Recurrent Glioblastoma Multiforma – Targeted Alpha Therapy with Bi-213-DOTA-Substance P

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Why α?

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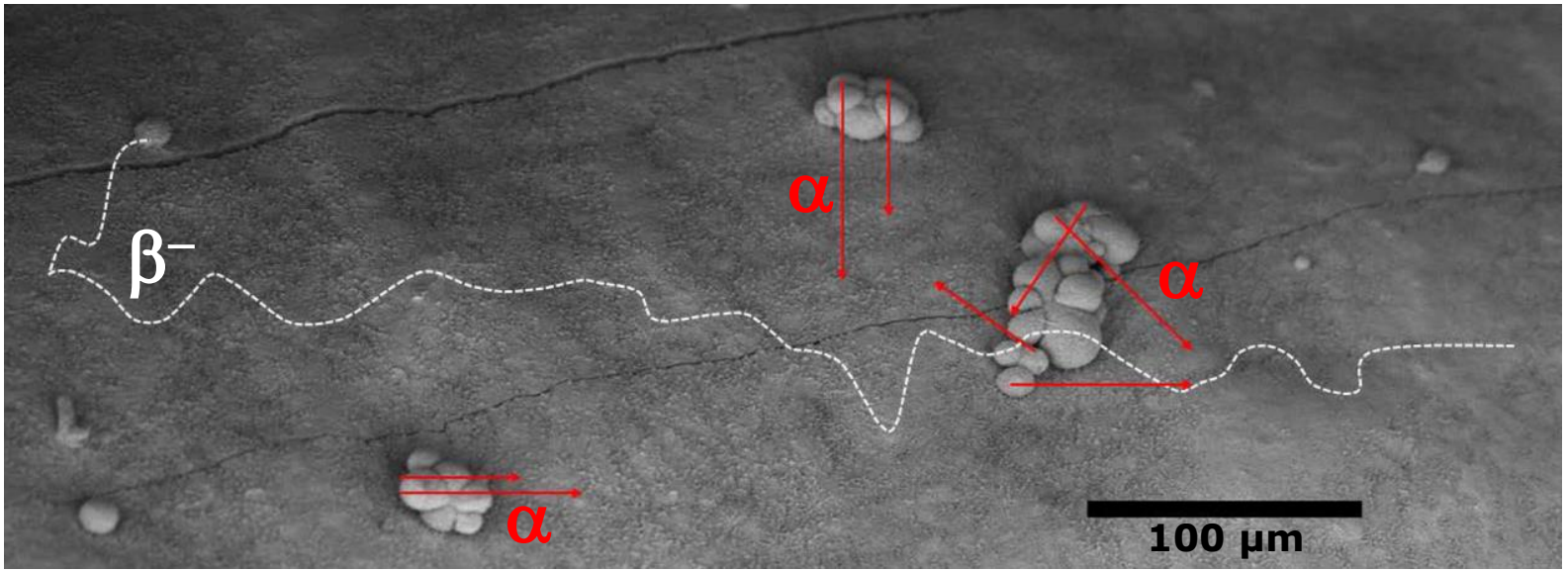
Therapeutic advantages of alpha emitting radionuclides

- Alpha radiation has high energy (4–9 MeV)
- High Linear Energy Transfer (~100 keV/µm)
- Short range in human tissue (< 0,1 mm)



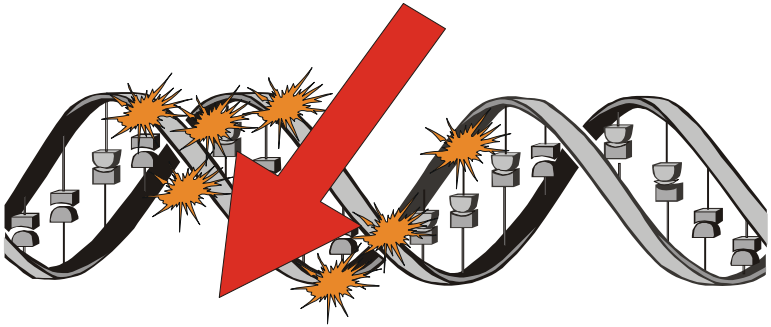
modified form Elqvist et al Front Oncol 2014

=> Alpha radiation provides very effective and selective cell kill

Why α?

European Commission

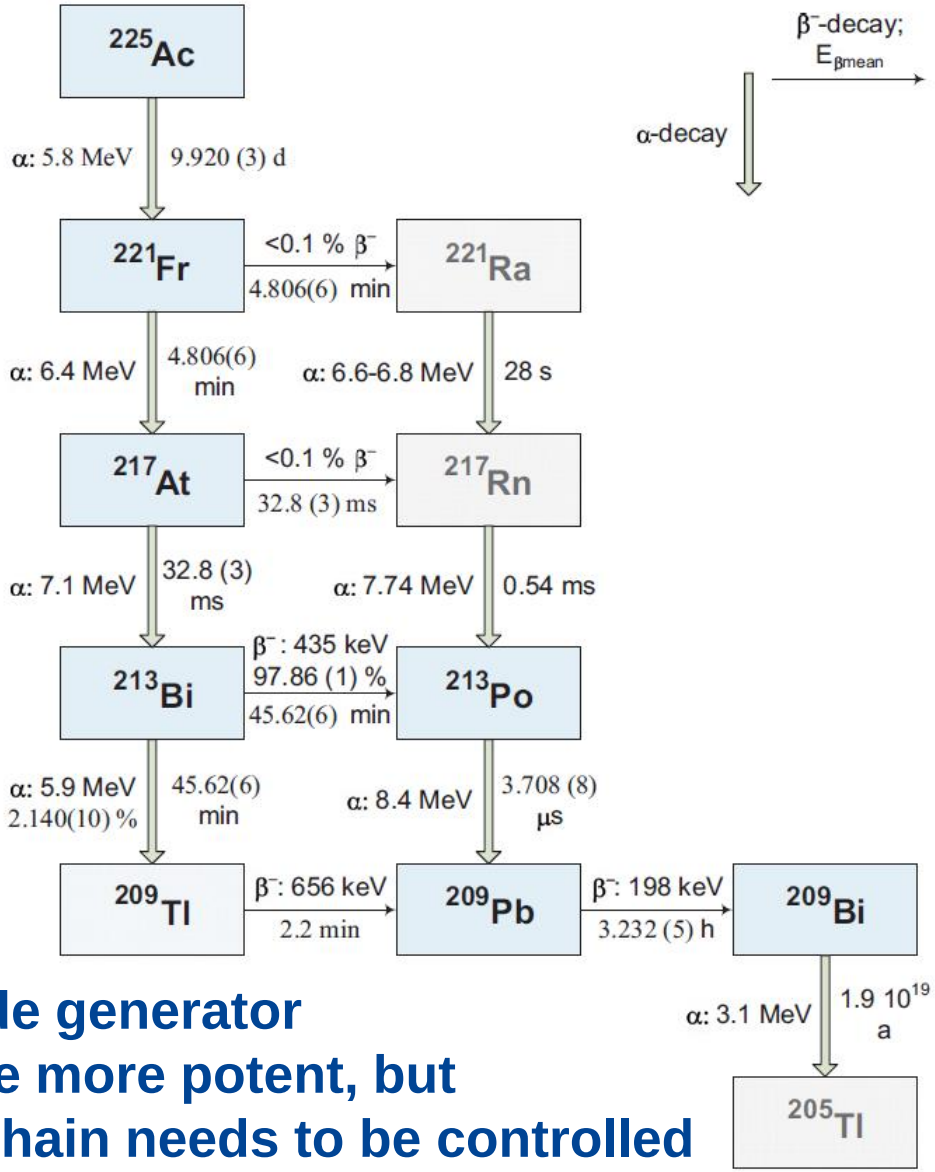
Alpha - radiation



- Alpha radiation primarily induces DNA double strand breaks
- Alpha induced cell kill is largely independent of cell cycle, oxygenation
- Alpha emitters can overcome resistance to beta-, gamma-radiation and chemotherapy

^{225}Ac and ^{213}Bi – main decay characteristics

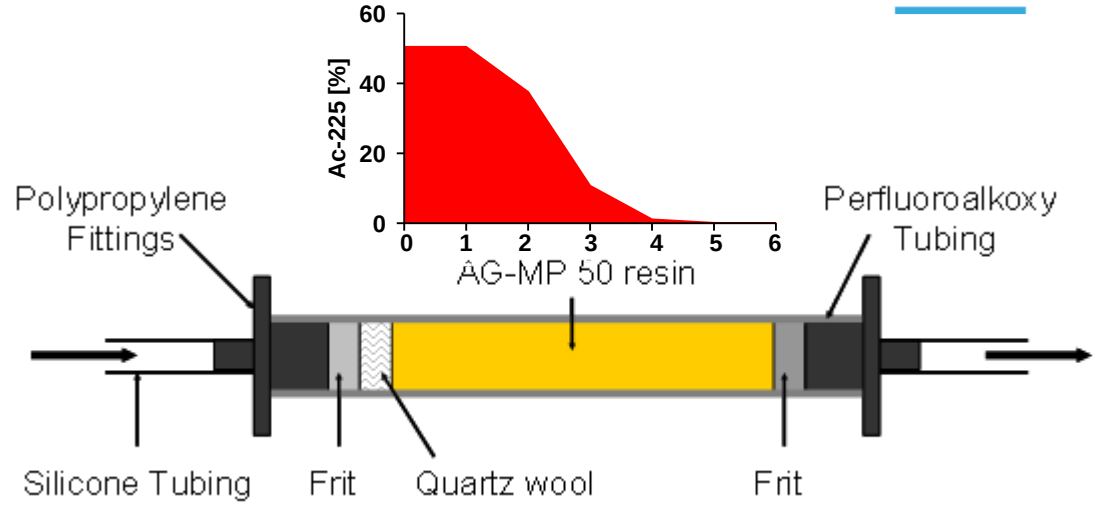
	^{213}Bi	^{225}Ac
Half-life	45.6 min	9.9 d
No. of α's per decay	1	4
Ratio of α's emitted at equal activities	1	1250
Total energy of α decay	8.4	27.7
Typical activity administered	4-6 GBq	20 MBq

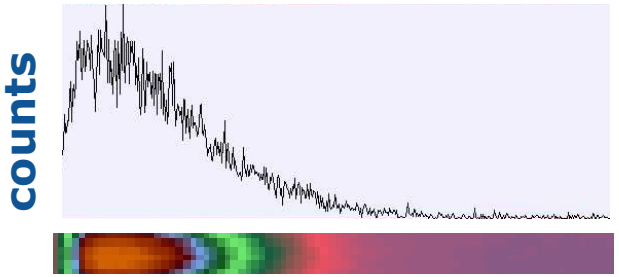


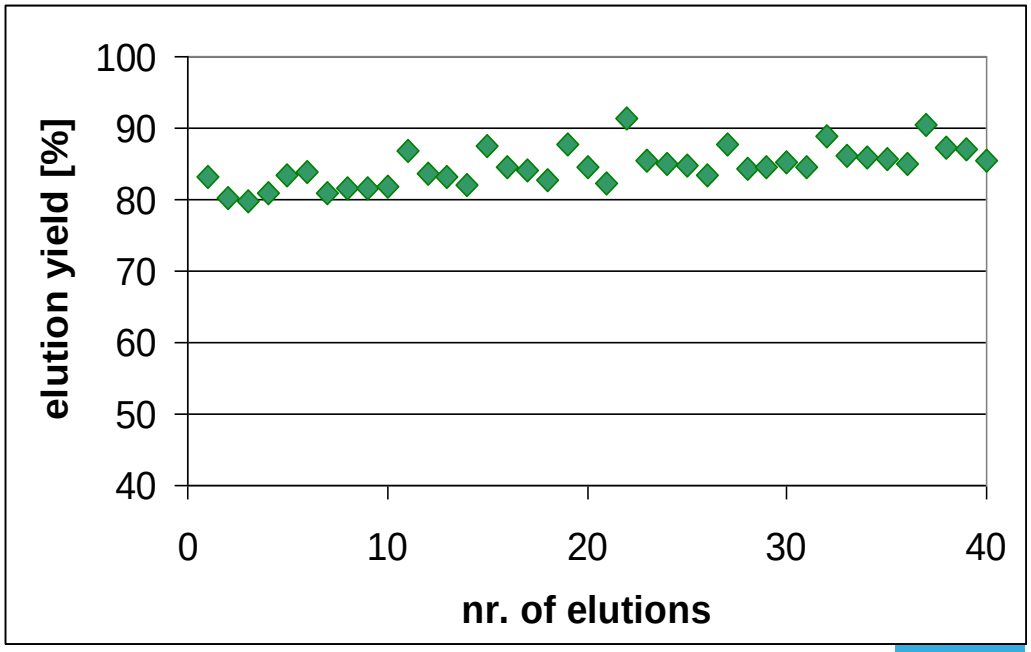
→ ^{213}Bi is available from radionuclide generator

→ ^{225}Ac several orders of magnitude more potent, but potentially also more toxic; decay chain needs to be controlled

$^{225}Ac/^{213}Bi$ generator







- stable ^{213}Bi elution yield (~ 85 %)
- ^{225}Ac breakthrough < 0,2 ppm

^{213}Bi-DOTA-peptide labelling

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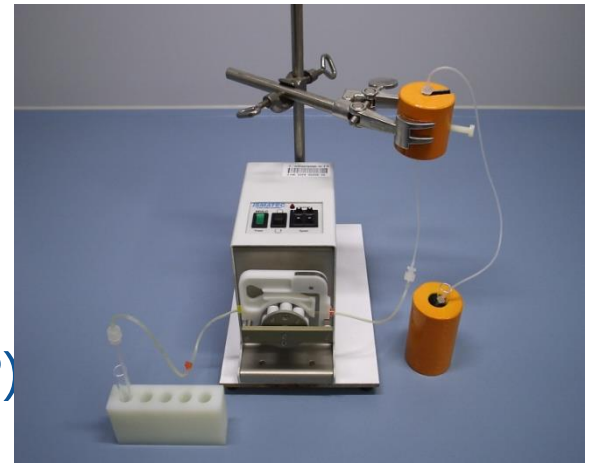
timescale

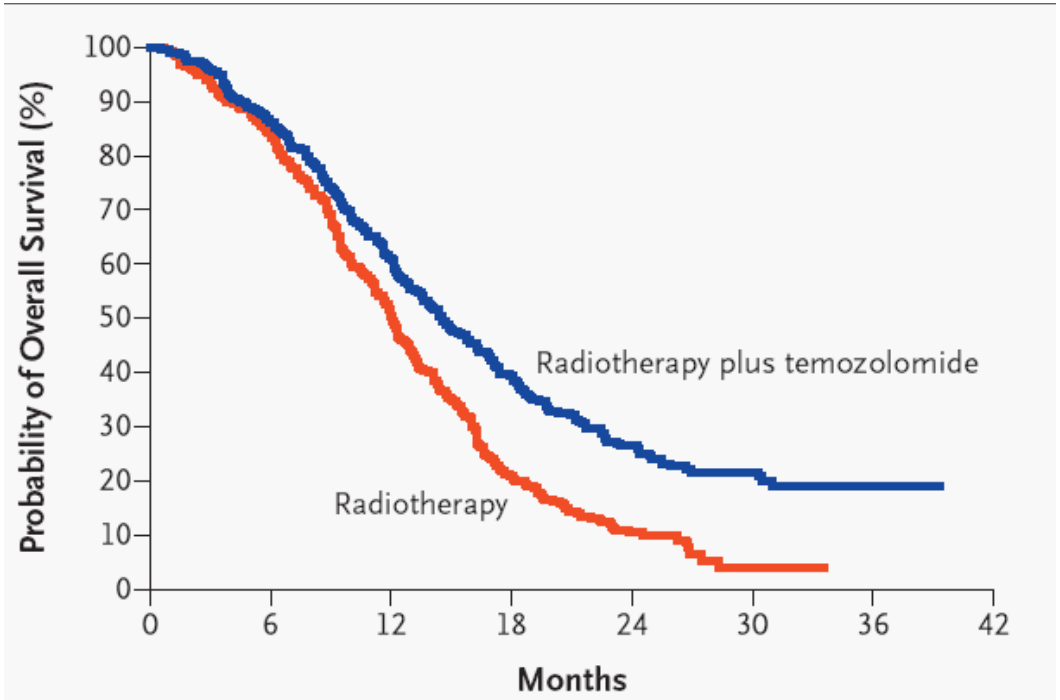
- **0 min** — **Elution of ^{225}Ac/^{213}Bi generator (e.g. 3.7 GBq (100 mCi) ^{213}Bi)**
- **3 min** — **Labelling of DOTA-peptide with microwave** (e.g. DOTA-SubstanceP) radiochemical purity > 99%
- **9 min** — **Quality control (ITLC + RadioHPLC) and syringe preparation**
- **12 min** — **Final approval and syringe transfer**
- **15 min** — **Patient application of ^{213}Bi-DOTA-peptide**



Glioblastoma multiforme

Glioblastoma multiforme (GBM) is the most common and aggressive malignant primary brain tumor in humans

Incidence: 2–3 cases per 100,000 in Europe and North America

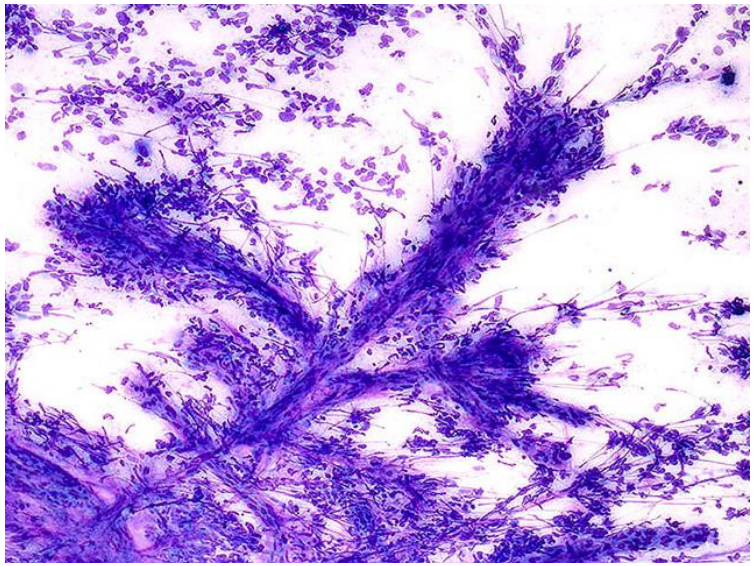


Stupp, NEJM 2005

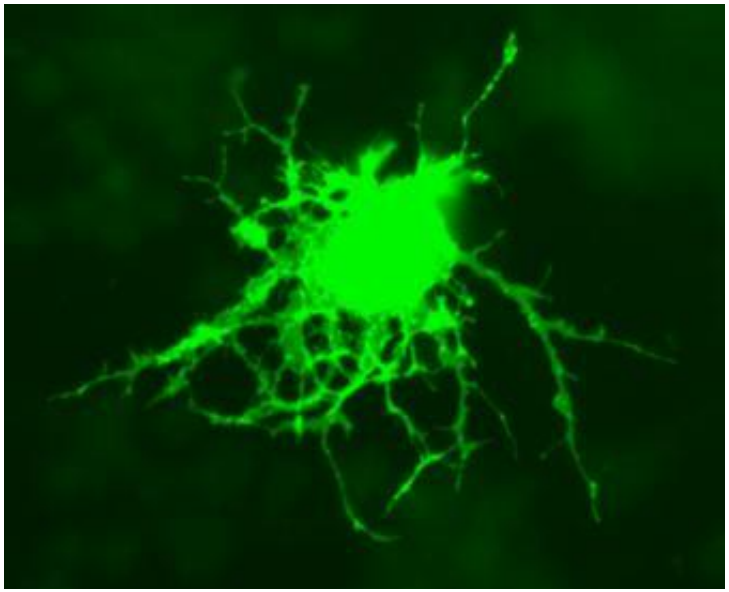
The median survival time is 14.6 months from time of diagnosis, in spite of aggressive surgery, radiation therapy and chemotherapy

Glioblastoma multiforme

Glioblastomas are *highly infiltrative, resistant to conventional therapies*, *contain hypoxic areas*=> promising target for targeted alpha therapy



Vascular endothelial proliferation along with perivascular aggregation of malignant glial cells (Johns Hopkins University)



Glioblastoma transfected with Green Fluorescent Protein (J. Broeke)

Targeting vector: DOTA-[Thi^{8}, Met(O_2)^{11}] – Substance P

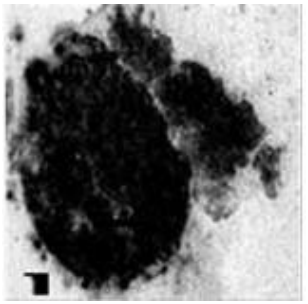
SubstanceP receptor: neurokinin 1 (NK1)

Receptor autoradiography

Tumour type	Positive tumour cells	Positive vessels
Glioblastoma	10/10 (100%)	6/10 (60%)
Astrocytoma	9/12 (75%)	9/12 (70%)

Int. J. Cancer 1995, 61, 786-792

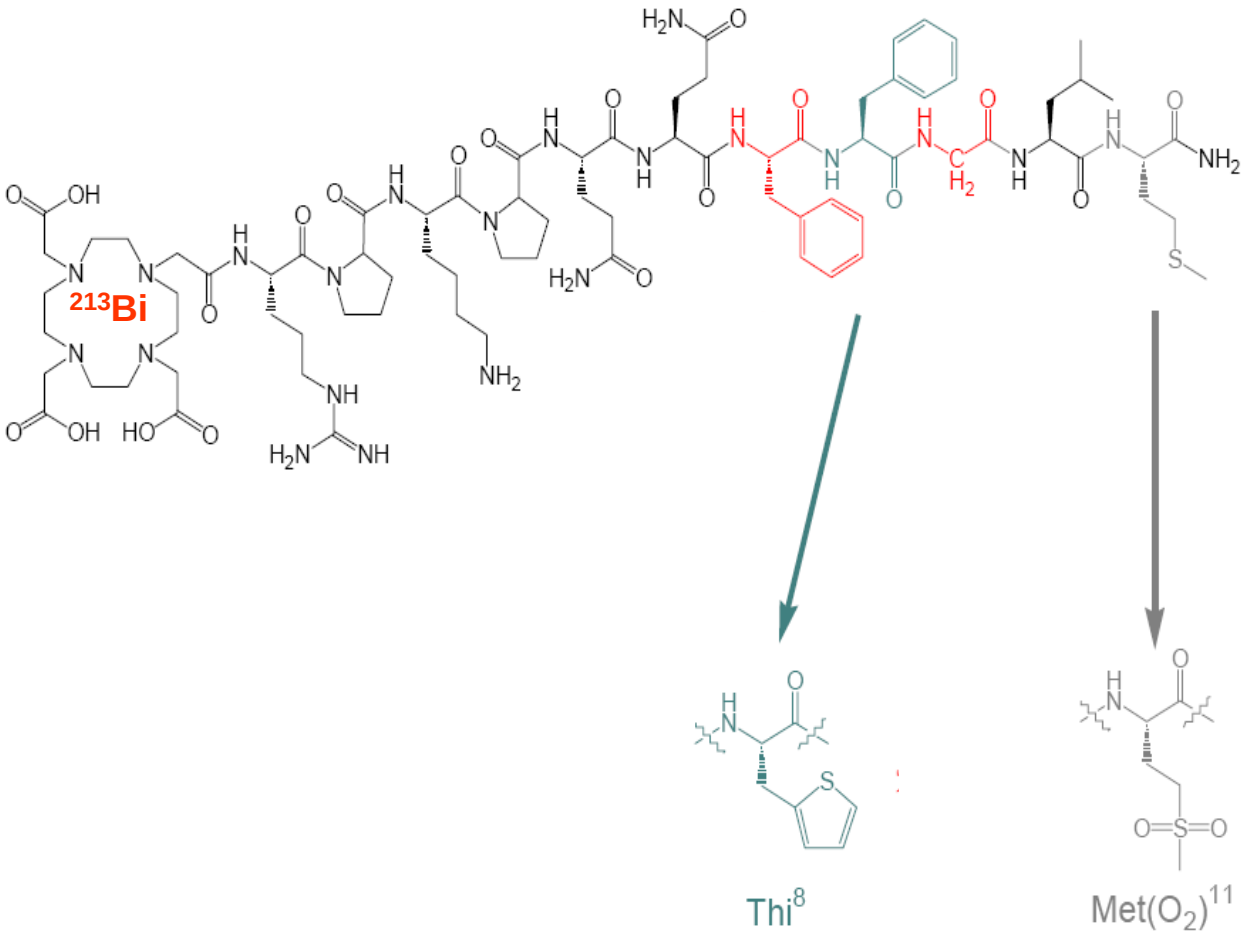
Tumour type	Incidence of NK1R
Glioblastoma	32/34 (94%)
Oligodendroglioma II/III	7/9 (78%)
Astrocytoma	15/15 (100%)



Clin. Cancer Res. 2006, 12, 3843-3850

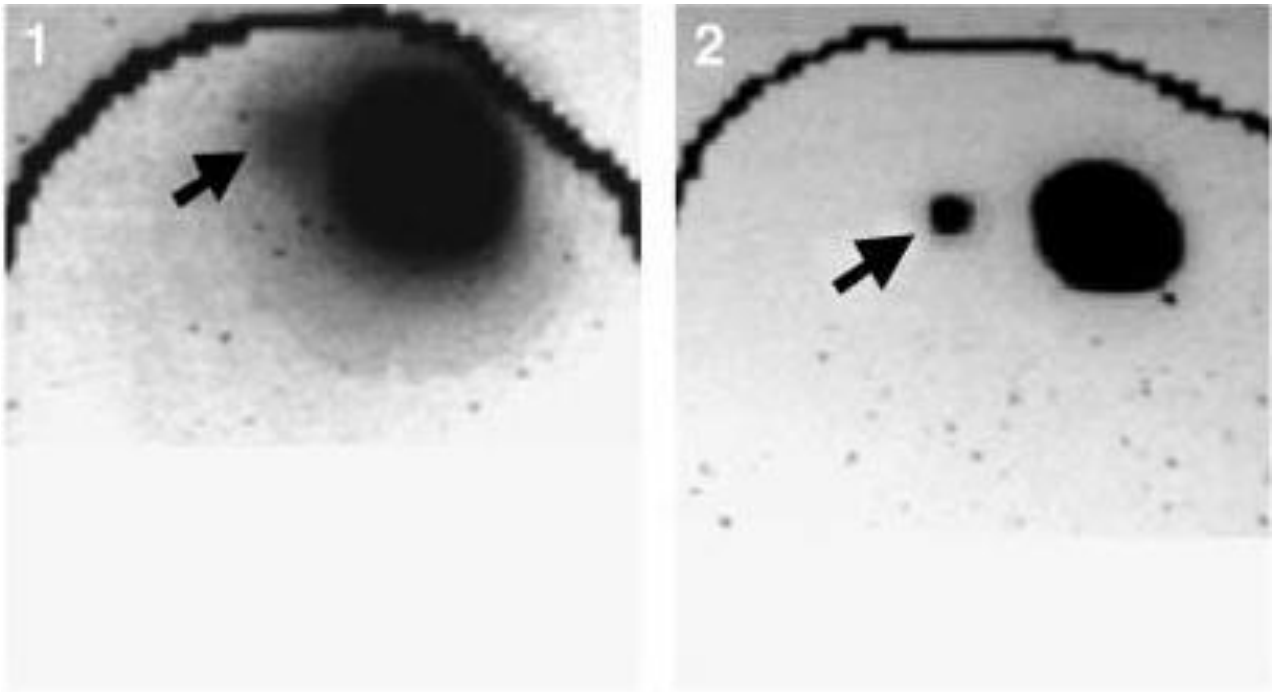
Substance P:

Arg^{1}-Pro^{2}-Lys^{3}-Pro^{4}-Gln^{5}-Gln^{6}-Phe^{7}-Phe^{8}-Gly^{9}-Leu^{10}-Met^{11}-NH_2



Native Substance P is metabolically unstable => Exchange of amino acids to increase stability => [Thi^{8}, $Met(O_2)^{11}$] – Substance P *(Good, 2006)*

Diffusion of DOTA-[Thi^{8}, Met(O_2)^{11}] – Substance P

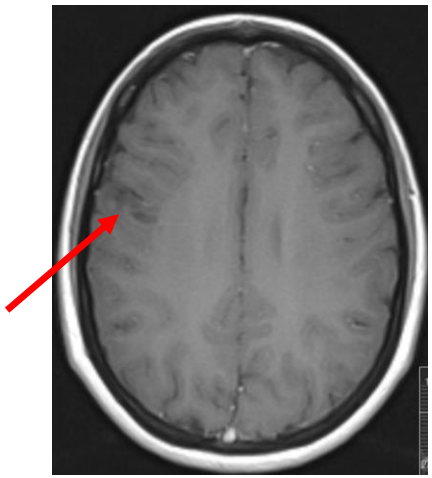


Planar scintigraphy 30 min (1) and 240 min (2) following i.t. injection of [^{111}In]-DOTAGA-SP marks glioblastoma satellite lesion (*Kneifel et al., CCR 2006;12:3843-50*)

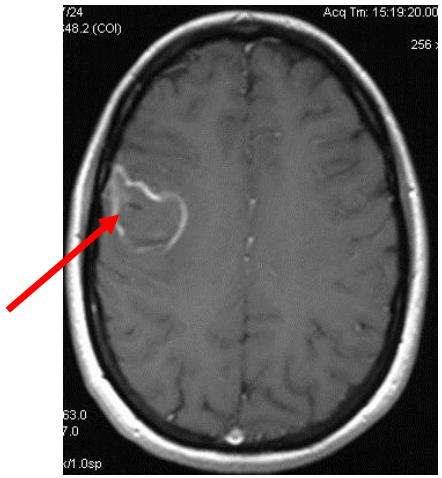
Starting point for targeted alpha therapy with ^{213}Bi-DOTA-Substance P

- High-LET (~100 keV/µm) alpha radiation is highly cytotoxic and selective (tissue range < 100 µm)
- ^{213}Bi-Substance P kills GBM cells *and* GBM stem cells effectively *in vitro*
- Intracavitary / intratumoral administration of low molecular weight peptide provides rapid tumor targeting
- Pilot study conducted at University Hospital Basel has shown feasibility, safety and therapeutic efficacy of intratumoral application (*Cordier et al, EJNMMI 2010;37(7):1335-44*)

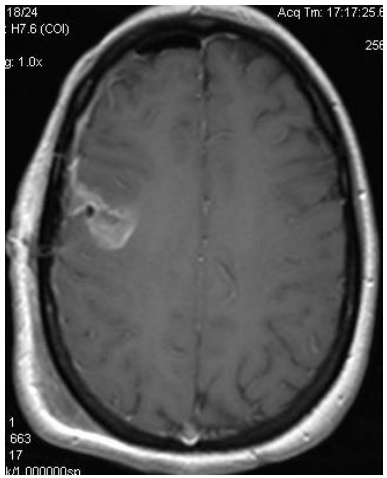
Patient Case – WHO Grade II Glioma (34 y, female)
Intratumoral application



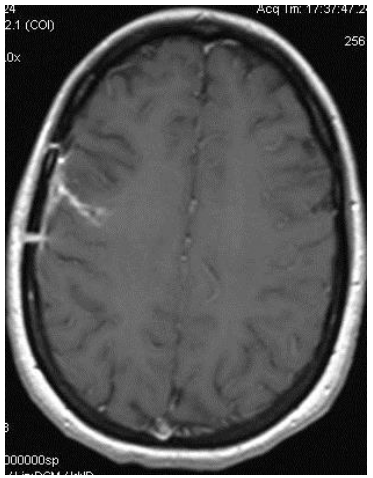
Pre-therapy: diffuse tumour boundaries (09/2007)



Post- ^{213}Bi-therapy: improved demarcation of tumour (10/2007)



Early post surgery (01/2008)



2 months post surgery (03/2008)

^{213}Bi-Substance P Therapy Tumor resection

1.85 GBq (50 mCi) ^{213}Bi-Sustance P

=> Current status: 8 years after initial diagnosis (7/2007): no symptoms, no residual tumour detectable, no toxicity

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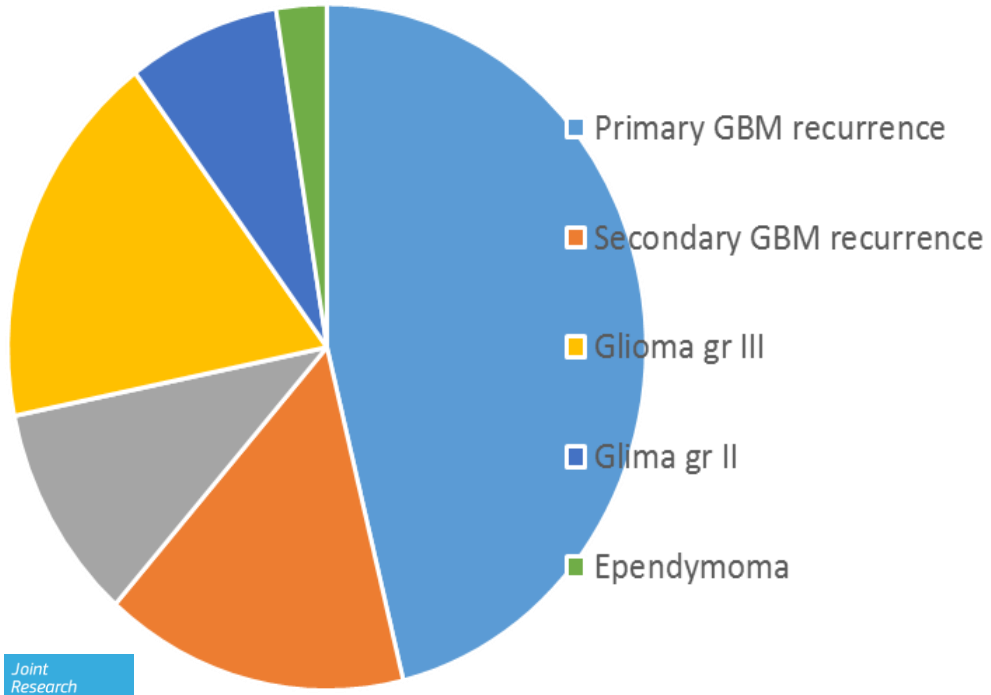
Clinical experiences - Patient cohorts

18 patients - primary GBM with recurrence (protocol A)
6 patients - secondary GBM (initially grade II/III)
4 patients - primary GBM without recurrence (protocol B)

3 patients - grade II
7 patients - grade III
1 patient - ependymoma

39 patients



Treatment of Patients with ^{213}Bi-DOTA-Substance P

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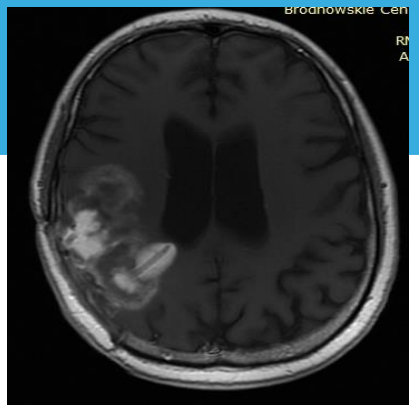
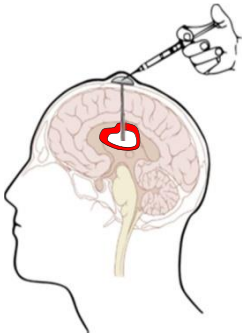
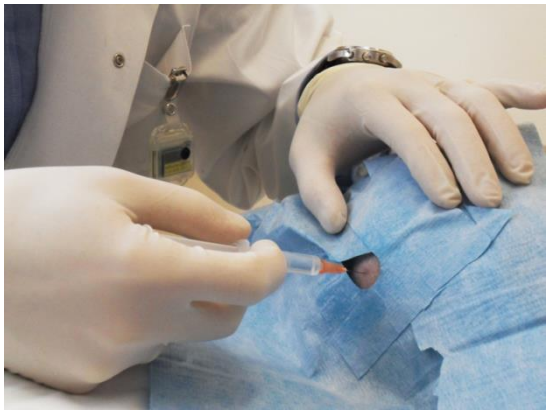


- All patients receive standard treatment (surgery + radio-chemo-therapy)
- Recurrence/progression => 2nd resection, and implantation of catheter was performed
- 2-3 weeks later the position of the catheter was checked
- Intracavitary / intratumoral injection of 2 GBq (54 mCi) ^{213}Bi-substance P every 2 months



- ^{68}Ga-substance P injection for controlling the application
- monitoring of toxicity and overall survival



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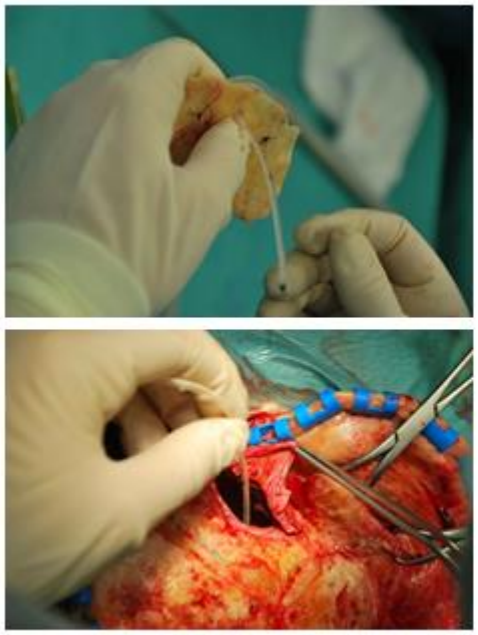
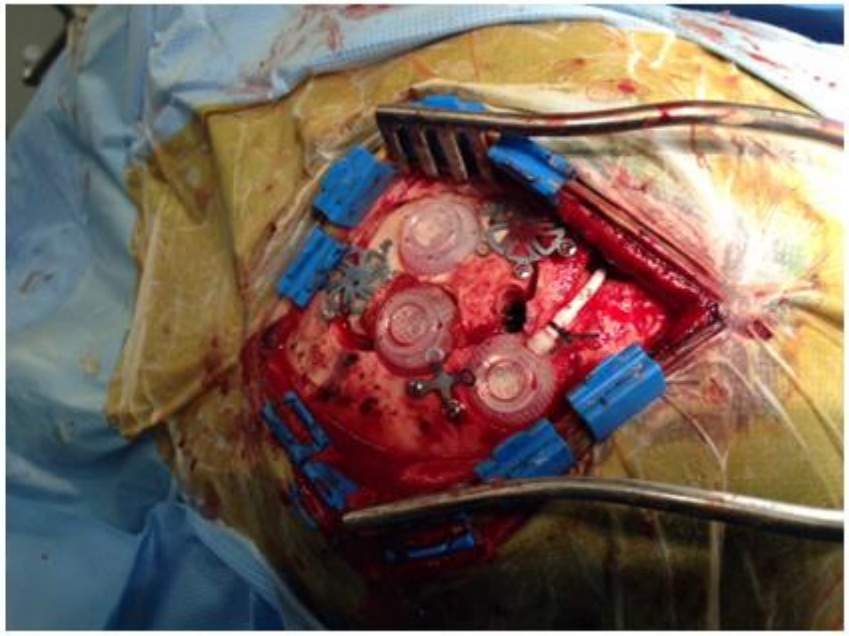
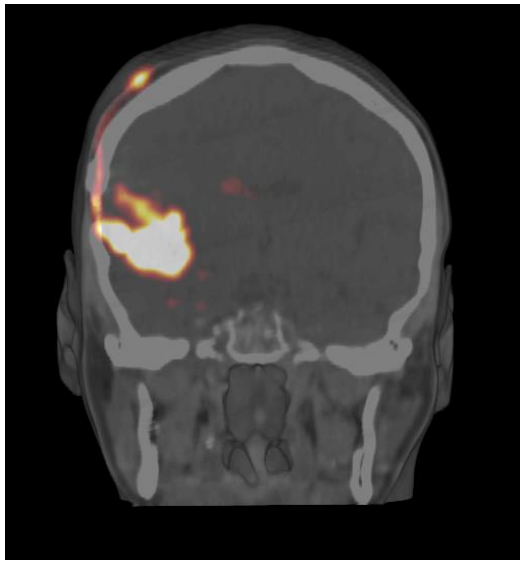
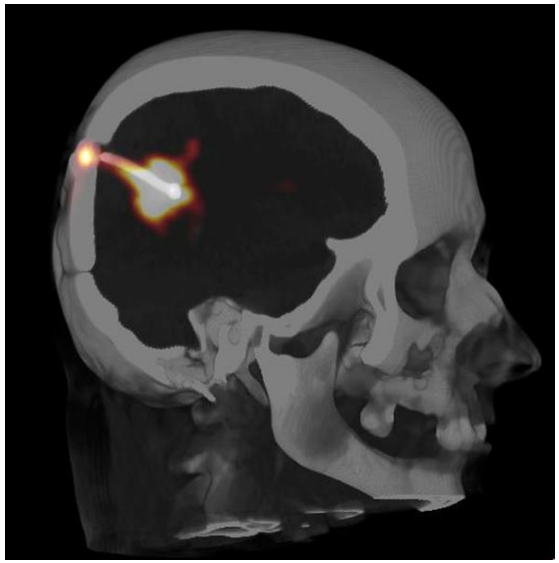
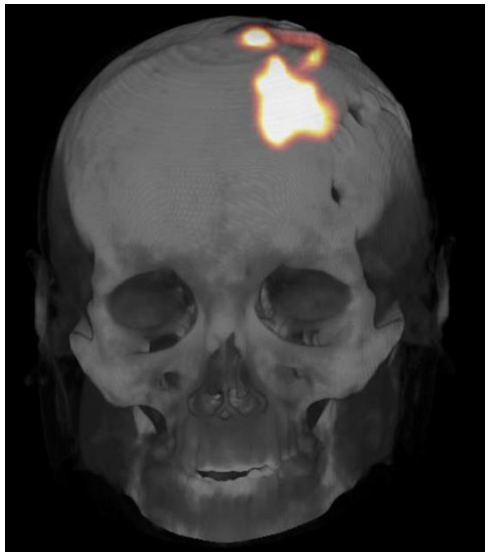




Placement of catheter system







^{68}Ga-PET/CT examination, 30 min after injection of ^{213}Bi-DOTA-Substance P

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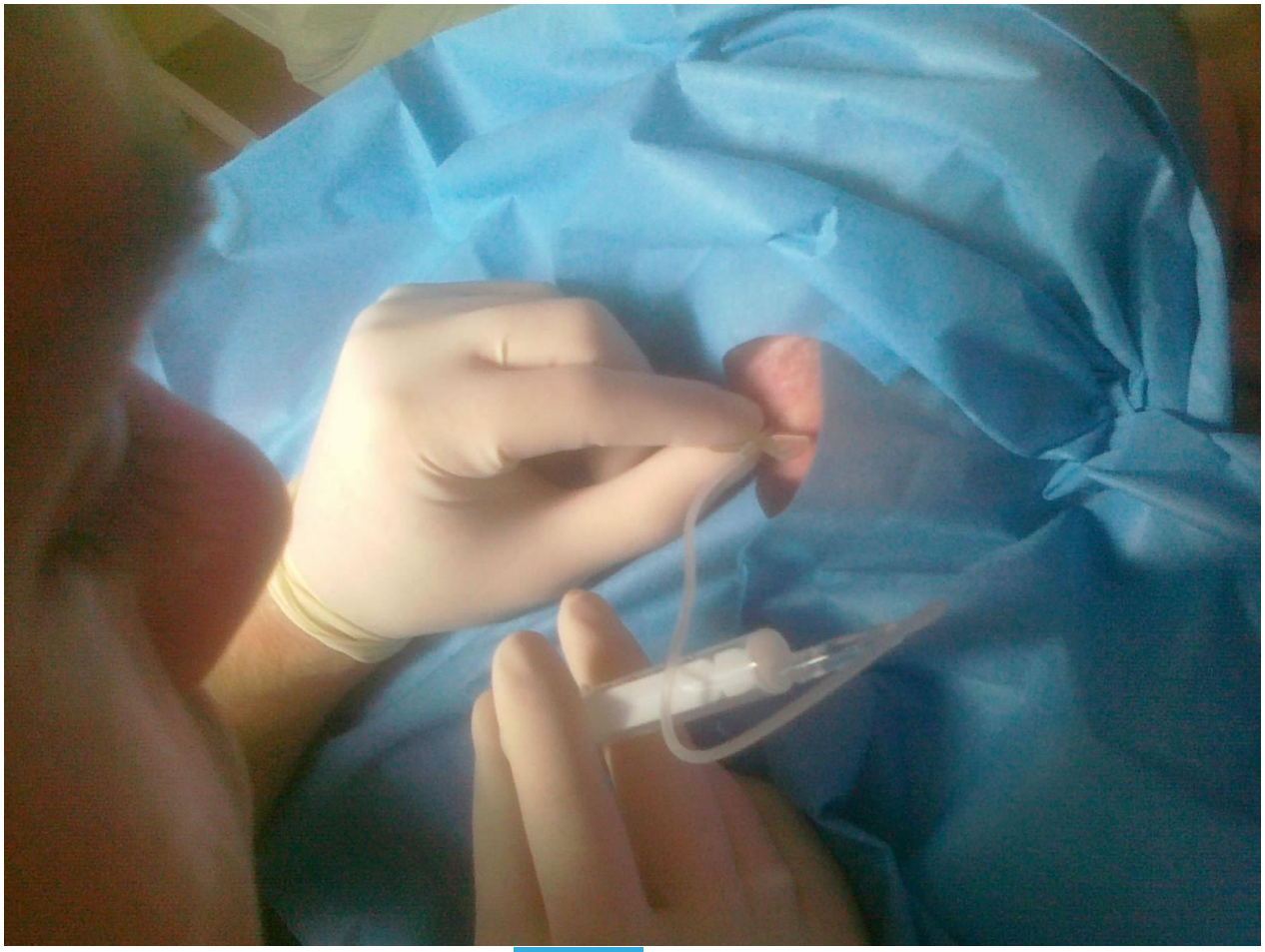
Application of $^{213}Bi/^{68}Ga$–DOTA-Substance P by butterfly catheter



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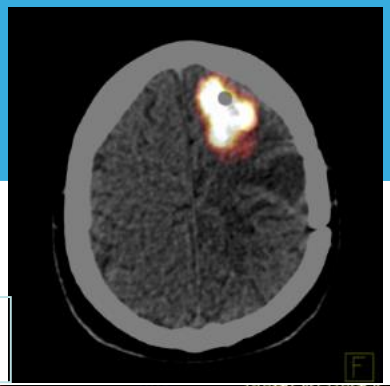
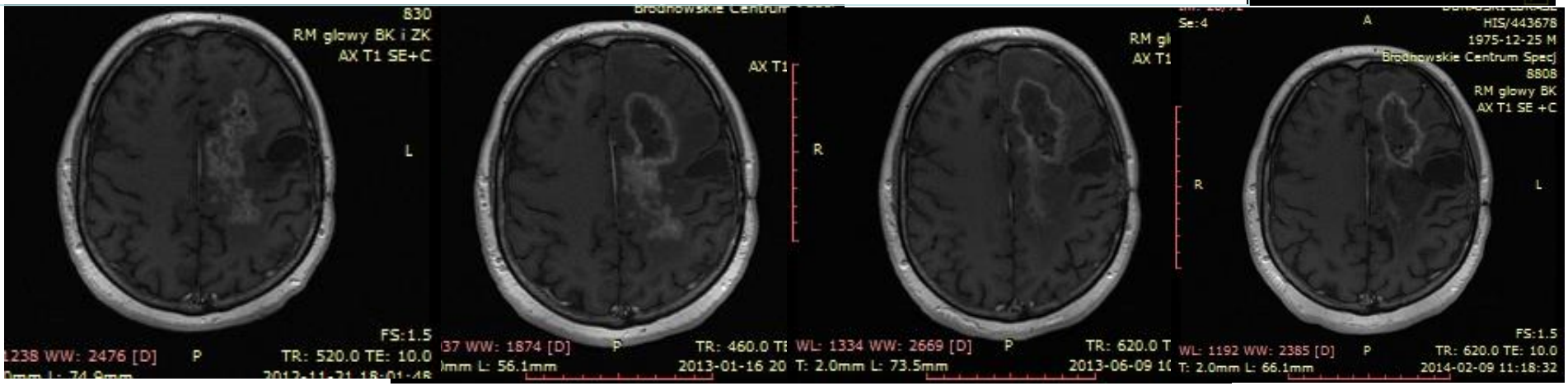
Patient A: Astrocytoma WHO III (male 37 y) 7 cycles, 14 GBq (378 mCi) total ^{213}Bi-DOTA-Substance P

First operation Juli `11; Progression May `12; First treatment Dec `12

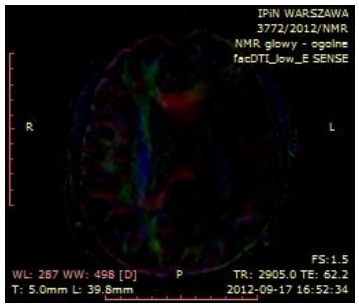


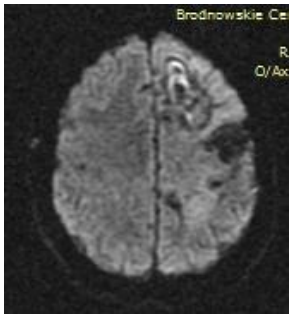


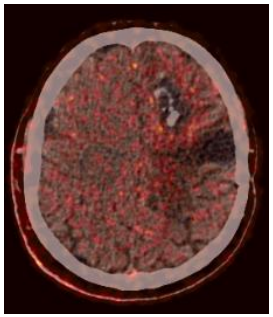
Before treatment **6 weeks** **29 weeks** **58 weeks**

^{213}Bi-SP treatment (1.12.2012):

Survival after initiation of 213 Bi-SP treatment: +30 months (+46 months)







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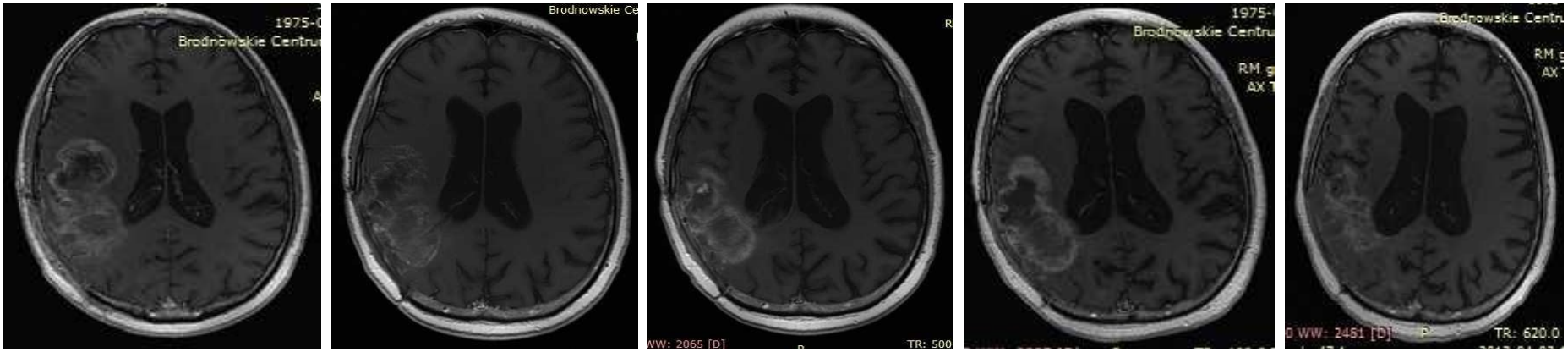
Tractography DWI ^{18}FET

Patient B: GBM – primary, WHO IV (male, 37 y)
4 cycles, 7.8 GBq (210 mCi) total ^{213}Bi-DOTA-Substance P

First operation Feb `12; Progression June `12; First treatment July `12; Death Feb `14

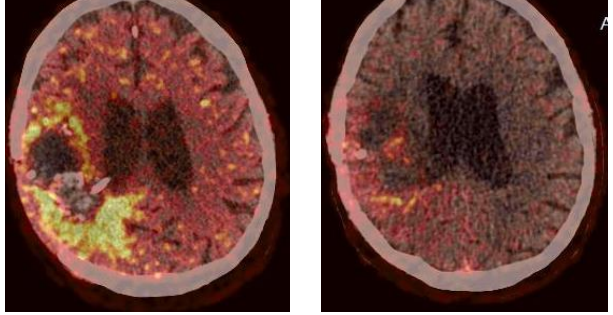


Before | 6 weeks: after first | after second | after third | after fourth treatment

Resection 4 months after last ^{213}Bi-therapy discloses massive necrosis, few vital tumor cells

Overall survival: 24 months
Survival after diagnosis of recurrence: 20 months

18FET - PET



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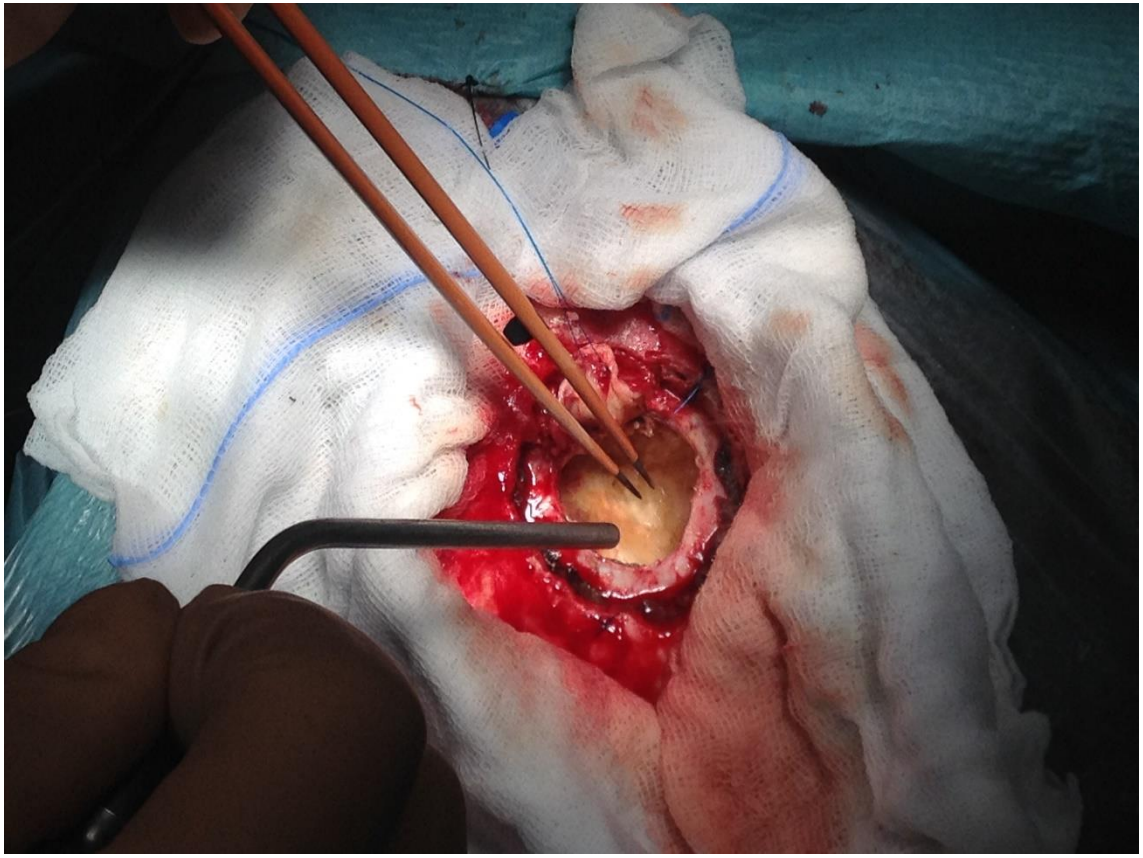
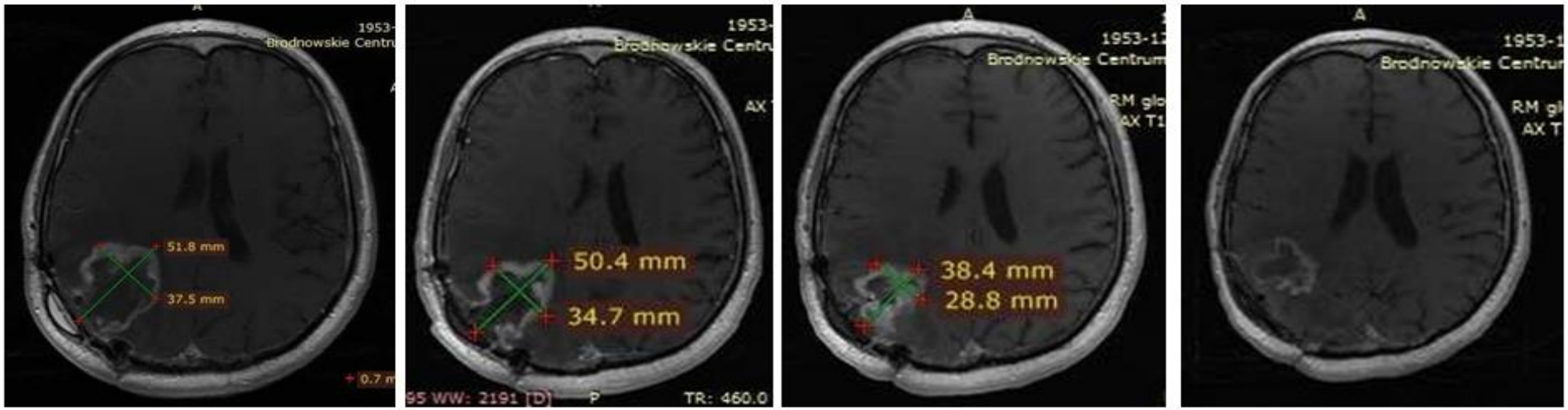
Patient B: GBM – primary, WHO IV (male, 37 y)
4 cycles, 7.8 GBq (210 mCi) total ^{213}Bi-DOTA-Substance P



Necrotic remnants in the post-operative cavity
4 months after last application of ^{213}Bi-DOTA-SP

Patient C: GBM – primary, WHO IV (male, 59 y)
6 cycles, 9.2 GBq (249 mCi) total ^{213}Bi-DOTA-SubstanceP

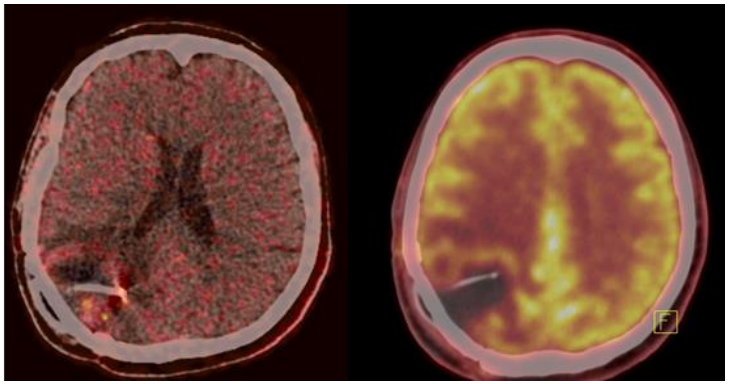
First operation Nov 2011; Progression Feb 2012; First treatment May 2012; Death May 2014



Before treatment | 6 weeks | 14 weeks | 22 weeks

after the start of treatment

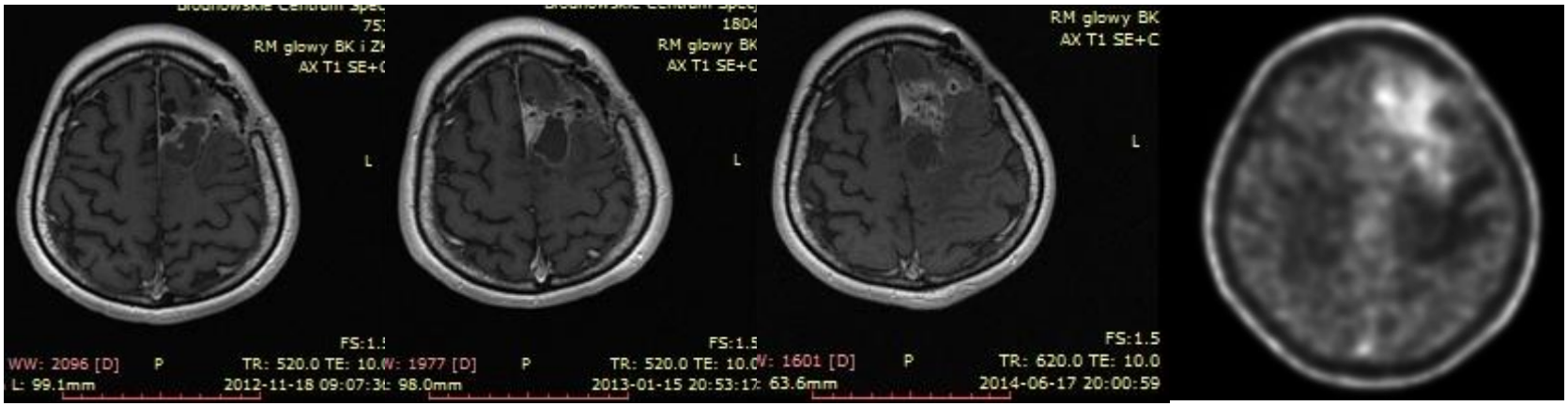
- Resection 6 months after 4th ^{213}Bi-therapy discloses massive necrosis, few vital tumor cells
- 2 more cycles
- Overall survival: 29 months



18FET (Jan 2013) 18FDG

Patient D: GBM – secondary, WHO IV (f, 40 y)
3 cycles, 5.8 GBq (157 mCi) total ^{213}Bi-DOTA-SubstanceP

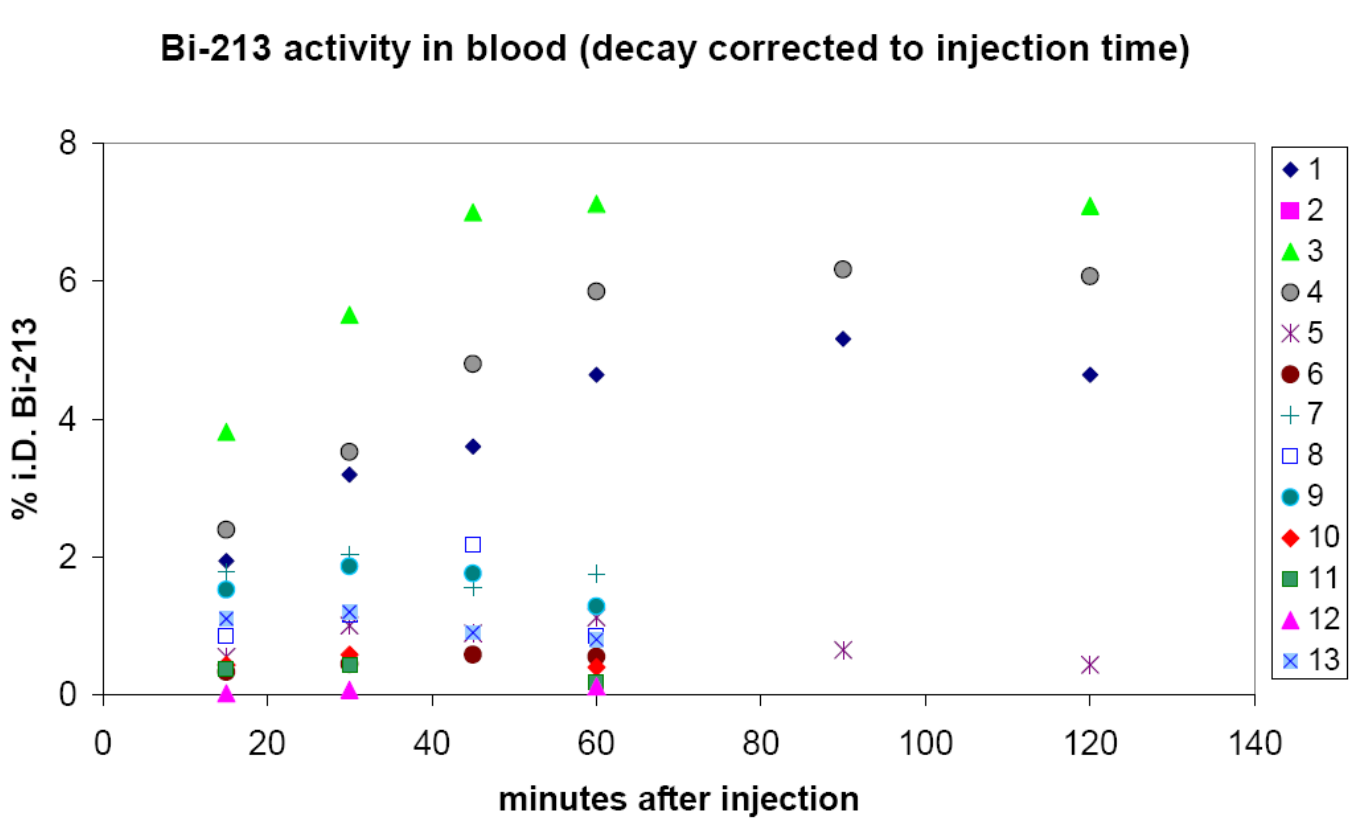
Confirmation of Glioma gr II Apr 2011;
Second op. and confirmation of GBM IV - Feb 2012; progression Oct 2012;
first treatment - Nov 2012

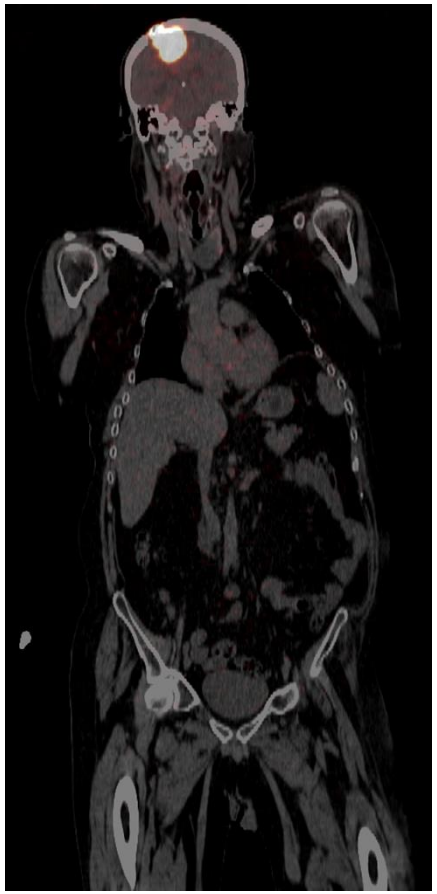


Before two months 19 months FET-PET 24 months

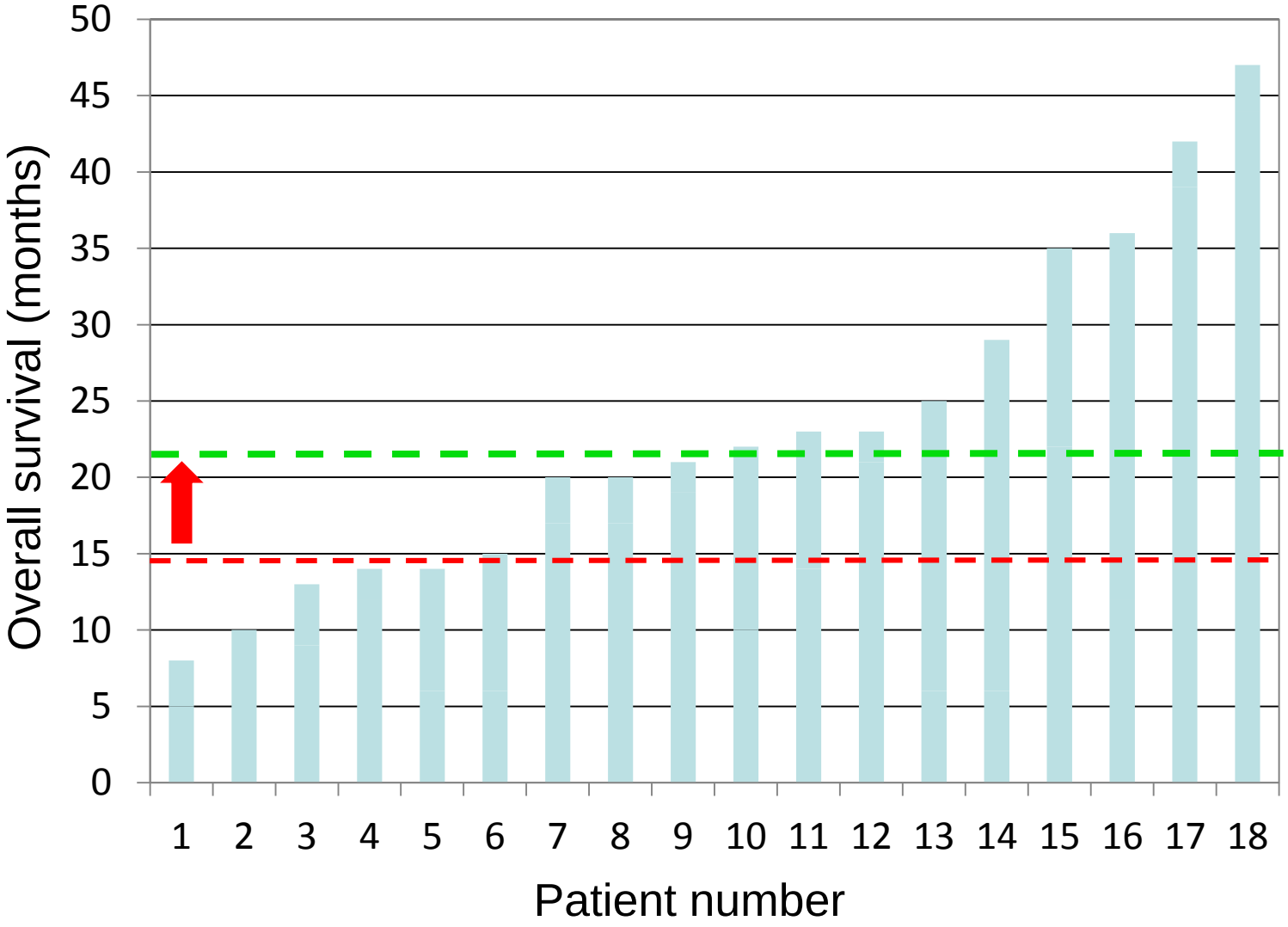
Overall survival since manifestation of grade IV: + 36 months

Limited transfer of ^{213}Bi-DOTA-Substance P to the blood pool





analysis of survival: ^{213}Bi-substance P



median survival: **21.5 months**

Standard therapy: **14.6 months**

Caveats of the method

- Large tumor mass
- connection between postoperative cavity and ventricular system
  → injection of the tracer is not possible if tumor cells are located near the ventricle wall
- reposition of the catheter to the ventricle, as a result of of the tumor volume reduction and retraction
- occlusion of the catheter

Interim results: feasibility and toxicity

- Current follow up period: 2 to 36 months
- Co-injection of ^{68}Ga-DOTA-Substance P allows imaging of biodistribution with PET/CT
- High retention of ^{213}Bi-DOTA-Substance P at tumour site
- Intracavitary / intratumoral injection of ^{213}Bi-substance P is tolerated well
- Only mild, temporary adverse effects observed up to 14 GBq (378 mCi) ^{213}Bi-DOTA-SubtanceP
  → edema, epileptic seizures, aphasia,
  1 case of temporary ventricuitis

Interim results – primary GBM: survival and outlook

- survival data of GBM patients indicates 50% longer survival compared to standard treatment alone (21.5 vs. 14.6 months)
- 14 out of 18 primary GBM patients treated after recurrence died (progression of disease (*n=12*) or pulmonary embolism (*n=2*))
- Patient recruitment and dose escalation is ongoing
- Earlier start of ^{213}Bi-therapy – before manifestation of recurrence - might improve outcome; to be studied in follow-up protocol

Acknowledgements

Institute for Transuranium Elements
Christos Apostolidis
Alfred Morgenstern
Mirjam Weis

Medical University Warsaw
Leszek Krolicki
Bartosz Krolicki
Henryk Koziara
Agata Kopatys

Oak Ridge National Laboratory
Rose Boll
Saed Mirzadeh
Karen Murphy

University Hospital Basel
Helmut Mäcke
Adrian Merlo

The author is indebted for use of Ac-225/Bi-213 to the U.S. DoE's, Office of Nuclear Physics, Isotope Development and Production for Research and Applications Program