Interim Analysis of a Phase II Trial of Intraoperative Radiotherapy with Low-Energy X-rays (INTRABEAM) after Surgical Resection of Brain Metastases (NCT05084092)

Medical Physics, ICO
P. Saldaña Gutierrez
R. R. Martin Vaello

Neurosurgery, HUB
G. Plans Ahicart
A. Fernandez Coello
A. Rosselló Gómez

Radiation Oncology, ICO
M. Macià i Garau
A. Lucas Calduch
N. García Expósito

Neuroradiology, IDI
C. Majós Torró
A. Pons Escoda

Neuropathology, HUB
N. Vidal Sarró

Institut **C**atalà d'**O**ncologia. Hospital Duran i Reynals. L'Hospitalet. Barcelona. Spain
Hospital **U**niversitario de **B**ellvitge. L'Hospitalet. Barcelona. Spain

No conflict of interest

Salut/ ICO Institut Català d'Oncologia

Generalitat de Catalunya
Departament de Salut

Bellvitge Hospital

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Rationale

Recurrence Rate at the Primary Site of Resected Brain Metastases

Patchell 1998	46%	Median follow-up of 48 weeks
Kocher 2011	59%	At 2 years
Mahajan 2016	55%	At 1 year

Rationale

Postoperative WBRT reduces the rate of local recurrence, the rate of regional relapse in the brain but has no impact on survival and affects neurocognitive function and decreased QoL

WBRT has been replaced by SRS (2 randomized trials) / SFRT (2 meta analysis)

SRS/ SFRT reduces the rate of local recurrence but is expensive, time-consuming, with risk of geographical errors due to the difficulty in delineating the surgical cavity, not negligible rate of radiation necrosis and delays the start of systemic treatment

Treatment Options

Preop. SRS/SFRT
(ongoing RCT)

M1(BRA) → pM1(BRA)

Observe (some RCT)

WBRT (some RCT)

SFRT (No RCT)

SRS (2 RCT)

Peroperative
histological confirmation

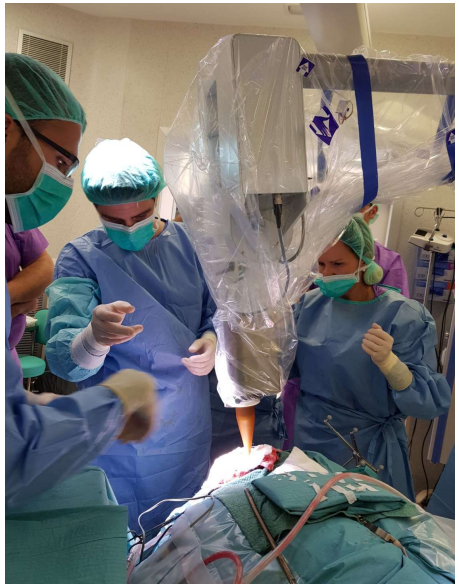
IORT
(No RCT)

IORT with INTRABEAM after Surgical Resection of Brain Metastases: Feasibility and Efficacy Phase II Trial

Open, single arm, monocentric, prospective Phase II Trial to determine the feasiblity, efficacy and safety of IORT with low-energy photon to the resection cavity after surgery of brain metastases

- *Precise targeting of tumor bed*
- *Potentially reduction of radiation-related complications*
- *Avoidance of tumor repopulation (less dose ?)*
- *Quick start of systemic treatment if indicated*

Procedure



Tumor Board
Inclusion
Proposal
Informed
Consent

→ **Surgery** →

Per-operative
Histological
Confirmation of
Brain Met of an
Extracranial
Origin

↗ **YES** → **IORT 15,40 Gy at 2 mm depth** → Early Post-operative RMN within 72 h

↘ **NO** → Screening Failure

IORT with INTRABEAM after Surgical Resection of Brain Metastases: Feasibility and Efficacy Phase II Trial

- **Primary endpoint** : Local (cavity) Progression Free Survival *

- **Secondary endpoints:**
· Regional (brain) Progression Free Survival
· General Progression Free Survival
· Overall Survival
· Neurocognitive Function
· QoL
· Radiation-related Secondary Effects
· Time to the Initiation of Systemic Therapy

* time elapsed between surgery and recurrence within 5 mm around the resection cavity

Inclusion Criteria

· > 18 years old
· KPS ≥ 70%
· Suspected brain metastases amenable to resection
· Complete resection judged by Neurosurgeon
· Peroperative histological confirmation of M1(BRA)
· No dural attachment
· Adequate distance to optic nerves, chiasm and brainstem
· Informed consent

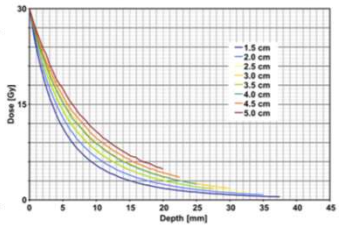
Exclusion Criteria

· Leptomeningeal spread or dural attachment
· Radiosensitive tumors
. Contraindication for anesthesia or surgery
· Pregnant or breast-feeding women

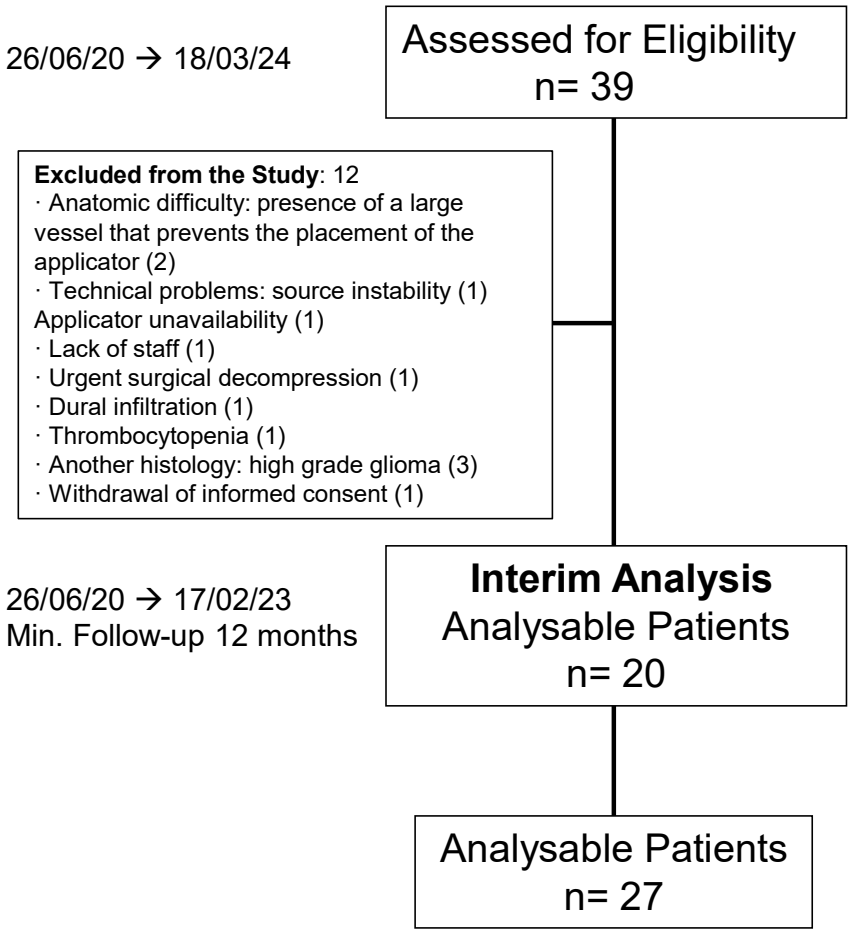
· Multiple cerebral metastases are not an exclusion criteria
· Previous radiation therapy to the brain is not an absolute exclusión criteria

Dose Prescription

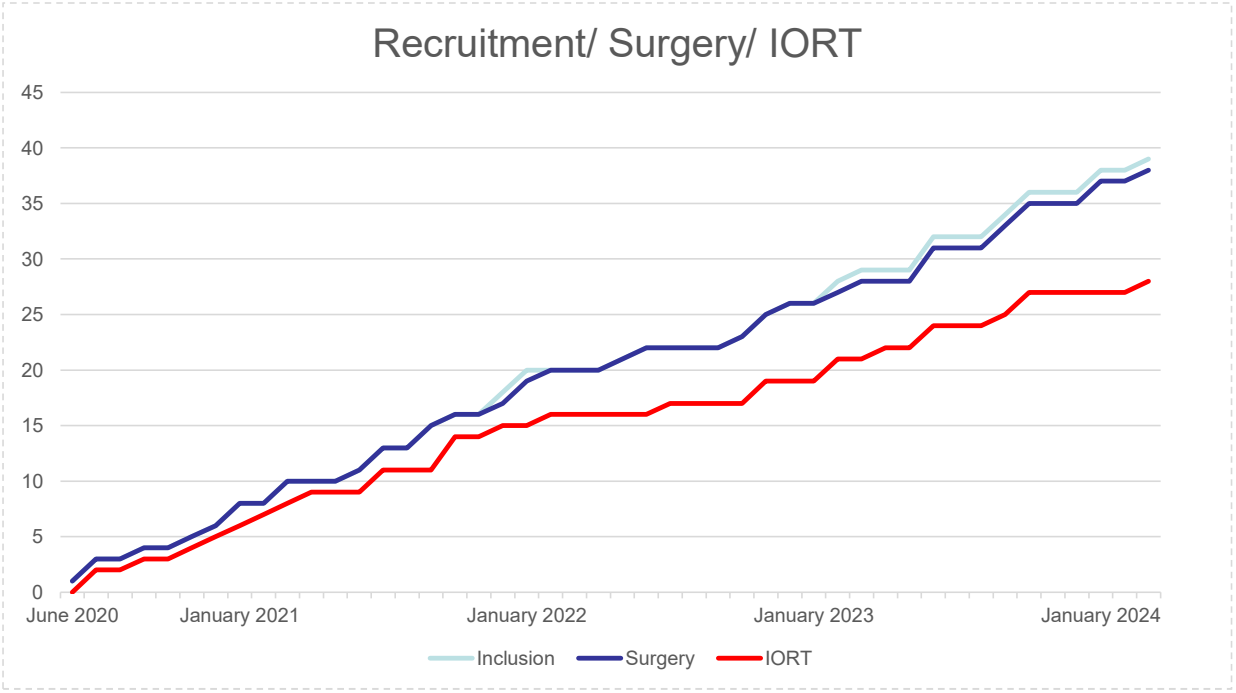
	Surface Dose (Gy)	2 mm depth Dose (Gy)	2 mm Depth Dose (Gy $_{RBE\ 1,3}$)	N $_{M1(BRA)}$ (patients)	**Local Control** (%)	RN (%)
Cleveland Clinic Prospective study Weil RJ et al. J Neurosurg 2015	17,50 - 20,0	**14,00**	18,20	23	**70** 5 years follow-up	
ICO Phase II Trial	19,25 - 22,00	**15,40**	20,00			
Augsburg University Kahl K-H et al. Strahlenther Onkol 2021	**20,00**	12,60-16,80	16,40-21,80	44 14 suspected incomplete resection by postop MRI (40)	1 year **84,3**	**2,5** 1 patient in an pre-irradiated area
West Virginia Universisty Vargo JA et al. J Neuro-oncol 2018	**30,00**	21,00-24,00	27,30-31,20	7	**86** median follow-up of 6,2 months	**0**
International Coperative Study Cifarelli CP J Neuro-oncol 2019	**30,00**	21,00-24,00	27,30-31,20	54	1 year **88**	



Interim Analysis



Recruitment



Baseline Patient Characteristics (Interim analisis - Analysable Patients - n=20)

Characteristics	Number (%)
Sex	
Female	8 (40)
Male	12 (60)
Median Age (range)	58,8 years (43 - 78)
Primary Site	
Lung Adenocarcinoma	9 (45)
Melanoma	3 (15)
Breast Cancer	3 (15)
Colo-rectal cancer	2 (10)
Renal Cancer	1 (5)
Urotelial Cancer	1 (5)
Lung Squamous	1 (5)
Previous Loco-regional RT	
Yes	1 (5)
Not	19 (95)
Number of Mets (only 1 treated by surgery and IORT)	
1	18 (90)
2	2 (10)
CNS Location	
Frontal	5 (25)
Parietal	5 (25)
Temporal	6 (30)
Occipital	3 (15)
Cerebellum	1 (5)
Maximum Diameter	
1 - 2 cm	3 (15)
2 - 3 cm	13 (65)
3 - 4 cm	2 (10)
> 4 cm	2 (10)

Characteristics	Number (%)
DS-GPA 2020	
1	1 (5)
2	2 (10)
2,5	2 (10)
3	7 (35)
3,5	4 (20)
4	2 (10)
Unknown	2 (10)
KPS	
100	3 (15)
90	11 (55)
80	3 (15)
70	2 (10)
60	1 (5)
RTOG Neurologic Function Status	
0	11 (55)
1	6 (30)
2	1 (5)
3	2 (10)
Metastatic Status:	
Polimetastatic	1 (5)
Synchronous Oligometastatic	7 (35)
Metachronous Oligorrecurrence	7 (35)
Induced Oligoprogression	2 (10)
Induced Oligorecurrence	1 (5)
Repeat Oligoprogression	1 (5)
Repeat Oliogorrecurrence	1 (5)

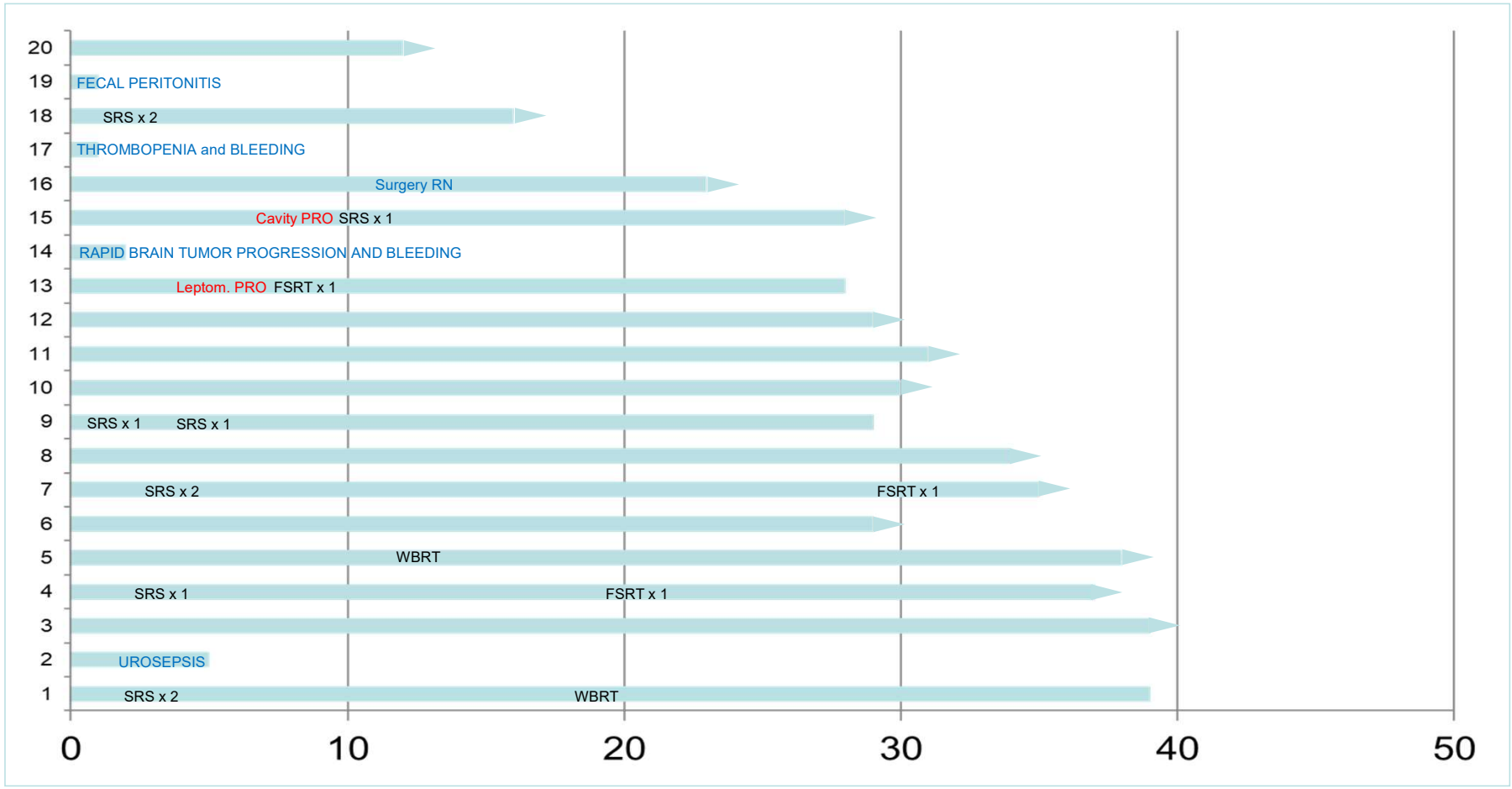
Surgical and IORT Details (Interim analisis - Analysable Patients - n=20)

Characteristics	Number (%)
Indication of surgery Large Mets Histological confirmation Salvage Therapy	 17 (85) 2 (10) 1 (5)
Suregy En Bloc Resection Piecemeal Resection	 20 (100) 0
Per-operative Histological Confirmation Yes No	 20 (100) 0
Complete Resection Judged by Neurosurgeon Yes Not	 20 (100) 0
Postoperative MRI No Yes ≤ 3 days Yes > 3 dyas	 2 (10) Claustrophobia 11 (55) Post-op complication 7 (35)
Postoperative MRI Findings Complete Resection Suspected Incomplete	 16 (80) 2 (10)
Other Radiological Findings	Venous thrombosis of the lateral sinus and ipsilateral vein of occipital cortex confirmed by ANGIO CT. Asymptomatic patient.
Postoperative Mortality within 3 Days	1 (5) Intraoperative thrombocytopenia and fatal cerebral bleeding inside and outside surgical bed

Characteristics	Number (%)
Spherical Applicator size (mm) 10 15 20 25 30 35 40 45	 0 6 (30) 5 (25) 4 (20) 2 (10) 2 (10) 0 1 (5)
Delivered Dose 15,40 Gy at 2 mm Depth	20 (100)
Median Surface Dose (Gy) (range)	22,34 (20,06 - 23,97)
Median Irradiation Time (min) (range)	16,45 (8,10 - 39,29)
Intraoperative Incidents	Interruption of 5 minutes due to the patient's tendency towards high blood pressure
Median Days of Hospitalization (range)	6,75 (4 - 28)
Median Days to Start Systemic Treatment (range) Mode P85	 26 (17 - 54) 17 30,6

Preliminary Results

Minimum follow-up: 12 months
Median Follow-up of surviving patients: 29,4 months



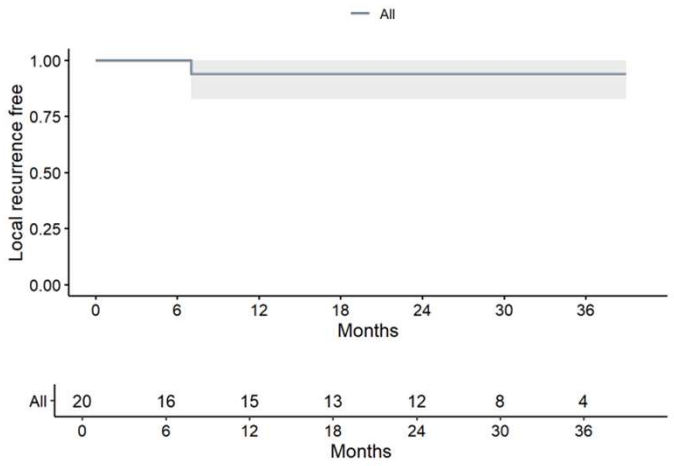
Preliminary Results

Postoperative Radiological Findings: distal jugular and left lateral sinus (sigmoid and transverse) thrombosis in an asymptomatic patient. Not related to IORT

Postoperative Mortality within 30 days: 1 patient (5%) heavily treated with chemotherapy for a breast cancer had an intraoperative thrombocytopenia and fatal bleeding inside and outside surgical bed. Not related to IORT

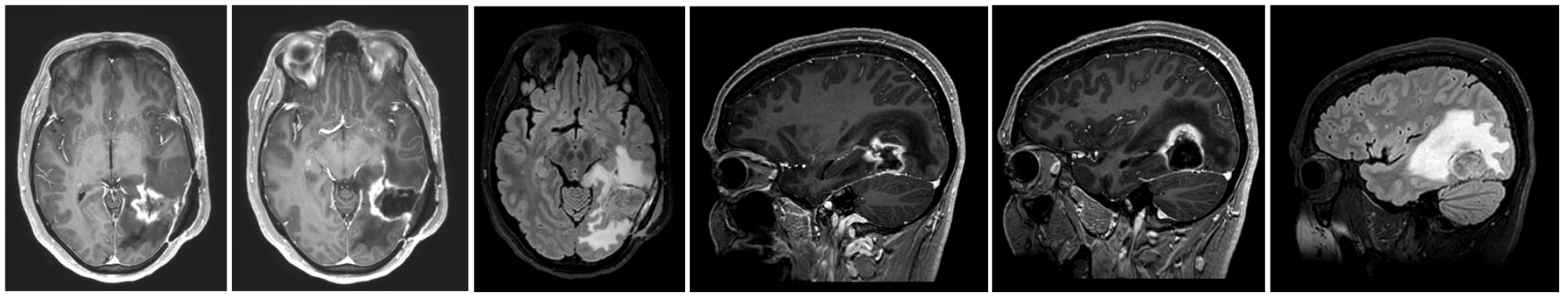
Regional Brain Progression of the remaining 16 patients
43,8% including 1 nodular leptomeningeal disease
6 months after surgery

Local (cavity) control at 1 and 2 years:
93,8% (15/16) [CI 0.83;1] and 92,9% (13/14) [CI 0.83;1]



Preliminary Results

Radiation-related Secondary Effects: 1 early symptomatic radiation necrosis (1,5 months after IORT), histologically confirmed, in a patient previously locally treated by adjuvant FSRT after primary surgery for temporo-occipital metastasis.



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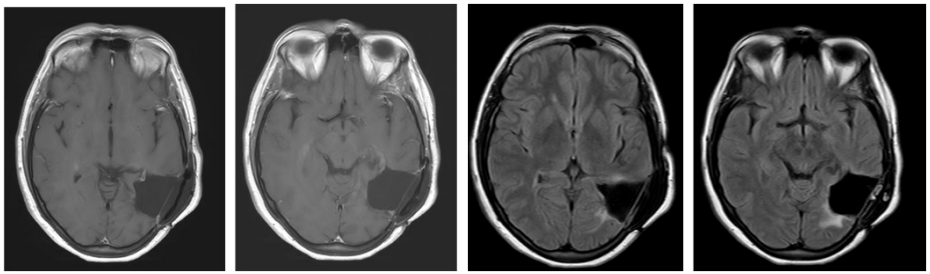

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Conclusions

1. 50 Kv X-ray IORT seems to be a safe way to apply focal radiation therapy after resection of brain metastases. It seems not to increase the perioperative complication rate

2. The lengthening of surgical time due to irradiation is moderate: 16,45 minutes with a range of 8,10 to 39,29 minutes

3. IORT appears as a highly effective option to ensure local control after surgery of BM with minimal risk of complications

4. The two procedures performed at a single time would allow the rapid initiation of systemic therapy if indicated

5. These preliminary results are encouraging and we continue recruiting patients until the trial is completed