



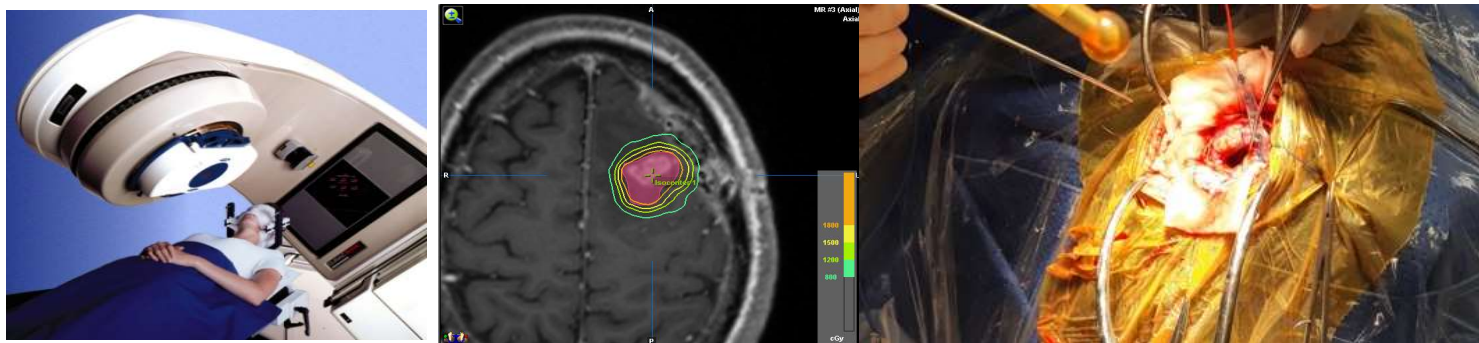
Radioterapia Intraoperatória nos Tumores Cerebrais

Douglas Guedes de Castro



RTIO nos Tumores Cerebrais

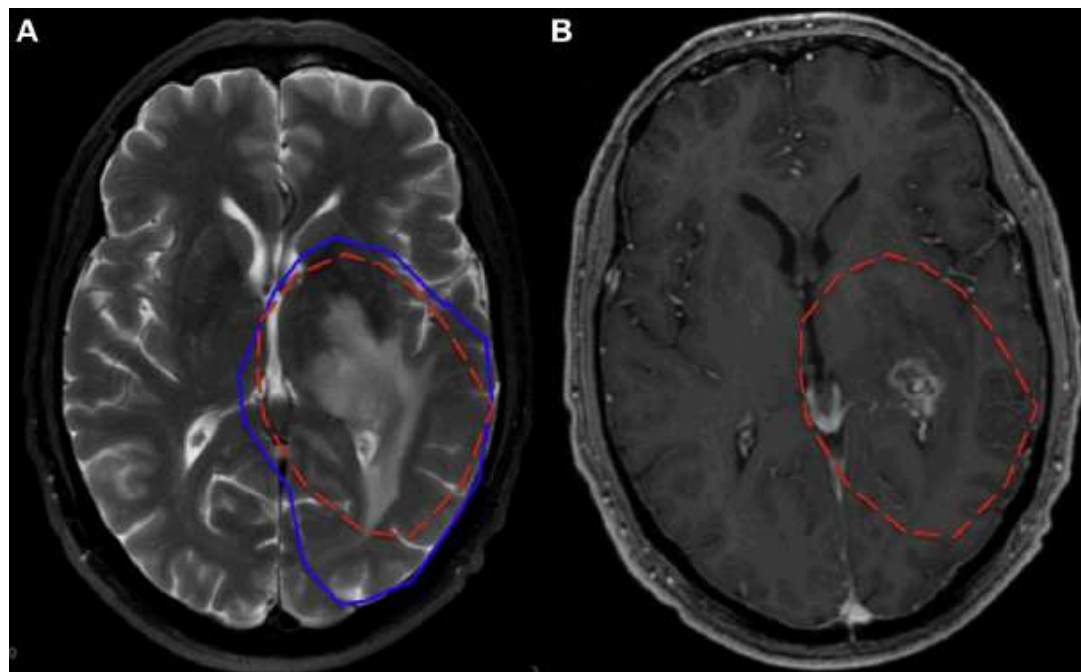
- RTIO Cerebral: relatos iniciais há cerca 40 anos (Matsutani M et al., Japão)
- Desenvolvimento técnico e difusão do método nos últimos 20 anos
- Premissas: precisão, conformidade e rápido gradiente de dose



RTIO nos Glioblastomas

**Fator limitante ao escalonamento de dose:
volume irradiado**

Padrão de falha após teleterapia

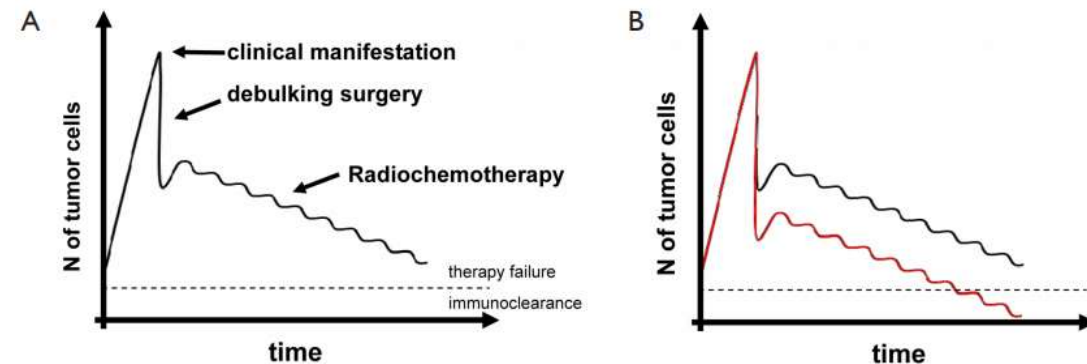


Volumes: A (RTOG) e B (EORTC)

Recurrence volume within field (%)	MDACC 50 Gy	RTOG 46 Gy
Central (>95)	40	40
In-field (80–95)	3	3
Marginal (20–80)	3	3
Distant (<20)	2	2

RTIO nos Glioblastomas

Volume tumoral durante o tratamento



Séries de RTIO nos GBMs

Study	N of Pat.	Delivery technique	Controls	Dose (mean or range) (Gy)	Prescription depth (cm)	Other therapies	1y/2y/3y survival rates (%)	Median OS (mo)	P
Sakai <i>et al.</i> 1989 (29)	11 ^(B)	IOERT	--	15-50	1-2	STR, EBRT	80 /50/n.r.	n.r.	--
Sakai <i>et al.</i> 1991 (36)	26 ^(B)	IOERT	16 (all GBM)	26.7	1-2	STR, EBRT, ACNU	n.r./48.4/25.8 (IOERT); n.r./23.7/14.6 (ctrl.)	22.4 (IOERT); 15.9 (ctrl.)	<0.01
Matsutani <i>et al.</i> 1994 (28)	30 ^(B)	IOERT	--	17	2.6±1.0	STR, EBRT, CHT	100/80/60 (with RN); 95/51/15 (without RN)	45 (with RN); 29 (without RN)	0.04
Shibamoto <i>et al.</i> 1994 (31)	6	IOERT	--	23-40	0.5-1.5	2 PR, 4 STR	n.r.	17	--
Fujiwara <i>et al.</i> 1995 (30)	13	IOERT	16 (AA and GBM)	25	2-3	STR, EBRT, CHT	n.r.	14 (IOERT); 10 (ctrl.)	<0.05
Ortiz de Urbina <i>et al.</i> 1995 (32)	7 ^(B)	IOERT	--	10-20	1-2	STR, EBRT	56/n.r./n.r. (primary) ^(B, D) ; 47/n.r./n.r. (recurrent) ^(B, D)	13 ^(B)	--
Chung <i>et al.</i> 1995 (38)	4	IOERT	--	15	n.r.	STR, EBRT	n.r.	3	--
Gouda <i>et al.</i> 1997 (35)	7 ^(B)	IOERT	--	10-20	1	STR, CHT	n.r.	n.r.	--
Takakura and Kubo 2000 (39)	19	INTRABEAM	Japanese tumor registry	n.r.	n.r.	STR, ACNU/ vincristine	n.r./42/n.r. (IOERT); n.r./21%/n.r. (registry)	n.r.	--
Nemoto <i>et al.</i> 2002 (33)	21	IOERT	42 (historical ctrl.)	15	1-3	STR, EBRT	63/26 /n.r. (IOERT); 70 /18/n.r. (ctrl.)	13.3 (IOERT); 14.6 (ctrl.)	>0.05
Schueller <i>et al.</i> 2005 (37)	45	IOERT	32 (all GBM)	20	1-2	STR, EBRT	59/6.8/n.r. (IOERT); 31.3/12.5 n.r. (ctrl.)	14.2 (IOERT); 9.33 (ctrl.)	0.28
Lyons <i>et al.</i> 2012 (40)	35 ^(B)	INTRABEAM	38 (all GBM)	11.1	0.5	STR, PDT, undefined standard therapy	26.7/7/n.r. (all GBM)	19.8 mo (IORT + PDT); 12 mo (IORT); 5 mo (ctrl.)	--
Total	224								

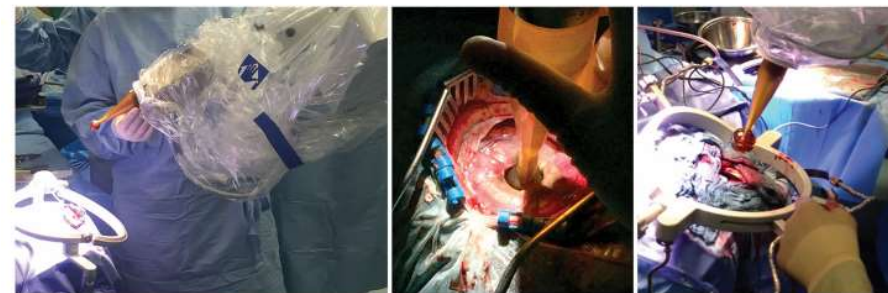
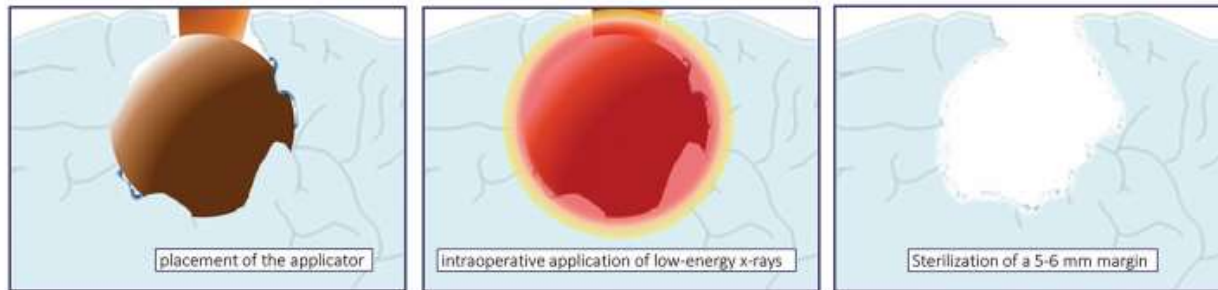
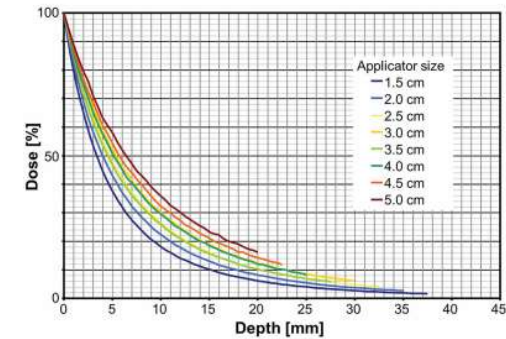
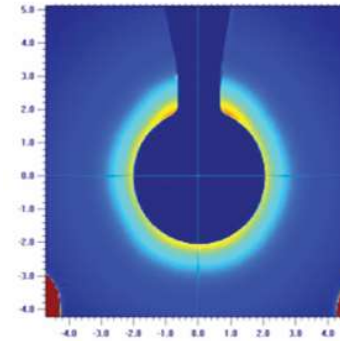
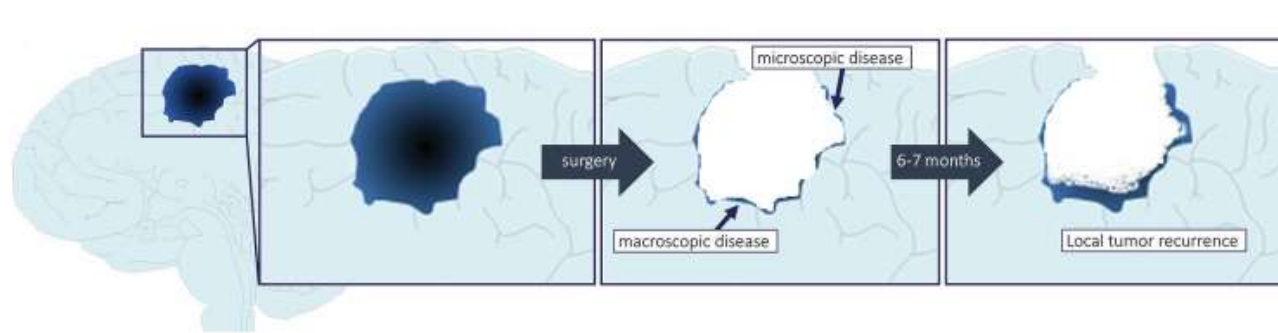
RTIO nos Glioblastomas

Intraoperative Radiotherapy in Newly Diagnosed Glioblastoma (INTRAGO): An Open-Label, Dose-Escalation Phase I/II Trial

- Avaliação da segurança e tolerância com IORT após ressecção inicial de GBM
- Dose de 20-40 Gy com fótons de baixa energia (50 kV) em adição ao tratamento padrão
- 15 pacientes tratados com 3 níveis de dose: 20, 30 e 40 Gy

RTIO nos Glioblastomas

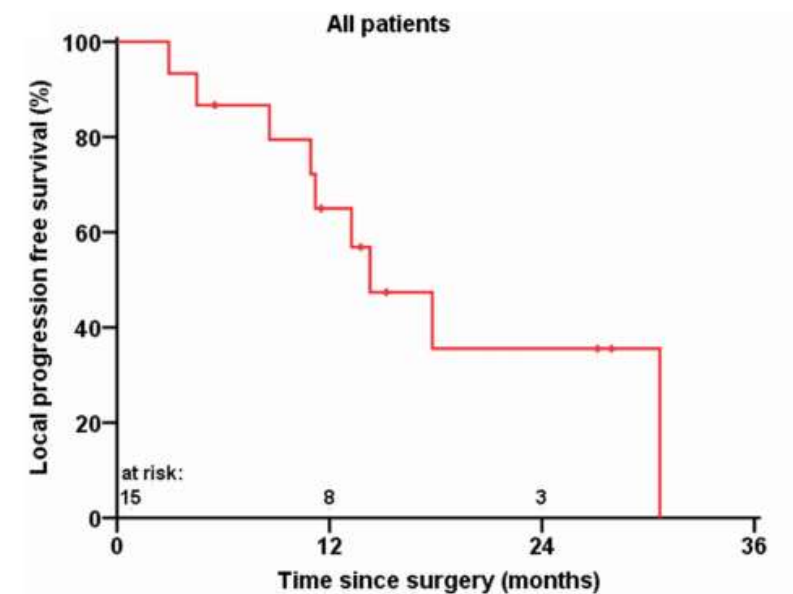
Intraoperative Radiotherapy in Newly Diagnosed Glioblastoma (INTRAGO): An Open-Label, Dose-Escalation Phase I/II Trial



RTIO nos Glioblastomas

Intraoperative Radiotherapy in Newly Diagnosed Glioblastoma (INTRAGO): An Open-Label, Dose-Escalation Phase I/II Trial

Pat. #	Program	Gender	Age [y]	KPS [%]	Satellite EOR	Lesion(s)	MGMT promoter	IORT dose [Gy]	Radio-dose necrosis (Grade)	PPT	N of adjuvant cycles	FU [mo]	Vital status	Cause of death
1	T	F	72	80	IC	yes	M	20	–	No	0	4.5	Deceased	LP
2	T	M	63	60	IC	no	U	20	II°	Yes	13	27.9	Alive	
3	T	F	65	90	IC	yes	M	20	–	Yes	14	27.1	Alive	
4	T	M	60	90	IC	no	n/a	20	III°	Yes	3	17.8	Deceased	DP
5	T	M	65	50	IC	yes	U	30	I°	Yes	6	14.3	Deceased	DP
6	T	F	59	80	CR	yes	U	30	–	Yes	2	13.2	Deceased	DP
7	T	F	68	90	IC	no	U	30	III°	Yes	3	11.2	Deceased	unclear (no LP at death)
8	T	F	46	70	IC	yes	U	40	–	Yes	3	15.2	Alive	
9	T	M	73	90	IC	no	U	40	–	No	0	8.6	Deceased	DP
10	T	F	55	80	IC	no	M	40	–	Yes	8	13.8	Alive	
11	T	M	62	70	IC	yes	U	40	I°	Yes	5	11.5	Alive	
12	T	F	57	90	IC	no	U	30	–	Yes	3	5.5	Alive	
13	CU	M	61	50	IC	no	U	20		No	0	4.5	Deceased	Seizures (no LP at death)
14	CU	M	59	90	CR	no	U	20	–	Yes	14	30.7	Deceased	Sepsis (no LP at death)
15	CU	M	70	90	IC	no	M	20	–	Yes	10	16.2	Deceased	LP
Median [Range]			62 [46-73]	80 [50-90]				25			3	13.8 [4.5-30.7]		

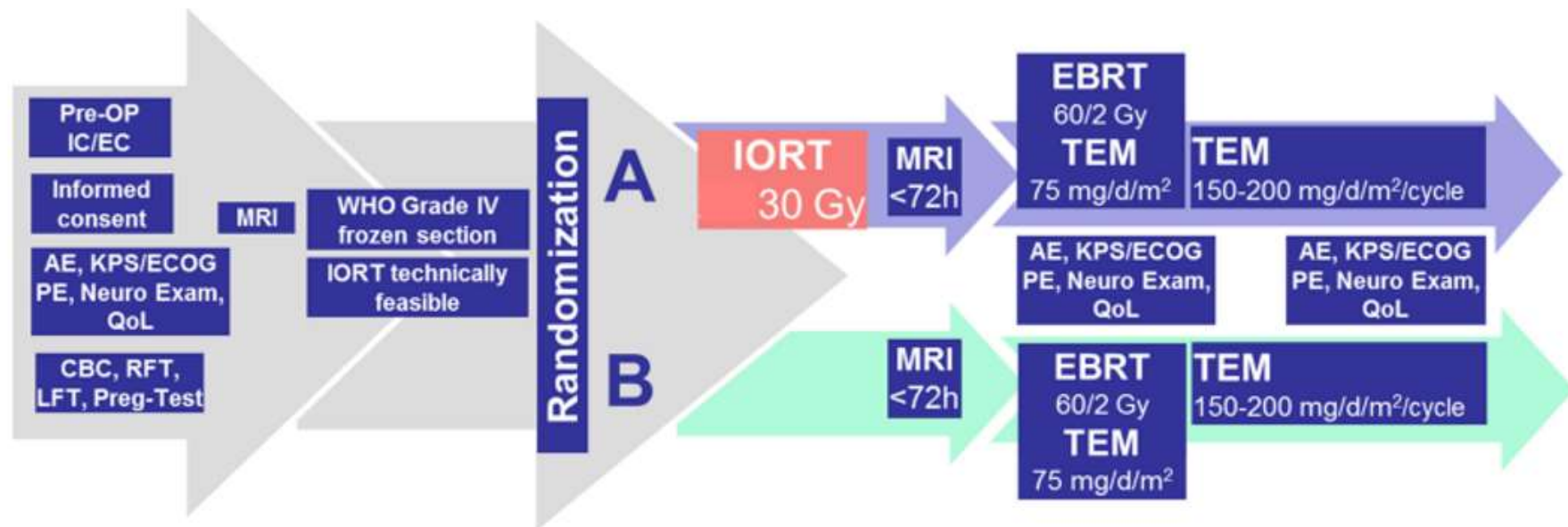


SG: 16,2 meses

Neurosurgery 84:41-9, 2019

RTIO nos Glioblastomas

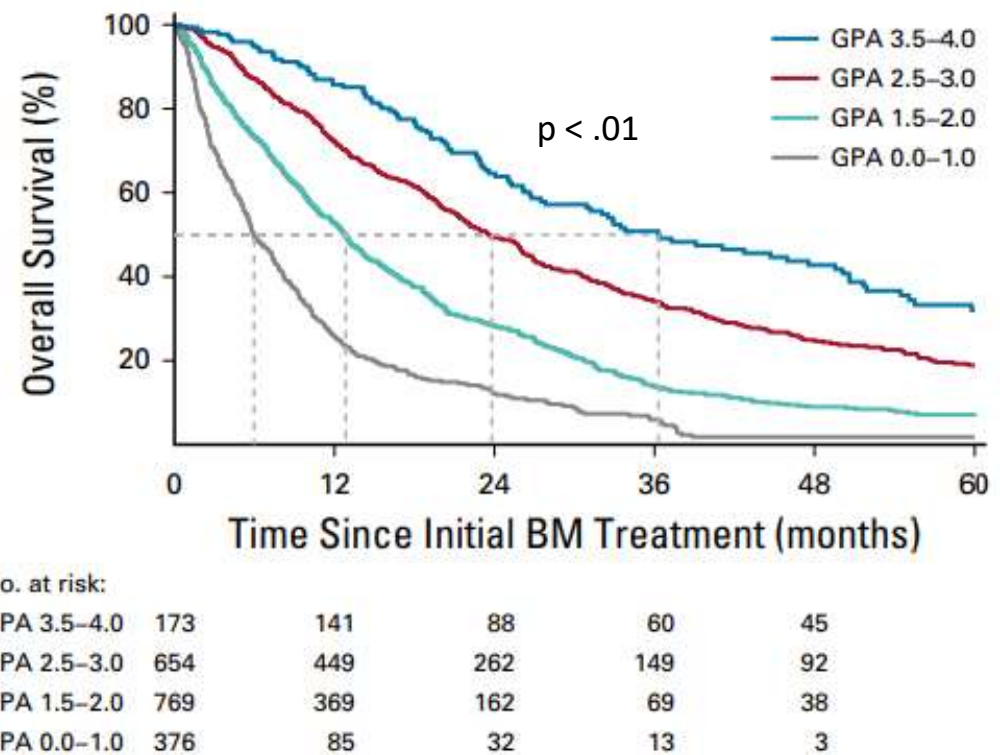
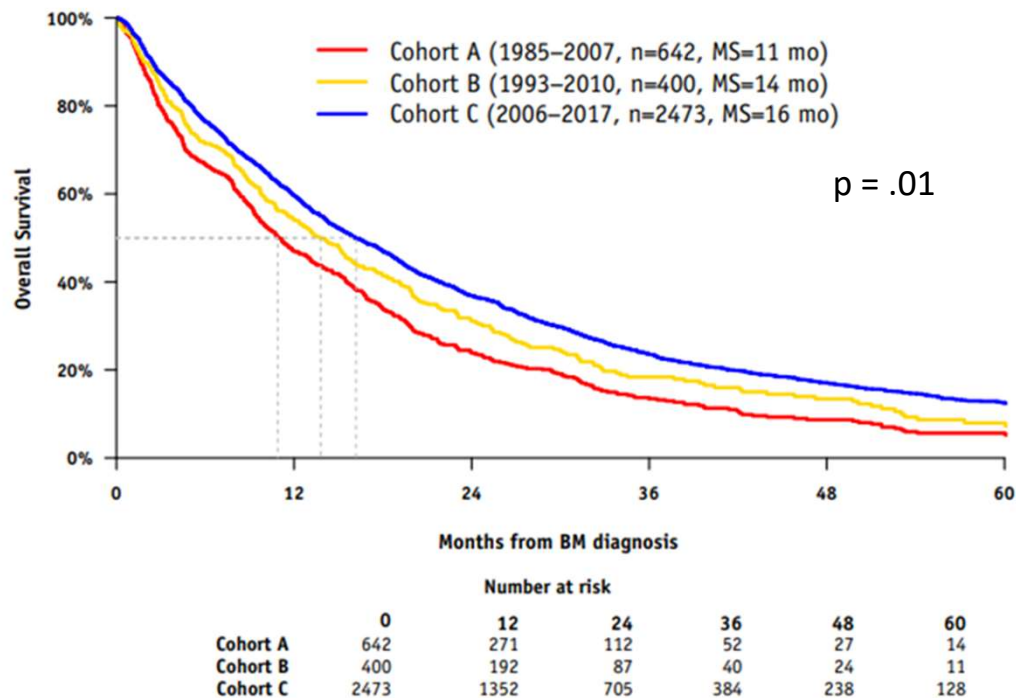
A MULTICENTER RANDOMIZED PHASE III TRIAL ON INTRAOPERATIVE RADIOTHERAPY IN NEWLY DIAGNOSED GLIOBLASTOMA MULTIFORME (INTRAGO II)



- 18 centros no mundo (Brasil – Hospital Alemão Oswaldo Cruz)
- 200/314 pacientes aleatorizados até jun/22

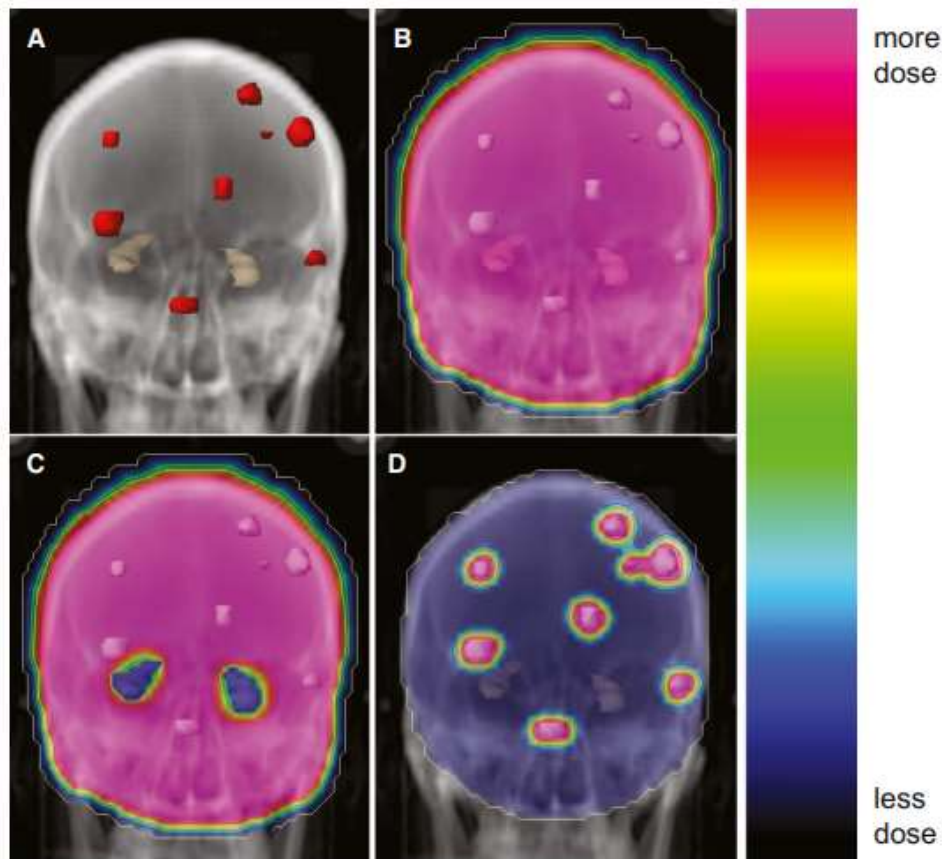
RTIO nas Metástases Cerebrais

- Survival evolution in patients with breast cancer BM (BCBM)



RTIO nas Metástases Cerebrais

Whole-Brain RT x Stereotactic Focal RT

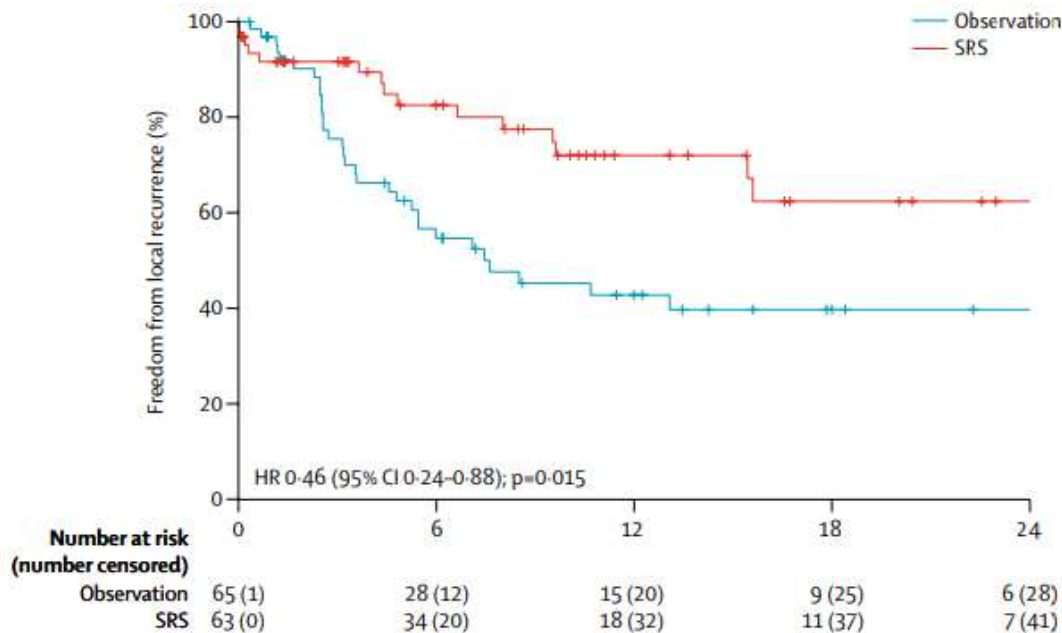


No difference in OS
Strategy: postpone WBRT

RTIO nas Metástases Cerebrais

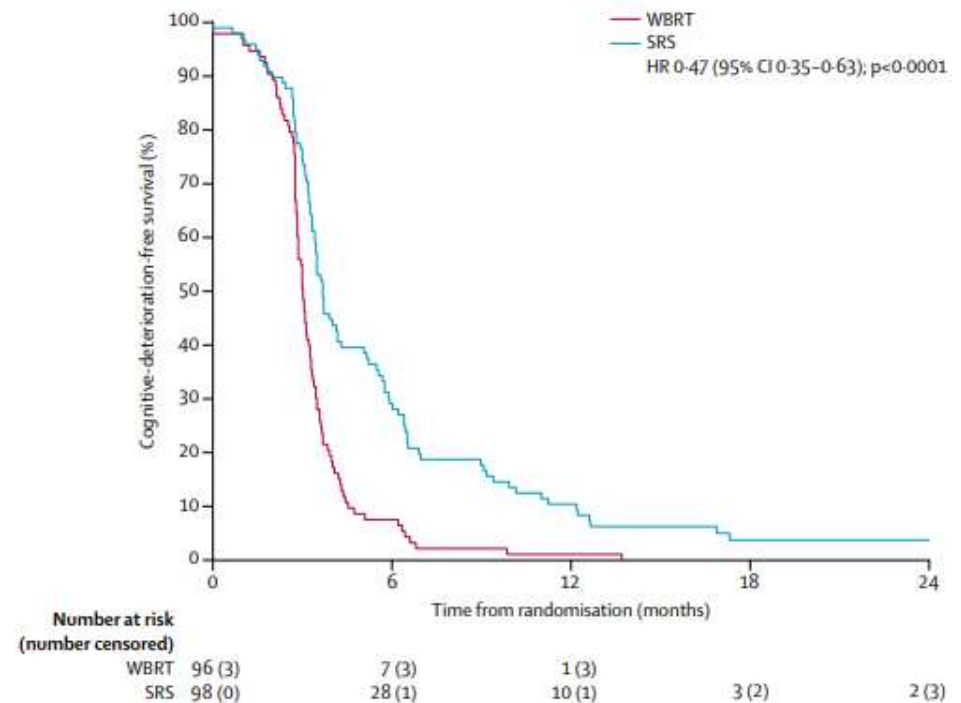
Postoperative Stereotactic RT

Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial



Mahajan A et al. Lancet Oncol 2017;18:1040-8

Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC-3): a multicentre, randomised, controlled, phase 3 trial



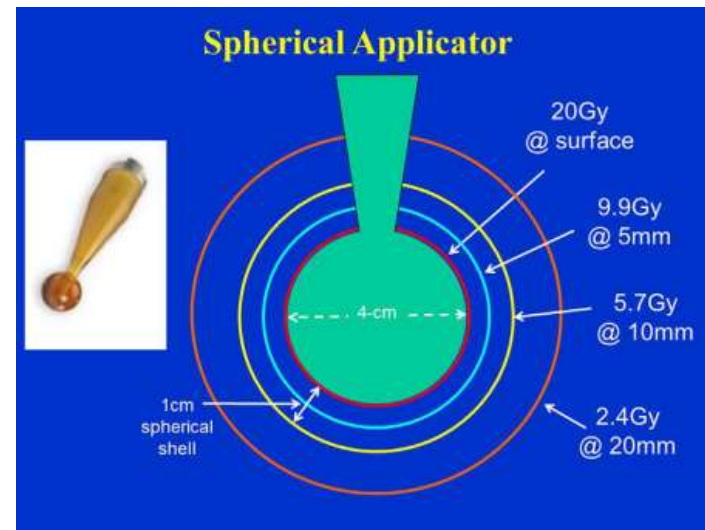
Brown PD et al. Lancet Oncol 2017;18:1049-60

RTIO nas Metástases Cerebrais

- Potential advantages of IORT for BM

- Target-volume definition

- Steep dose fall-off

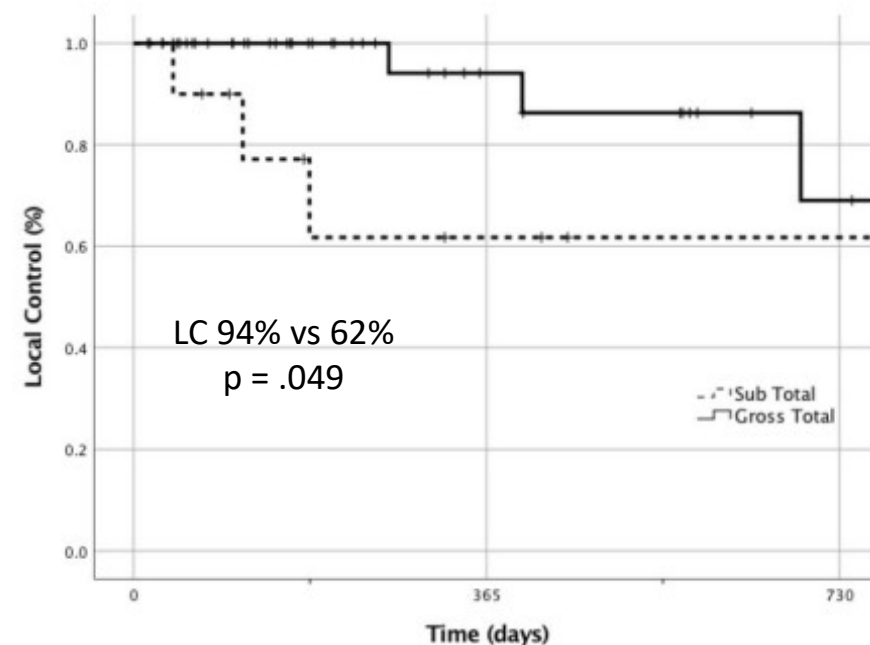
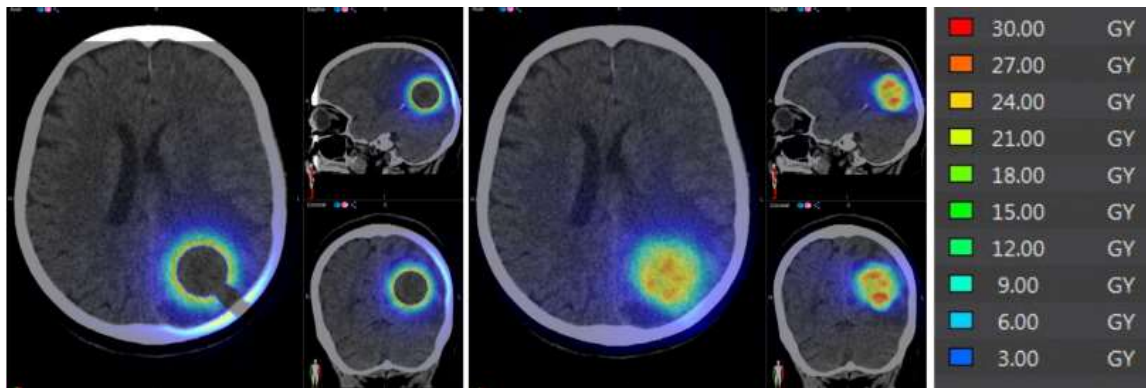


- Convenience and less delay in systemic therapy

RTIO nas Metástases Cerebrais

Intraoperative radiotherapy (IORT) for surgically resected brain metastases: outcome analysis of an international cooperative study

- 54 patients from centers in Germany and USA
- IORT with Intrabeam; Dose: 18-30 Gy @ surface
- FU med: 7.2 months



N at Risk: GTR	44	24	12	10	4
N at Risk: STR	10	3	5	1	1

IORT for Brain Metastases: Final First-Stage Results of a Single-Arm, Open Label, Phase 2 Trial



- **Investigator-initiated research**

- Partially funded by Carl Zeiss Meditec AG

- **Population**

- Adult patients ≥ 18 years
- No previous cranial RT
- One potential BM resection in the presence of up to 10 BM
- Lesions with > 10 mm distance from brainstem and optical pathway

IORT for Brain Metastases: Final First-Stage Results of a Single-Arm, Open Label, Phase 2 Trial

- **Methods**

- Complete resection with histological confirmation
- All patients underwent IORT with Intrabeam
- Dose: 18 Gy @ 1 mm of surface of spherical applicator

- **Endpoints**

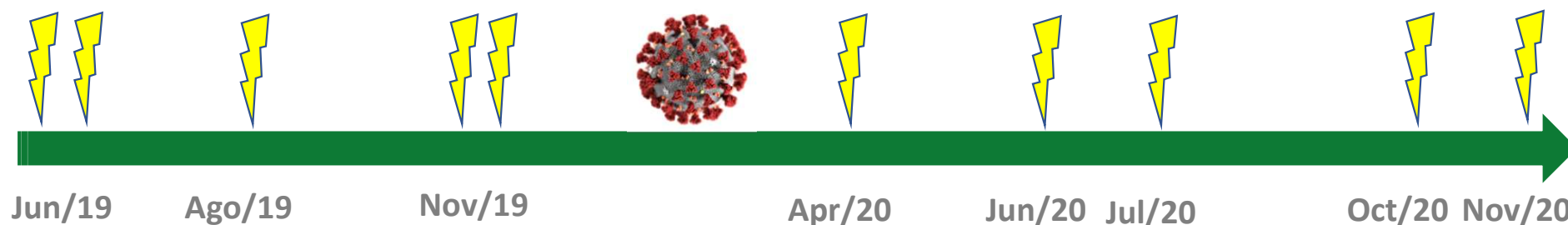
- Primary: Local Failure (LF) and Distant Brain Failure (DBF), death as a competing risk
- Secondary: Overall Survival and Radiation Necrosis (RN)



IORT for Brain Metastases: Final First-Stage Results of a Single-Arm, Open Label, Phase 2 Trial

- Results

- 12 patients screened and 10 accrued between June 2019 and November 2020



IORT for Brain Metastases: Final First-Stage Results of a Single-Arm, Open Label, Phase 2 Trial

- Results

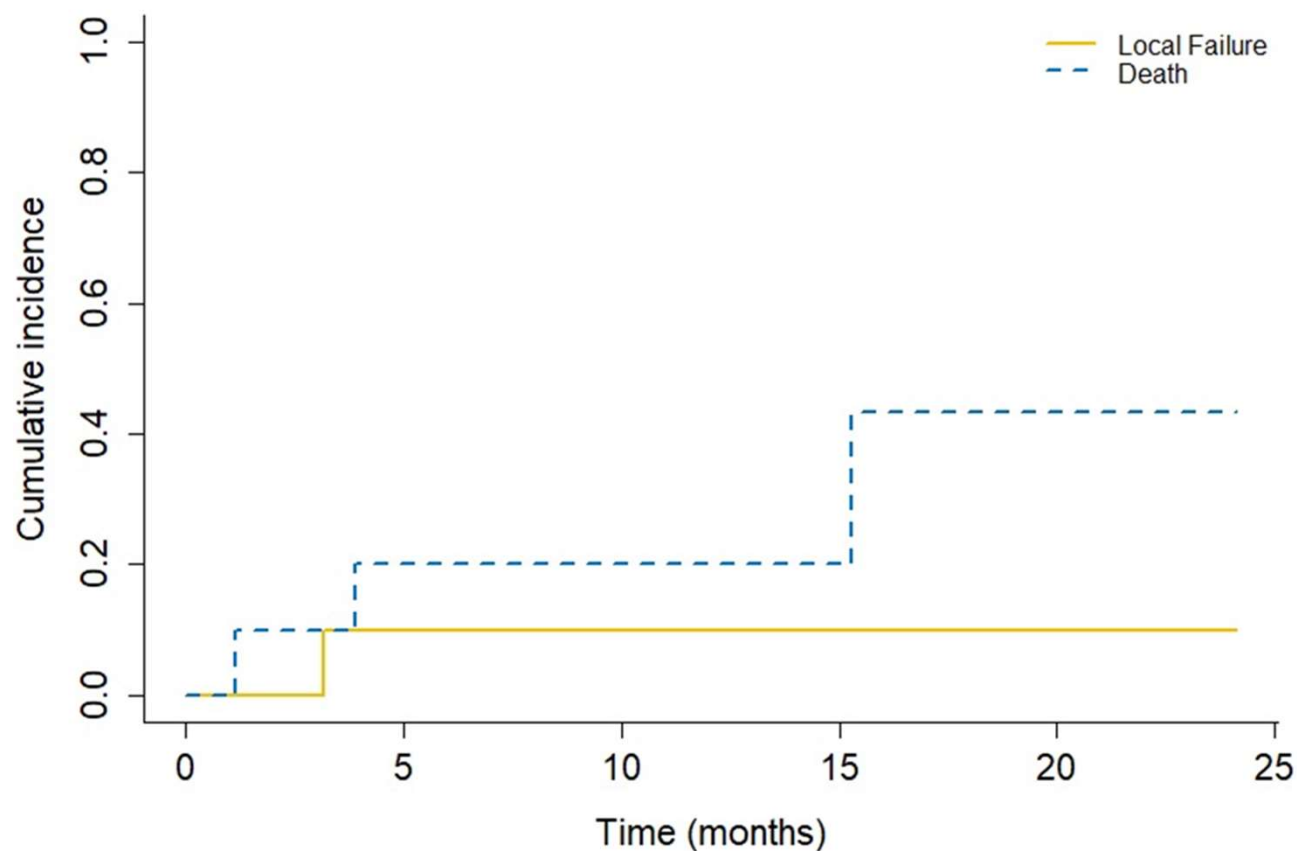
- Patient and Treatment Characteristics

Patient N°	Age	Sex	Primary	DS-GPA	Total N° Lesions	Maximum Lesion Diameter (cm)	Applicator Diameter (cm)	Time (minutes)
1	66	M	Melanoma, BRAF + , ICI	3	9*	4.3	2.5	20
2	61	M	Melanoma, BRAF -, ICI	2.5	1	3	2	14
3	41	F	Lung, squamous	2.5	2	3.9	2.5	20
4	71	M	Colon	1.5	2*	2.2	1.5	8
5	42	F	Endometrium	4	2	2.6	2	14
6	55	F	Breast, luminal B	3.5	1	3.2	1.5	8
7	67	M	Lung, adenoca., ICI	2	7	2.2	1.5	8
8	70	M	Lung, adenoca., ICI	1	1	3.4	1.5	8
9	46	F	Lung, adenoca.	2.5	2*	3	2.5	20
10	27	F	Breast, triple negative	3.5	1	5.3	2.5	20
Median	58	-	-	-	2	3.1	-	13.5

IORT for Brain Metastases: Final First-Stage Results of a Single-Arm, Open Label, Phase 2 Trial

- Results of Local Failure

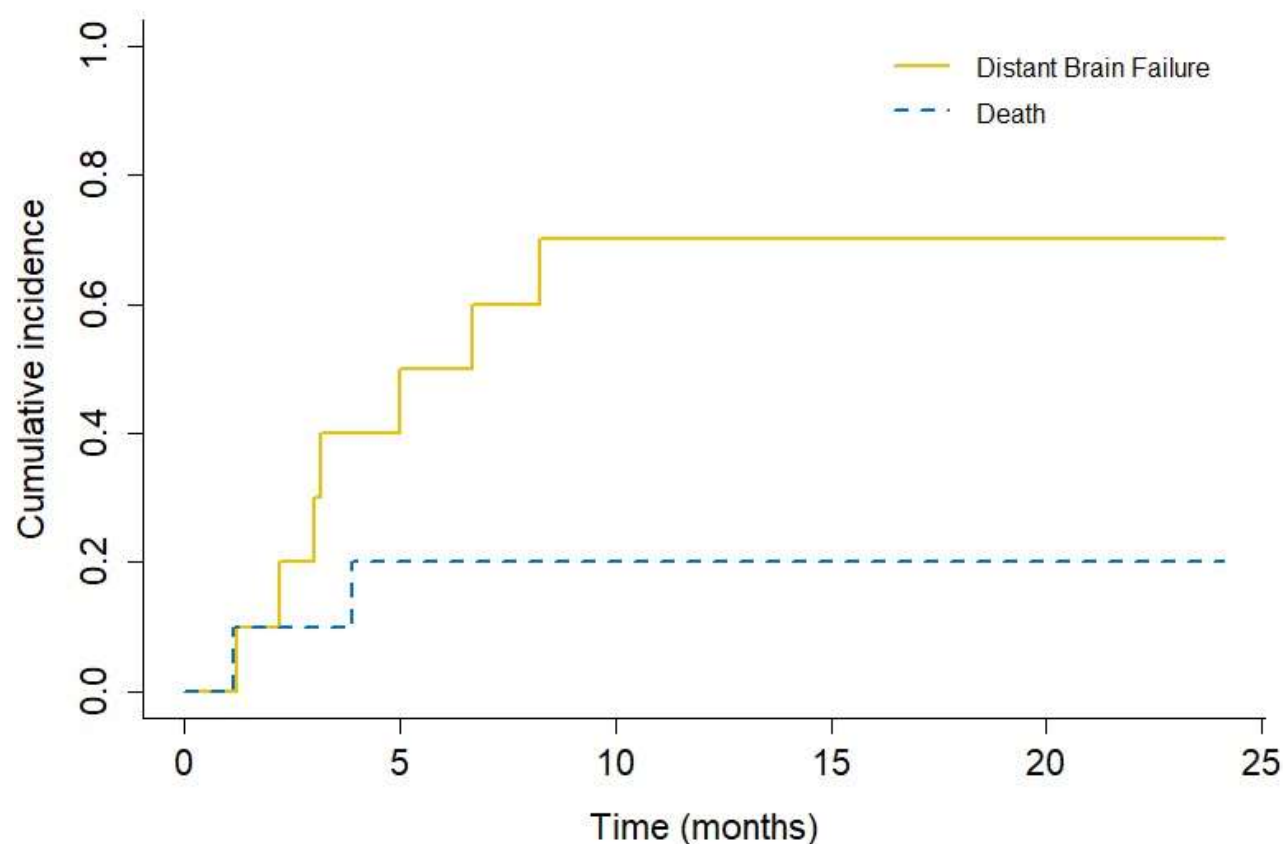
- Median Clinical FU: 11.2 m. (95%CI: 8.1-14.2)
- Median Imaging FU: 9.7 m. (95%CI: 6.4-12.9)
- LF @ 6 and 12 m.: 10%
- Unique LF 3 m. after IORT



IORT for Brain Metastases: Final First-Stage Results of a Single-Arm, Open Label, Phase 2 Trial

- **Results of Distant Brain Failure**

- DBF @ 6 months: 50%
- DBF @ 12 months: 70%
- All 7 DBF patients were salvaged with focal RT
- No failure with meningeal carcinomatosis



IORT for Brain Metastases: Final First-Stage Results of a Single-Arm, Open Label, Phase 2 Trial

- **Results**

- Median OS not reached; OS @ 6 and 12 months: 80%
- All three deaths due to extracranial metastases
- One patient with asymptomatic RN 10 months after IORT
- No patients with wound dehiscence

Obrigado!

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