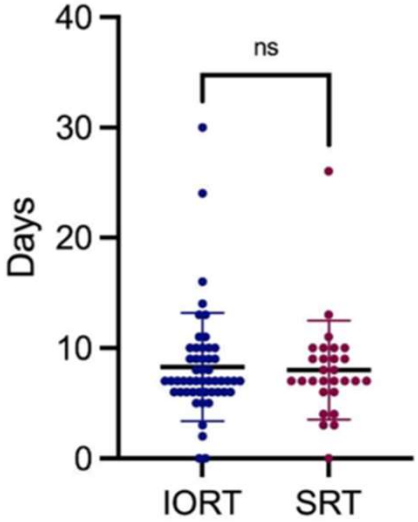
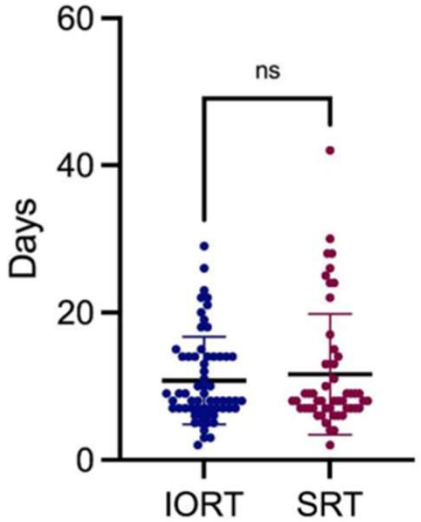
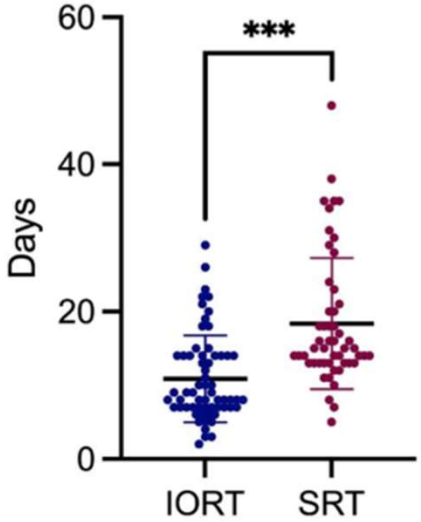
Time to corticoid discontinuation



Post surgery in-hospital times



Total in-hospital times



What does the literature say ?

author (year)	type	IORT outcome of published trials				*n*		TTNT (days)
		1yLCR (%)	1yDBC (%)	RN (%)	1yOS (%)	IORT	*SRT*	
Kahl et al. (2024)	retrospective DE	84	48	3	58	117	/	mean (range) **31 (1–136)**
Current (2023) **[*n* = 35]**	prospective study registry DE	97	74	3	58	62	*52*	mean (range) **IORT: 36 (9–94)** *SRT: 52 (11–126)*
Brehmer et al. (2023)	prospective phase II (preliminary) DE			20		35	/	mean (95% CI) **45 (35–55)**
Guedes de Castro et al. (2023)	prospective phase II	88	13	10	80	10	/	n.r.
Diehl et al. (2022)	retrospective DE	93	71	11	58	18	/	**in 5 IORT patients ≤ 15** (shorter than wound healing and adjuvant SRT would have required)
Cifarelli et al. (2019)	retrospective	88	58	7	73	54	/	n.r.
Brehmer et al. (2018)	prospective phase II (preliminary) DE					10	*19*	mean (range) **IORT: 46 (27–83)** *SRT: 61 (16–229)*
Weil et al. (2015)	prospective	n.r.	n.r.	13	n.r.	23	/	n.r.

Discussion

- **reasons** for longer TTNT in SRT ?
  - incomplete staging, postponed until after SRT (e.g. conflicting appointments)
  - side effects
  - undesirable combination with planned systemic therapy (e.g. BRAF/MEKi)
  - patient refusal to undergo parallel treatments

Conclusion

- rapid completion of interdisciplinary BM treatment is important
- IORT for resectable BMs can achieve this
  - feasibility rate 88%
  - *(comparable safety profile)* Hamed *et al.* Cancers 2022
  - *(comparable LC and RN rate)* Layer *et al.* J Neurooncol 2023
  - no prolonged corticosteroid intake
    - important in the current ICI/TT era Layer *et al.* Int J Radiat Oncol Biol Phys 2024

16 days

earlier start of extracranial oncological therapy (on average)

8 days

shorter total in-hospital time (on average)

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Future

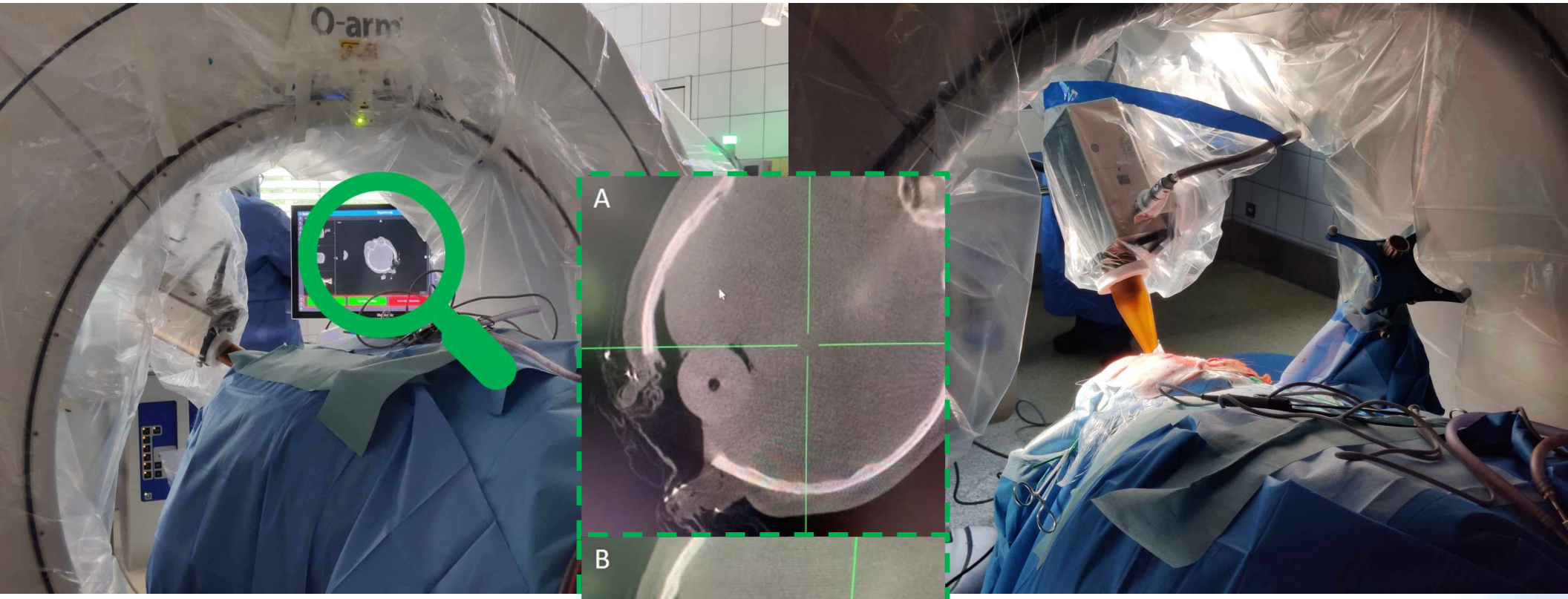
- impact on ...
  - resources/cost ?
  - quality of life ?
  - oncological outcome i.e. survival ?

⟶ randomized controlled trial needed (and planned)

Future

- reproduction of dose distribution/OAR constraints (e.g. future cranial target volumes) = advantage of SRT

  ⟶ IG-IORT and real-time/post-hoc planning Grimmer *et al.* Adv Radiat Oncol 2024



Grimmer *et al.* Adv Radiat Oncol 2024

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RESEARCH

Intraoperative or postoperative stereotactic radiotherapy for brain metastases: time to systemic treatment onset and other patient-relevant outcomes

Cas S. Dejonckheere[1] · Julian P. Layer[1,2] · Motaz Hamed[3] · Katharina Layer[1] · Andrea Glasmacher[1] · Lea L. Friker[2,4] · Anna-Laura Potthoff[3] · Thomas Zeyen[5] · Davide Scafa[1] · David Koch[1] · Stephan Garbe[1] · Jasmin A. Holz[1] · Fabian Kugel[1] · Molina Grimmer[1] · Frederic Carsten Schmeel[6] · Gerrit H. Gielen[4] · Helmut Forstbauer[7] · Hartmut Vatter[3] · Ulrich Herrlinger[5] · Frank A. Giordano[8] · Matthias Schneider[3] · Leonard Christopher Schmeel[1] · Gustavo R. Sarria[1]

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Cas.Dejonckheere@ukbonn.de

@CasDejonckheere

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