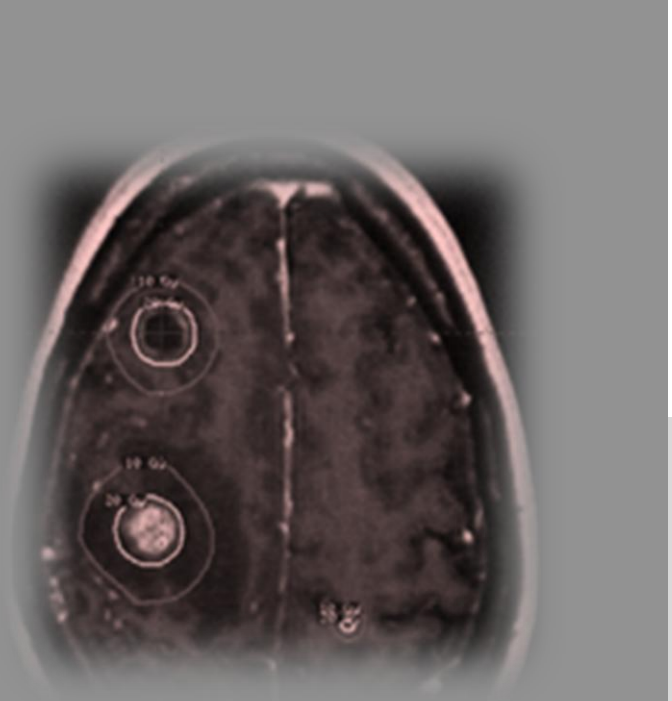
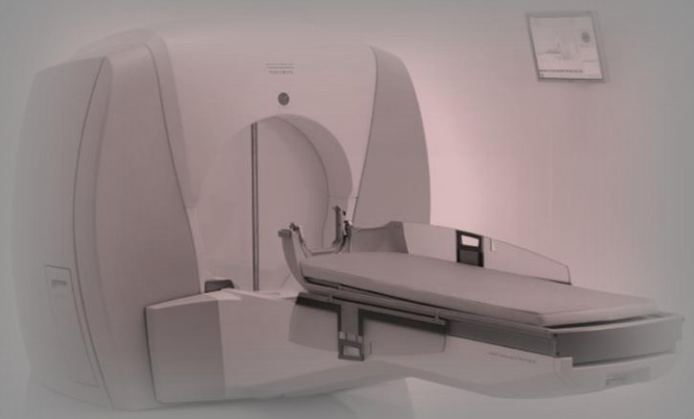
Gamma Knife
Zentrum Krefeld





Radiochirurgie multipler Hirnmetasen Machbarkeit &Toxizität

Frankfurt 20.10.17

Bert van Eck

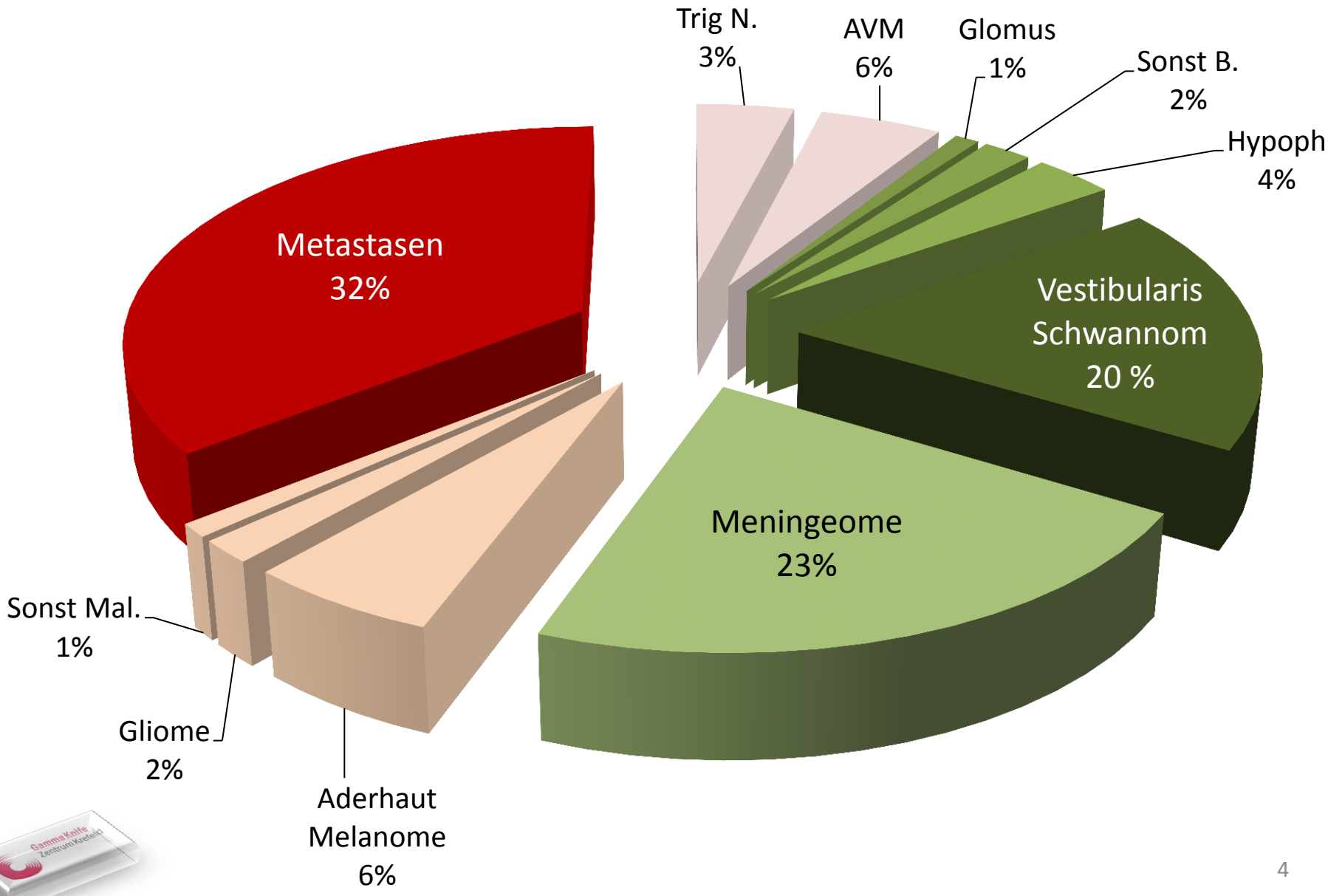
vaneck@gamma-knife.de

Übersicht

- Radiochirurgie in Krefeld
- Machbarkeit
- Toxizität
- Diskussion

Radiochirurgie in Krefeld

8865 Behandlungen (1999-2017)



Histologie

NSCLC	44,2%	
Mamma	19,4%	
Melanom	13,1%	
Colo-Rektal	5,9%	
SCLC (nach WBRT)	5,8%	
Niere	4,7%	
Uro-Genital	1,4%	
Exokrine	1,2%	
CUP (unbekannt)	0,9%	
Endokrine	0,9%	
Oesophagus	0,9%	
sonstige	0,9%	
Sarkom	0,5%	
Lymphom	0,1%	
	100%	

Indikationen

Allgemein:

- Im Rahmen eines gesamt palliativ onkologischen Behandlungskonzeptes.
- Lebensqualität!

Indikationen

Leitlinien Radiochirurgie DGNC, DEGRO, usw

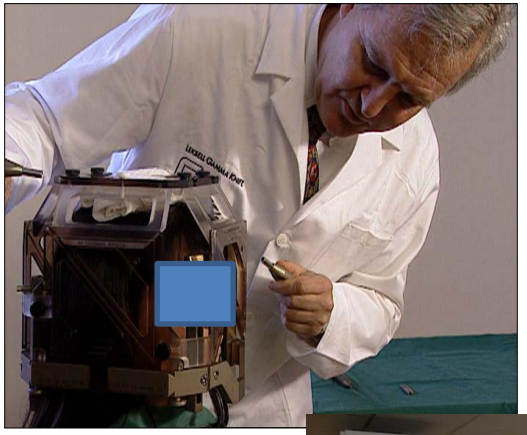
- Gesamt Tumorvolumen, (10 Gy Volumen)
  - *(Bhatnagar et al;2006 IJROBP)*

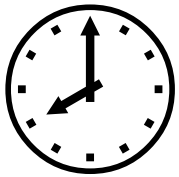
Machbarkeit

- Organisatorisch
- Finanziell
- Intrakranielle Dosisverteilung
- Wirksamkeit
- Toxizität

Machbarkeit

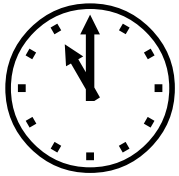
1. Rahmenfixierung



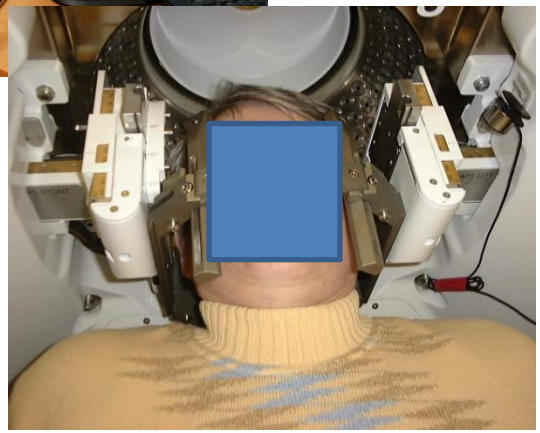


2. Bildgebung

3. Planung



4. Behandlung



ca. 20 min / Meta

Patienten 2007-2017

Patienten	Behandlungen	Metastasen
• 1799	• 2264	• 6968

Behandlungen pro Patient		
1x	1701	75 %
2x	370	16 %
3x	115	5 %
4x	47	2 %
5x	25	1 %
6x	4	
7x	2	
Mittelwert 1,25 Behandlungen pro Patient		

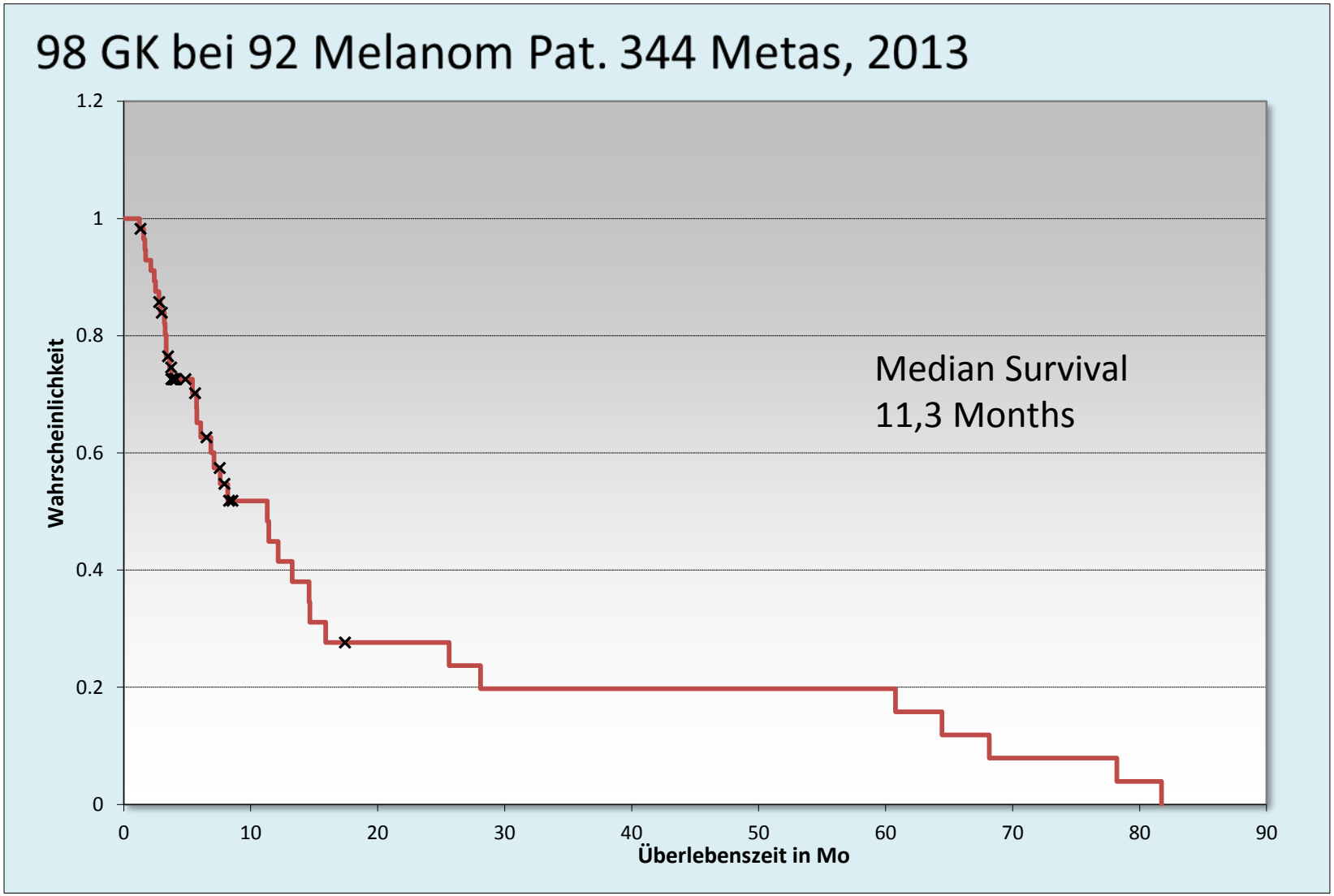
Metastasen pro Behandlung

Metas	GK´s	Metas	GK´s	Metas	GK´s
1	910	6	92	> 10	64
2	460	7	57	>15	13
3	287	8	43	>20	15
4	190	9	28	>25	0
5	108	10	24		
1-5	**1955**	**6-10**	**244**	**>10**	**92**
Mittelwert 3,0 Metastasen pro GK Behandlung					

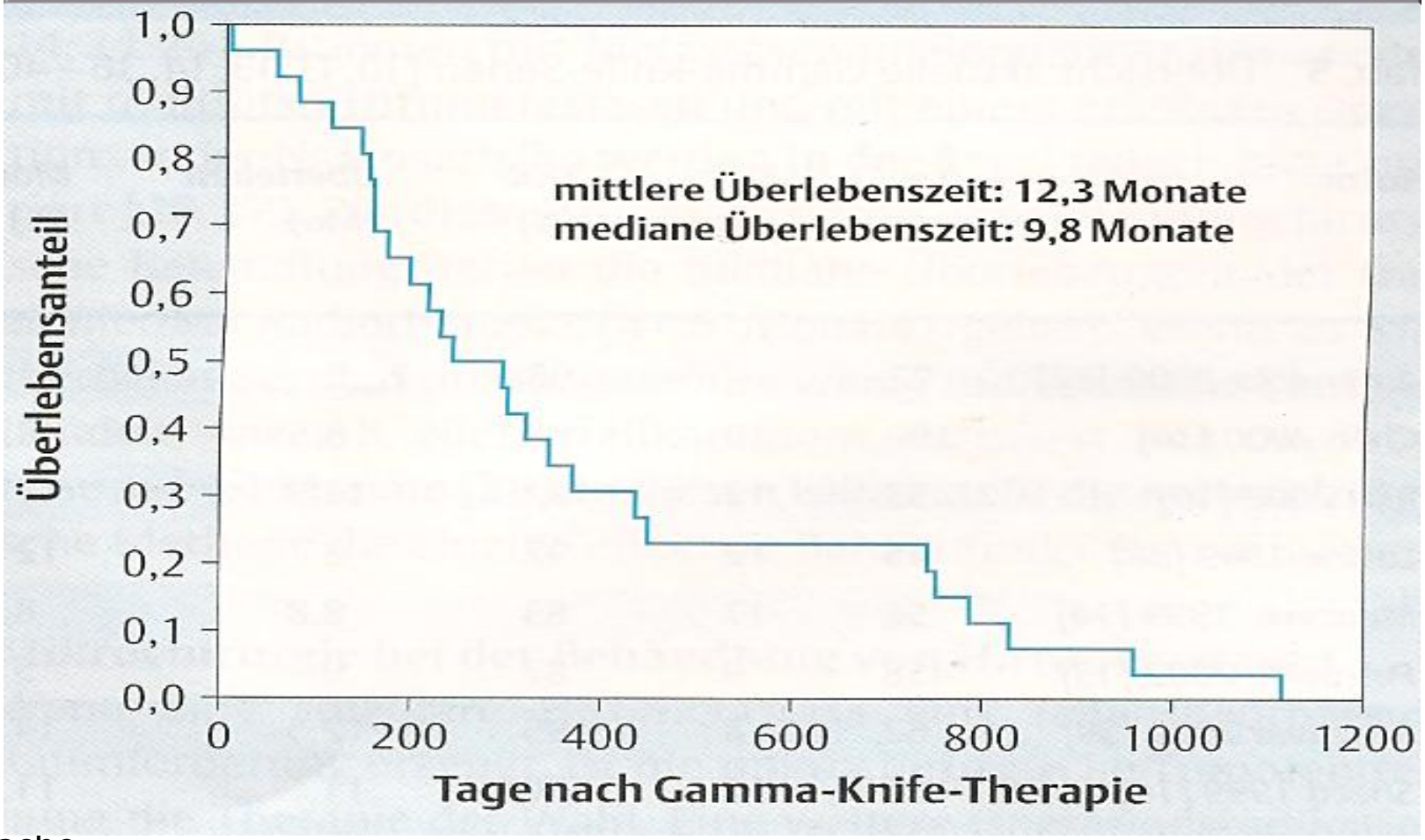
Behandlungsparameter

N=2264	Mittelwert	Standard Abw.	Von -bis
Randdosis	22 Gy	3 Gy	16-25 Gy
Therapeutische Isodosis	50%	13%	40-70%
Max. Dosis	43,5 Gy	5,7 Gy	30-55 Gy
10 Gy Volumen	28,9 ccm	28,4 ccm	1-120 ccm
Integraldosis Schädel	3,1 J	Grob ca. 1 Gy Ganzschädel Dosis	
Tumorvolumen (GTV)	5,3 ccm	6,6 ccm	0,02-31,6 ccm
PIV (PTV)	9,0 ccm	10,9 ccm	0,3-20,8 ccm
Nach Operation	27%		
Nach Ganzschädel RT	31%		

Hochrechnung Überlebenszeit nach Kaplan Meier



Kaplan-Meier Überlebenszeit Hochrechnung für 44 Mamma-CA Patientinnen



Todesursache

- 43% intrazerebraler Progress oder Lokalrezidiv
- Von diesen hatten 70% gleichzeitig einen Progress der extrakraniellen Erkrankung

Van Eck et al; Geburth Frauenheilk 2004; 64: 63-69

Machbarkeit

Organisatorisch

Finanziell

Intrakranielle Dosisverteilung

Wirksamkeit

Toxizität

Comparing the cost-effectiveness of two brain metastasis treatment modalities

Vuong DA, Rades D, van Eck AT, Horstmann GA, Busse R; Clin Neurol Neurosurg 2013 Mar;115(3):276-84.

	Resection + WBRT	**Repeated RS**
N =	113	260
N = After propensity score matching	98	98
Mean survival time	13,0	18,4
Mean tumor free survival	10,4	13,8
Average cost	€ 11.647	€ 9.964
LYS (life year safed)	1,08	1,53
Cost per LYS (life year safed)		€-3.740 / LYS

Survival

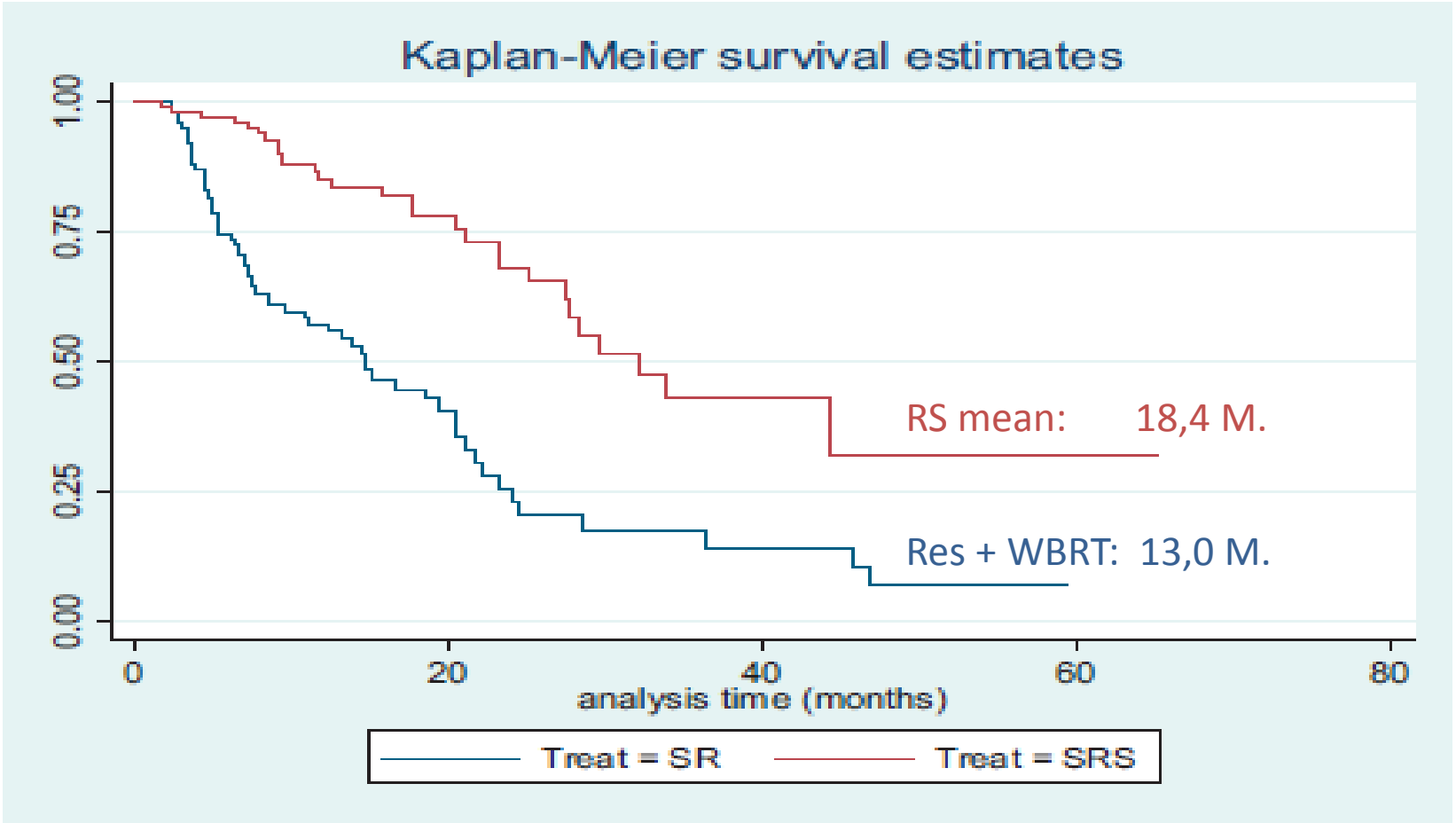


Fig. 2. Survival curves of two treatment groups (adjusted samples) – months post interventions.

Costeffectiveness, GK vs WBRT

2-5 Metastasen

GK vs WBRT

QALY: $ 10.381 vs $17.622

Lee, W. Y., Cho, D. Y., Lee, H. C., Chuang, H. C., Chen, C. C., Liu, J. L., Ho, L. H. (2009). Outcomes and cost-effectiveness of gamma knife radiosurgery and whole brain radiotherapy for multiple metastatic brain tumors. *Journal of Clinical Neuroscience*, *16*(5), 630-634. DOI: 10.1016/j.jocn.2008.06.021

Machbarkeit

Organisatorisch

Finanziell

Intrakranielle Dosisverteilung

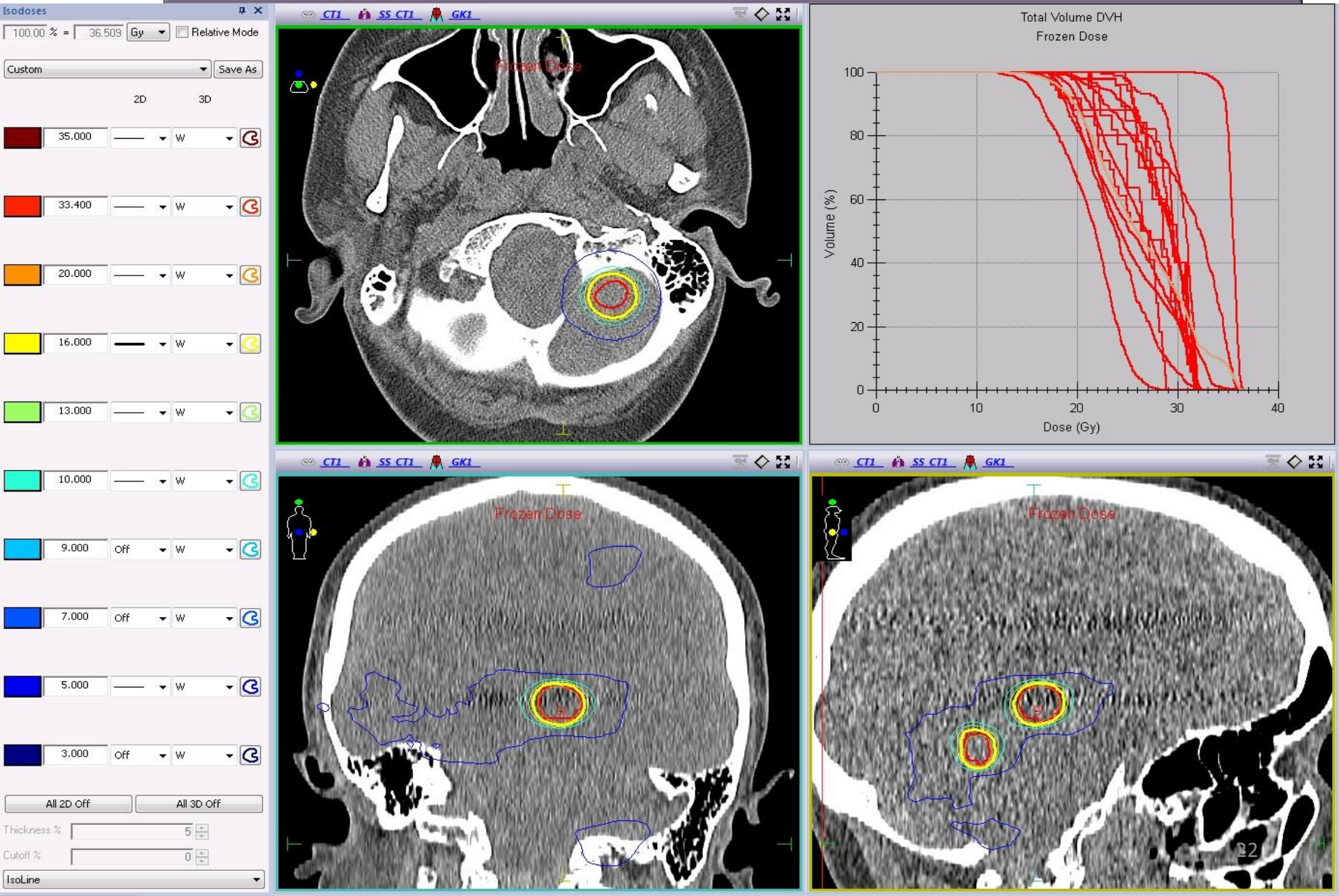
Wirksamkeit

Toxizität

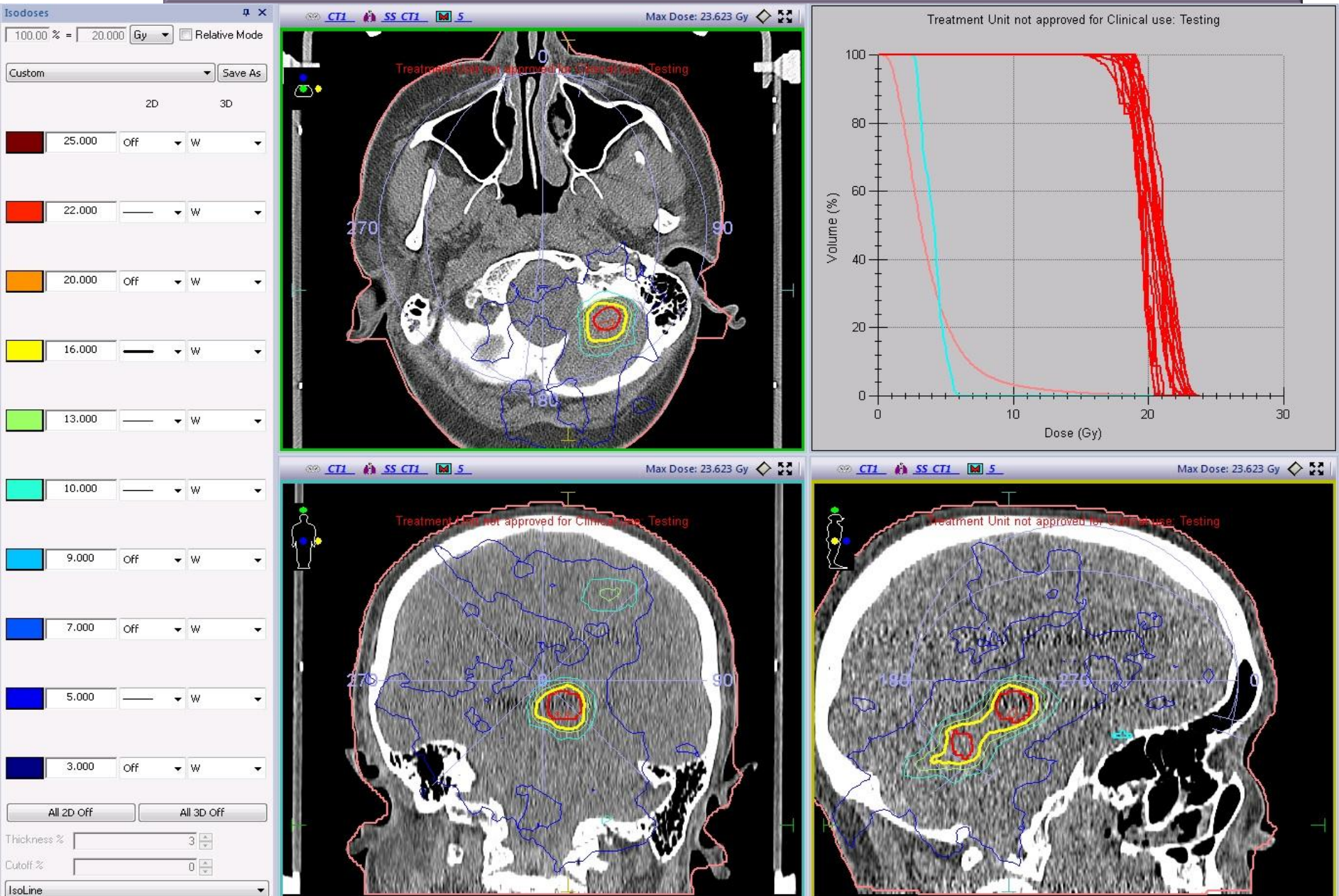
Dosisverteilung

16 Metastasen	Axess-Linac	Gamma Knife Perfection
Planungssystem	Monaco	Gamma Plan
Gesamttumorvolumen	5,68 ccm	5,68 ccm
Geplante Randdosis	16 Gy	16 Gy (auf die 50%)
Mittlere mean Dosis	20,3 Gy	27,8 Gy
Mittlere maximal Dosis	23,5 Gy	32,5 Gy
Gesamt PTV (PIV)	13,97 ccm	14,8 ccm
10 Gy Volumen Schädel	102,3 ccm	45,12 ccm
5 Gy Volumen Schädel	700 ccm	219 ccm
Integraldosis Schädel	11,25 Joule	7,1 Joule
Mean Dosis Schädel	3,75 Gy	2,2 Gy
Beam on Zeit	ca. 20 min. (doserate: ca 5 Gy/min)	215 min (doserate: 2,73 Gy/min)
Aufwand insgesamt	Ca. 5 Stn.	Ca. 5 Stn.

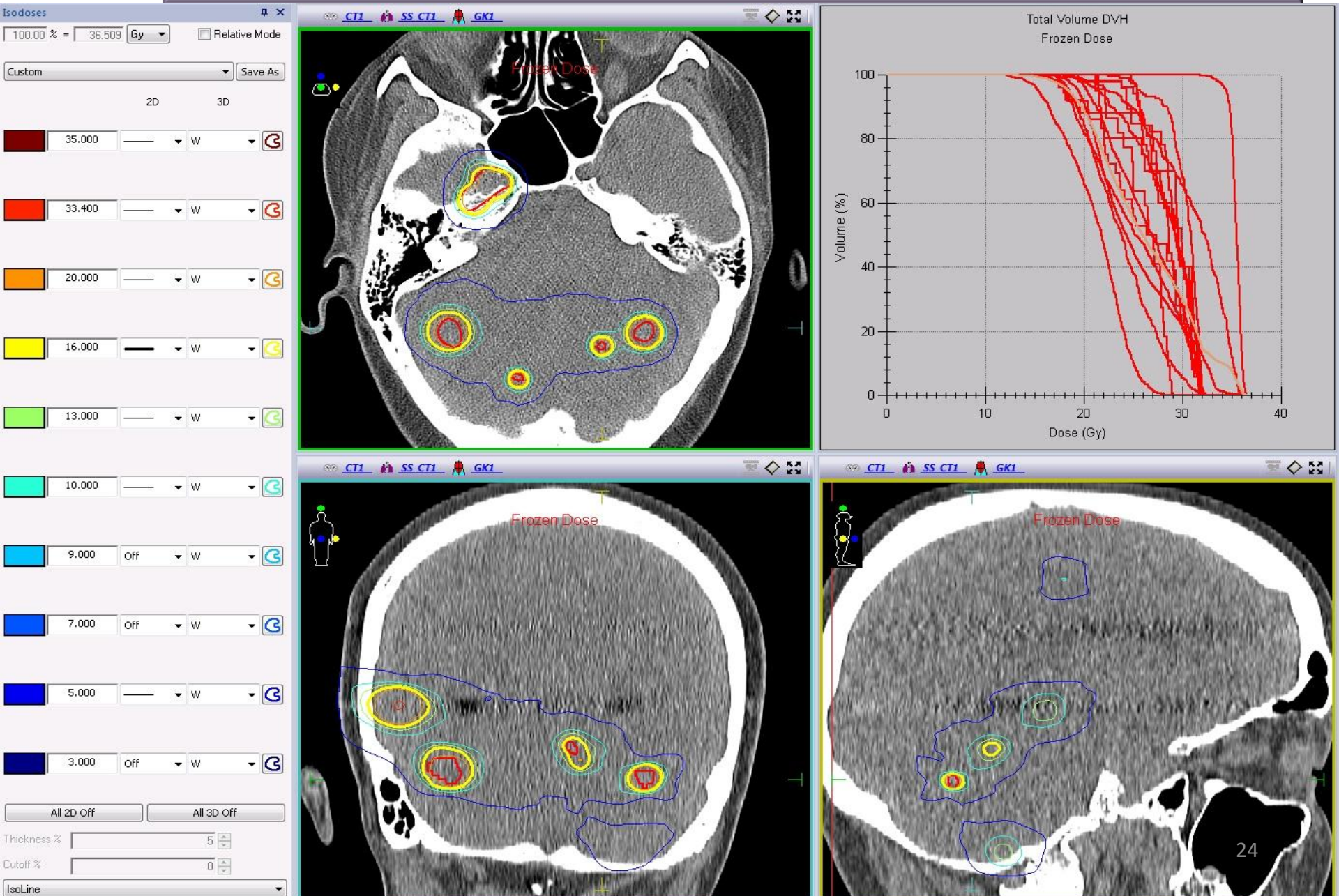
Dosisplan Gamma Knife



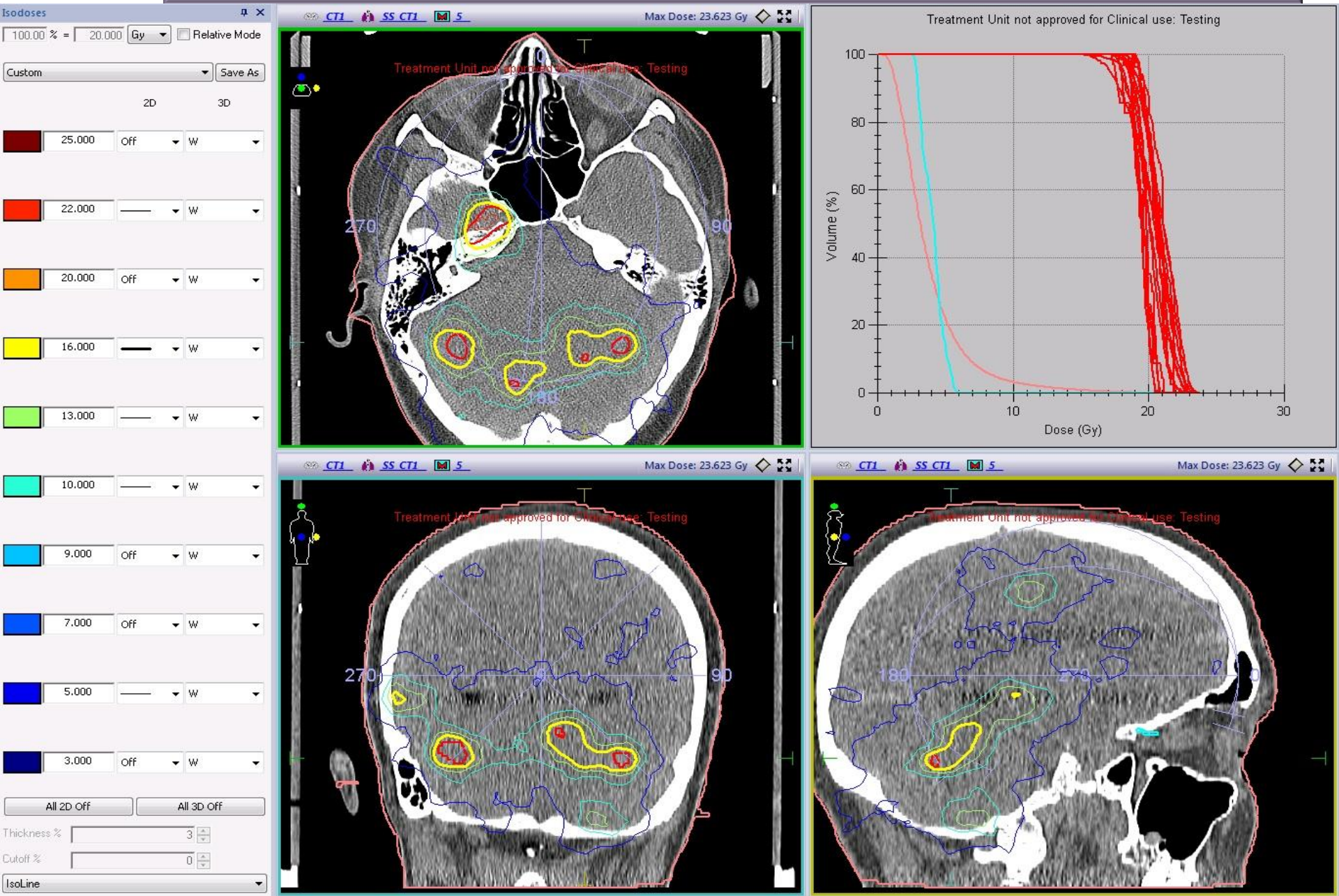
Axess


Isodoses
100.00 % = 20.000 Gy
Relative Mode
Custom
Save As
2D
3D
25.000
22.000
20.000
16.000
13.000
10.000
9.000
7.000
5.000
3.000
Off
W
All 2D Off
All 3D Off
Thickness %
Cutoff %
IsoLine
CT1
SS CT1
5
Max Dose: 23.623 Gy
Treatment Unit not approved for Clinical use: Testing
0
270
90
180
Volume (%)
Dose (Gy)
100
80
60
40
20
0
10
30

Gamma Knife


Isodoses
100.00 % = 36.509 Gy
Relative Mode
Custom
Save As
2D
3D
35.000
33.400
20.000
16.000
13.000
10.000
9.000
7.000
5.000
3.000
Off
W
All 2D Off
All 3D Off
Thickness %
Cutoff %
IsoLine
CT1
SS CT1
GK1
Frozen Dose
Total Volume DVH
Frozen Dose
Volume (%)
Dose (Gy)
0
10
20
30
40
60
80
100

Axess


Isodoses
100.00 % = 20.000 Gy
Relative Mode
Custom
Save As
2D
3D
25.000
22.000
20.000
16.000
13.000
10.000
9.000
7.000
5.000
3.000
Off
W
All 2D Off
All 3D Off
Thickness %
Cutoff %
IsoLine
CT1
SS CT1
5
Max Dose: 23.623 Gy
Treatment Unit not approved for Clinical use: Testing
270
90
180
Volume (%)
Dose (Gy)
0
10
20
30
40
60
80
100

Machbarkeit

Organisatorisch

Finanziell

Intrakranielle Dosisverteilung

Wirksamkeit

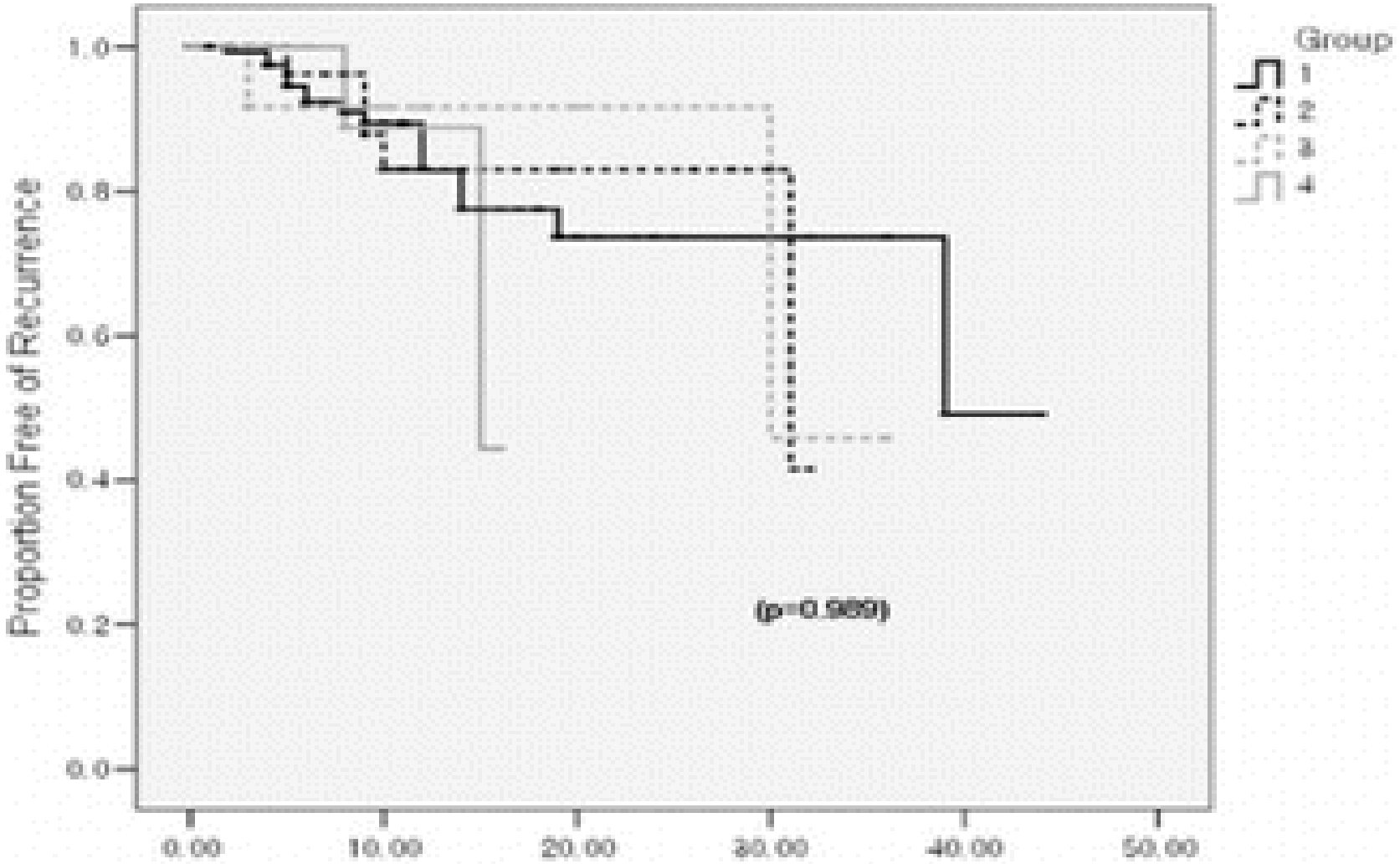
Toxizität

Wirksamkeit

Variable	Median Survival in Mo. (95% CI)	Median Progression-Free Survival in Mo. (95% CI)	No. of Patients w/ Radiation-Induced Change on MRI (%)
Group 1 -5 (N=215)	10.0 (8.3–11.7)	9.0 (6.5–11.5)	17/215 (7.9)
Group 6-10 (N=58)	10.0 (5.9–14.1)	11.0 (8.4–13.6)	6/58 (10.3)
Group 11-15 (N=17)	13.0 (5.5–20.5)	8.0 (2.9–13.1)	2/17 (11.8)
Group >15 (N=33)	8.0 (5.2–10.8)	6.0 (4.6–7.4)	1/33 (3.0)
p value	0.554	0.028	NA

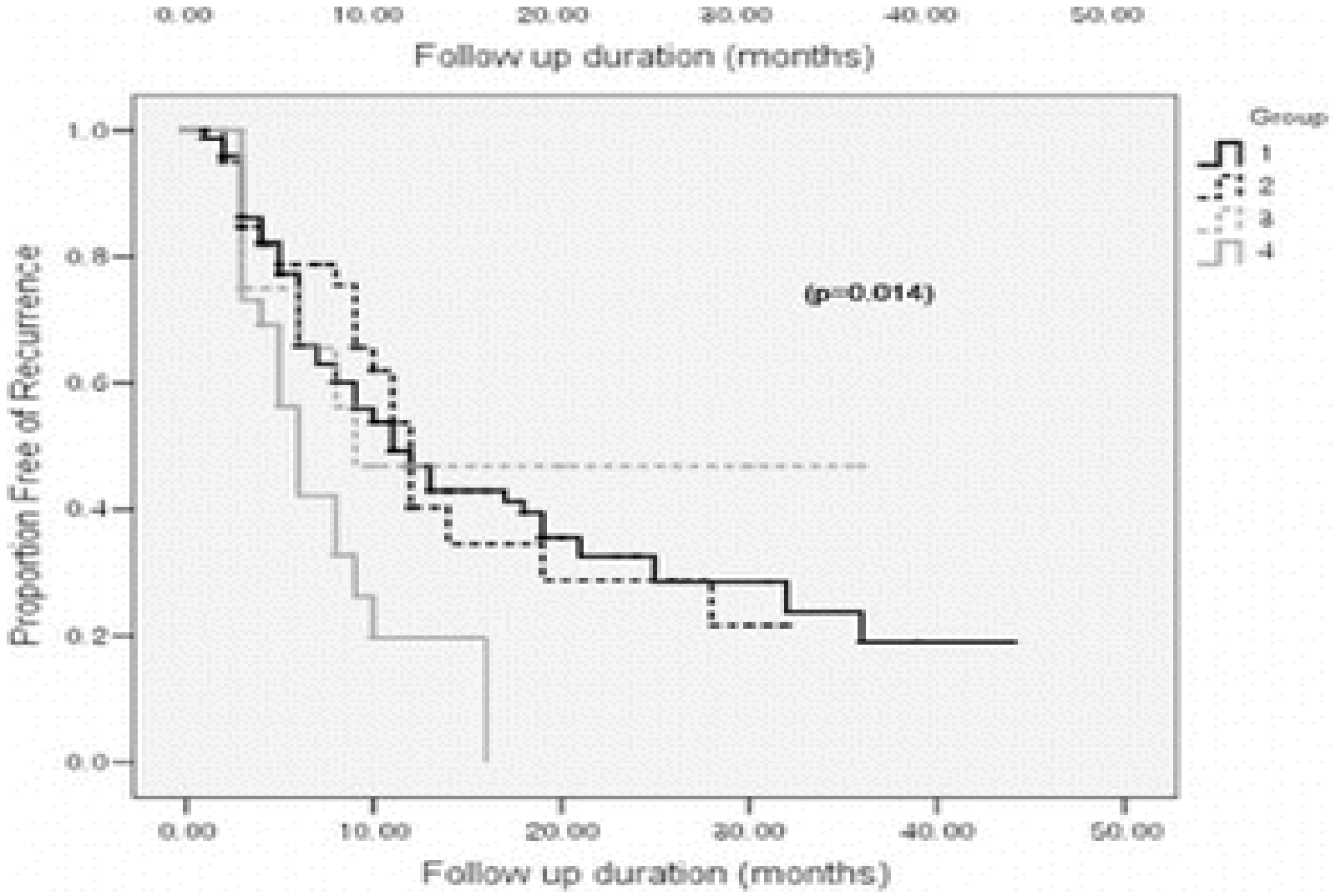
Chang et al: J Neurosurg/vol 113/dec 2010

Local tumor control



Chang et al: J Neurosurg/vol 113/dec 2010

Remote Tumor control



Chang et al: J Neurosurg/vol 113/dec 2010

Machbarkeit

Organisatorisch

Finanziell

Intrakranielle Dosisverteilung

Wirksamkeit

Toxizität

Toxizität

- Treten bei Einzeit-Behandlungen von multiplen Metastasen häufiger Nebenwirkungen auf?
- Treten andere Nebenwirkungen auf, z.B. Leukenzephalopathie?

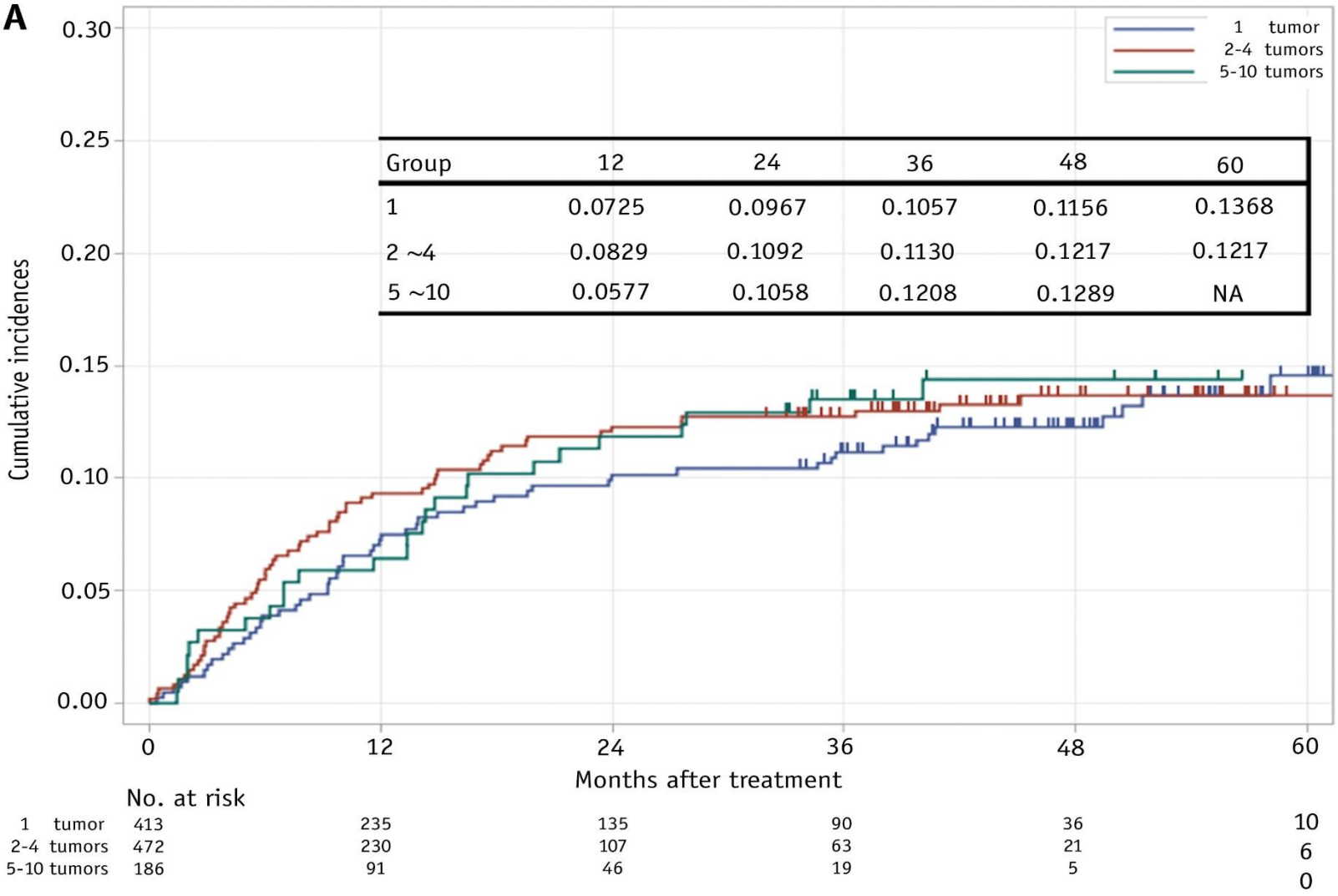
A Multi-institutional Prospective Observational Study of Stereotactic Radiosurgery for Patients With Multiple Brain Metastases (JLGK0901 Study Update): Irradiation-related Complications and Long-term Maintenance of Mini-Mental State Examination Scores

Masaaki Yamamoto, MD, PhD, Toru Serizawa, MD, PhD, Yoshinori Higuchi, MD, PhD, Yasunori Sato, PhD, Jun Kawagishi, MD, PhD, Kazuhiro Yamanaka, MD, PhD, Takashi Shuto, MD, PhD, Atsuya Akabane, MD, PhD, Hidefumi Jokura, MD, PhD, Shoji Yomo, MD, PhD, Osamu Nagano, MD, PhD, Hidefumi Aoyama, MD, PhD

International Journal of Radiation Oncology • Biology • Physics
Volume 99, Issue 1, Pages 31-40 (September 2017)
DOI: 10.1016/j.ijrobp.2017.04.037

1194 Patienten

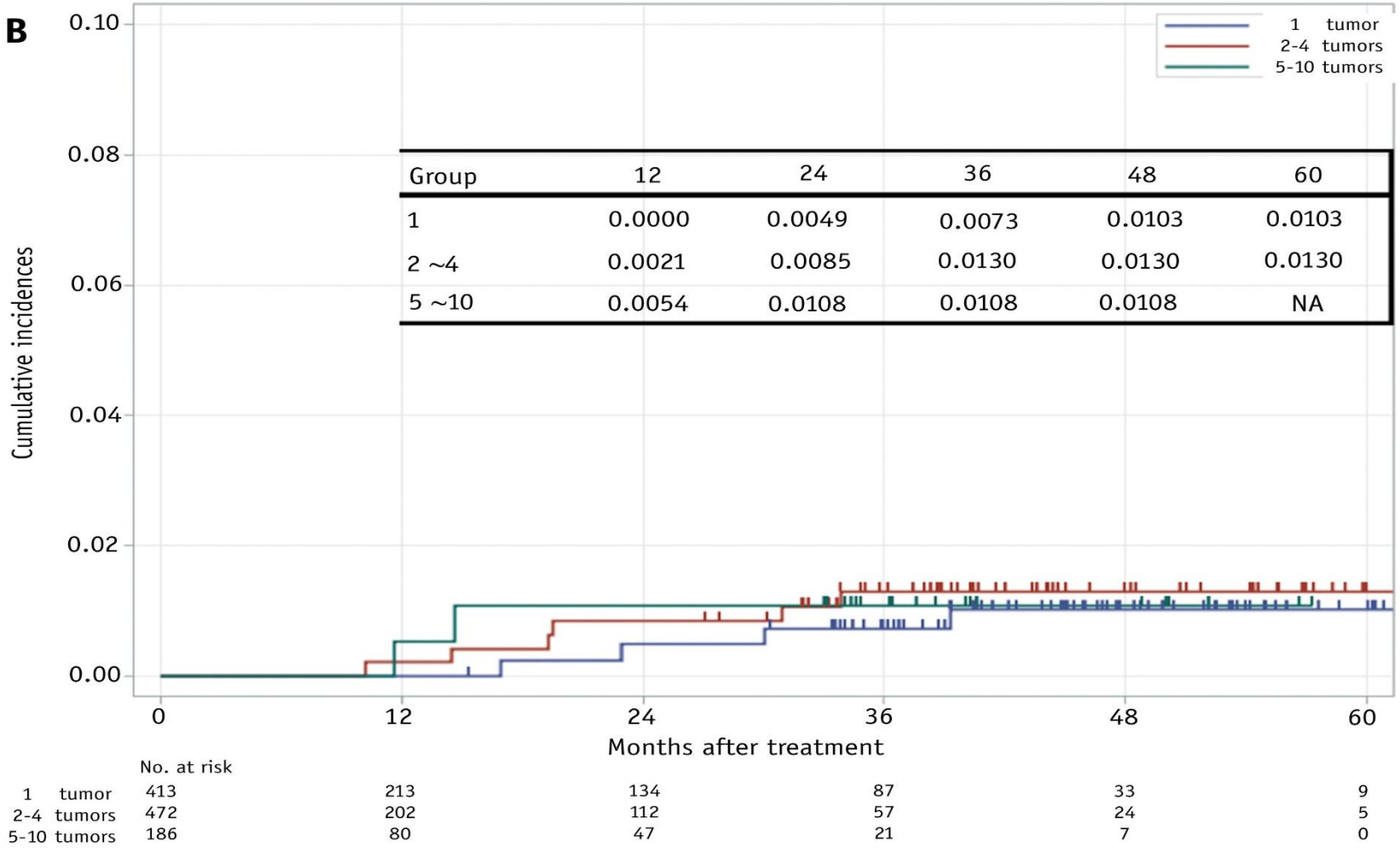
Kaplan Meier Toxizität Hochrechnung



Group	12	24	36	48	60
1	0.0725	0.0967	0.1057	0.1156	0.1368
2 ~4	0.0829	0.1092	0.1130	0.1217	0.1217
5 ~10	0.0577	0.1058	0.1208	0.1289	NA

Yamamoto et al. *International Journal of Radiation Oncology • Biology • Physics*
Volume 99, Issue 1, Pages 31-40 (September 2017) DOI: 10.1016/j.ijrobp.2017.04.037

Kaplan Meier Leukenceph. Hochrechnung

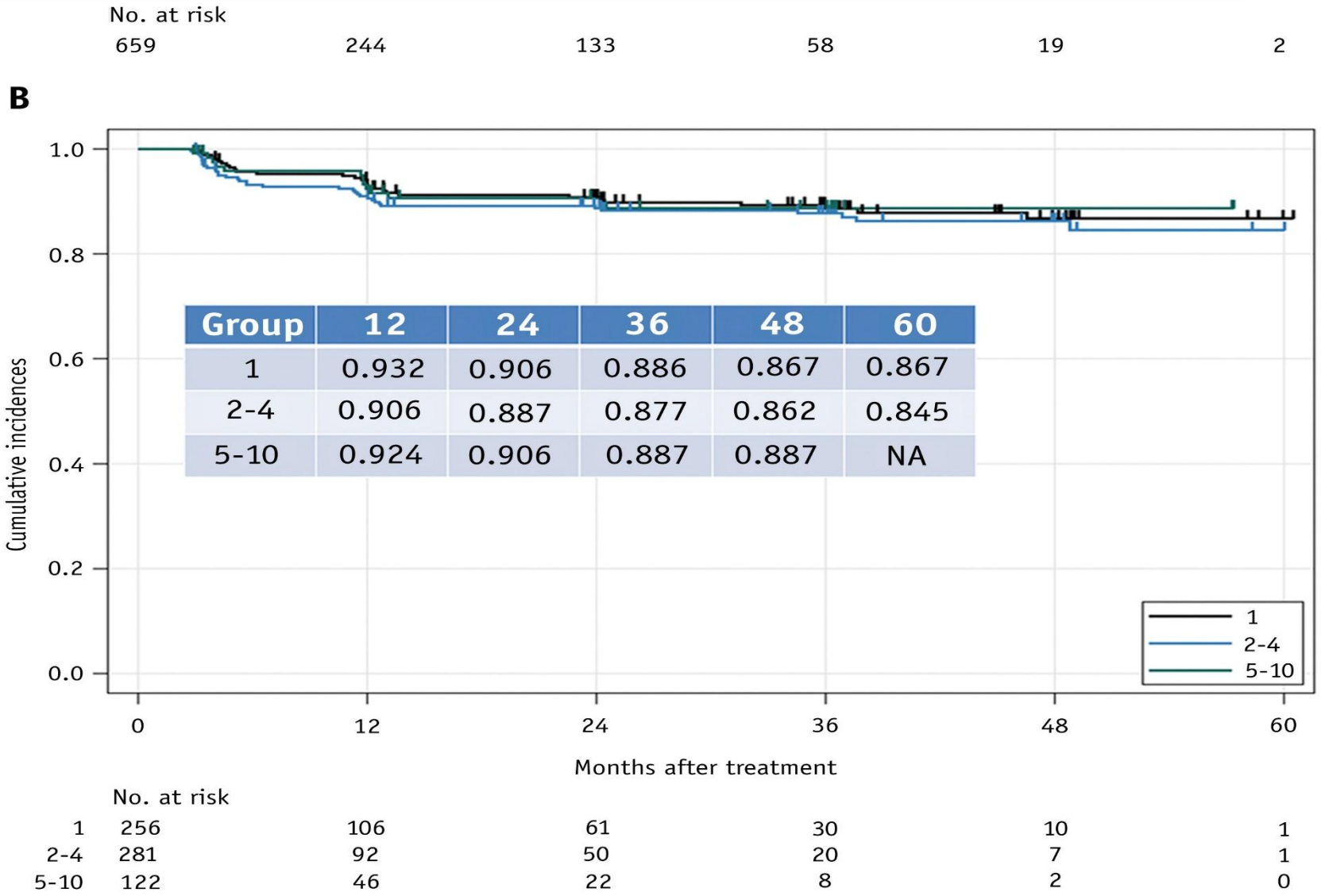


Group	12	24	36	48	60
1	0.0000	0.0049	0.0073	0.0103	0.0103
2 ~4	0.0021	0.0085	0.0130	0.0130	0.0130
5 ~10	0.0054	0.0108	0.0108	0.0108	NA

No. at risk						
1 tumor	413	213	134	87	33	9
2-4 tumors	472	202	112	57	24	5
5-10 tumors	186	80	47	21	7	0

Yamamoto et al. *International Journal of Radiation Oncology • Biology • Physics*
Volume 99, Issue 1, Pages 31-40 (September 2017) DOI: 10.1016/j.ijrobp.2017.04.037

Kaplan Meier Toxizität Hochrechnung MMSE



Yamamoto et al. *International Journal of Radiation Oncology • Biology • Physics*
Volume 99, Issue 1, Pages 31-40 (September 2017) DOI: 10.1016/j.ijrobp.2017.04.037

Factor	Univariate		Multivariate	
	HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Age: <65 y vs ≥65 y	1.432 (1.032-1.995)	.032	1.455 (1.045-2.035)	**.027**
Sex: female vs male	1.086 (0.782-1.506)	.62		
KPS: ≤70 vs ≥80	2.134 (1.353-3.339)	.0019	1.065 (0.641-1.710)	.80
Tumor number				
2-4 (group B) vs 1 (group A)	1.186 (0.827-1.706)	.35		
5-10 (group C) vs 2-4 (group B)	1.072 (0.667-1.973)	.77		
Maximum diameter of largest tumor: <1.6 cm vs ≥1.6 cm	0.326 (0.226-0.462)	<.0001	0.375 (0.217-0.667)	**.0011**
Cumulative volume: <1.9 mL vs ≥1.9 mL	0.442 (0.317-0.614)	<.0001	1.748 (0.988-2.961)	.055
Primary tumor category: lung vs non-lung	0.564 (0.401-0.803)	.0017	0.831 (0.583-1.199)	.32
Extracerebral disease status: not vs controlled	0.945 (0.644-1.356)	.76		
Neurologic symptoms: no vs yes	0.288 (0.207-0.402)	<.0001	0.413 (0.279-0.614)	**<.0001**
Peripheral dose maximum: <22 Gy vs ≥22 Gy	1.712 (1.216-2.389)	.0023	1.232 (0.860-1.752)	.25
Global maximum dose: <40 Gy vs ≥40 Gy	1.015 (0.721-1.416)	.93		
Skull volume receiving >5 Gy: <31 mL vs ≥31 mL	0.424 (0.299-0.594)	<.0001	0.798 (0.488-1.305)	.37
Systemic anticancer agent treatment: no vs yes	1.132 (0.746-1.666)	.55		

Machbar?

Organisatorisch? Ja

Kosteneffizienz? J/N

Dosisverteilung? Ja

Effektiv?

- lokaler Tumor Kontrolle: Ja
- Neuauftreten von Tumoren bei > 15 Tumoren: eher nicht

Sicher? Ja

Sinnvoll?

Alternative? WBRT?

QOL

Patientenwunsch

Vielen Dank !

Gamma Knife
Zentrum Krefeld

www.gamma-knife.de