Targeted Alpha Therapy from bench to bedside - overview of activities at JRC-ITU

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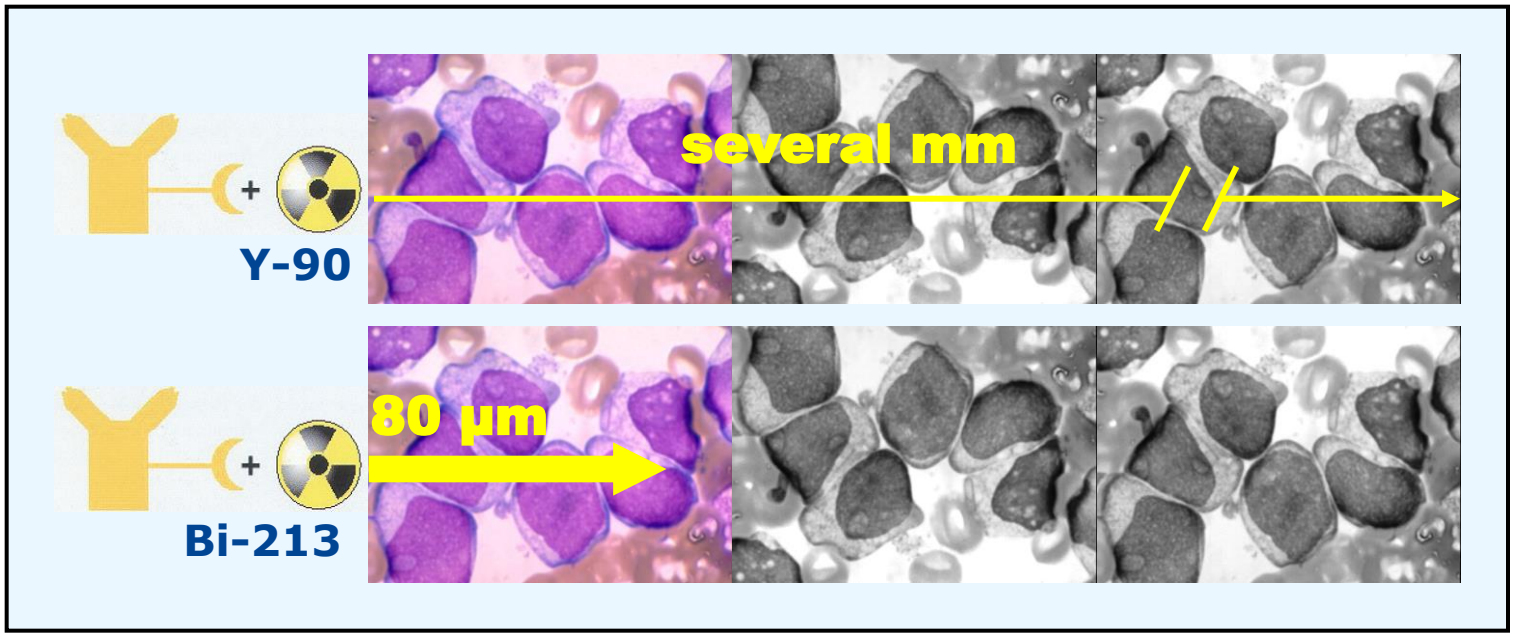
Therapeutic advantages of alpha emitting radionuclides

- Alpha radiation has high energy (4–9 MeV), high LET (~100 keV/µm) and short range in human tissue (< 0,1 mm)



=> Alpha radiation provides very effective and selective cell kill

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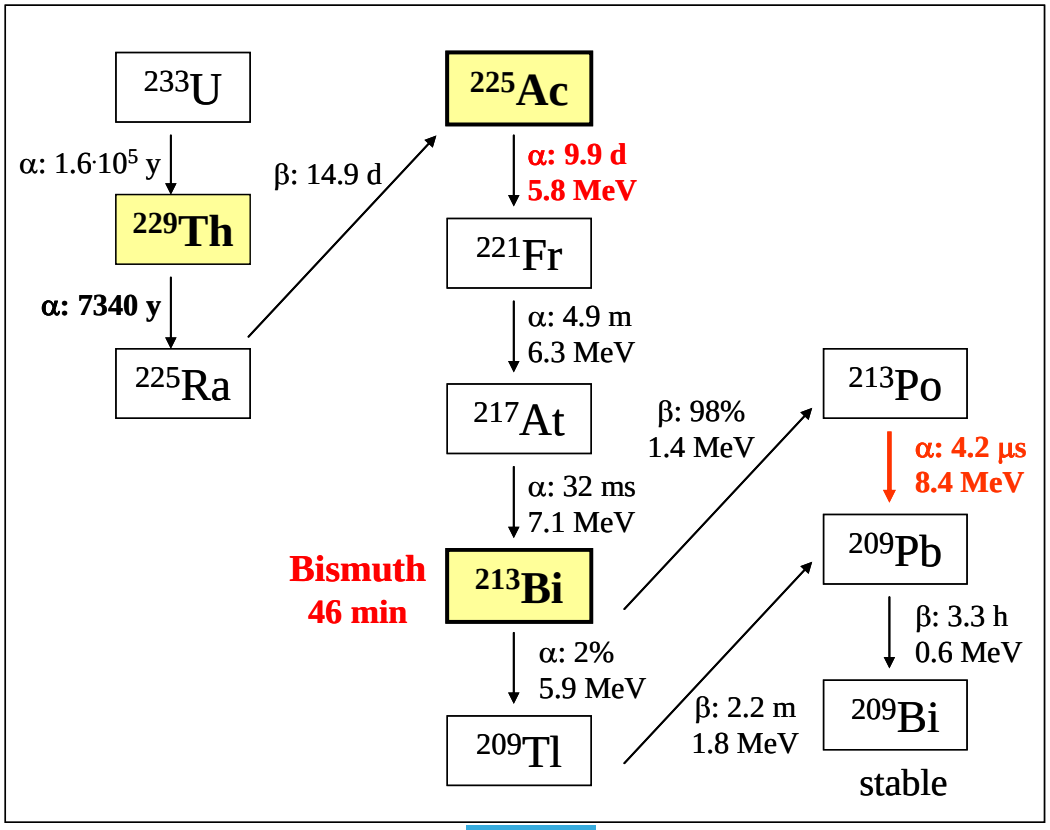
Choice of alpha emitter

- Clinically relevant alpha emitters include ^{223}Ra, $^{225}Ac/^{213}Bi$, ^{211}At, $^{212}Pb/^{212}Bi$
- Clinical experience in targeted alpha therapy available mostly with ^{225}Ac ($T_{1/2}$ = 9.9 days) and ^{213}Bi ($T_{1/2}$ = 46 min)
- ^{213}Bi is available from an established ^{225}Ac / ^{213}Bi radionuclide generator
- ^{213}Bi and ^{225}Ac readily form stable complexes with antibodies and peptides; imaging with ^{68}Ga-labeled analogs possible

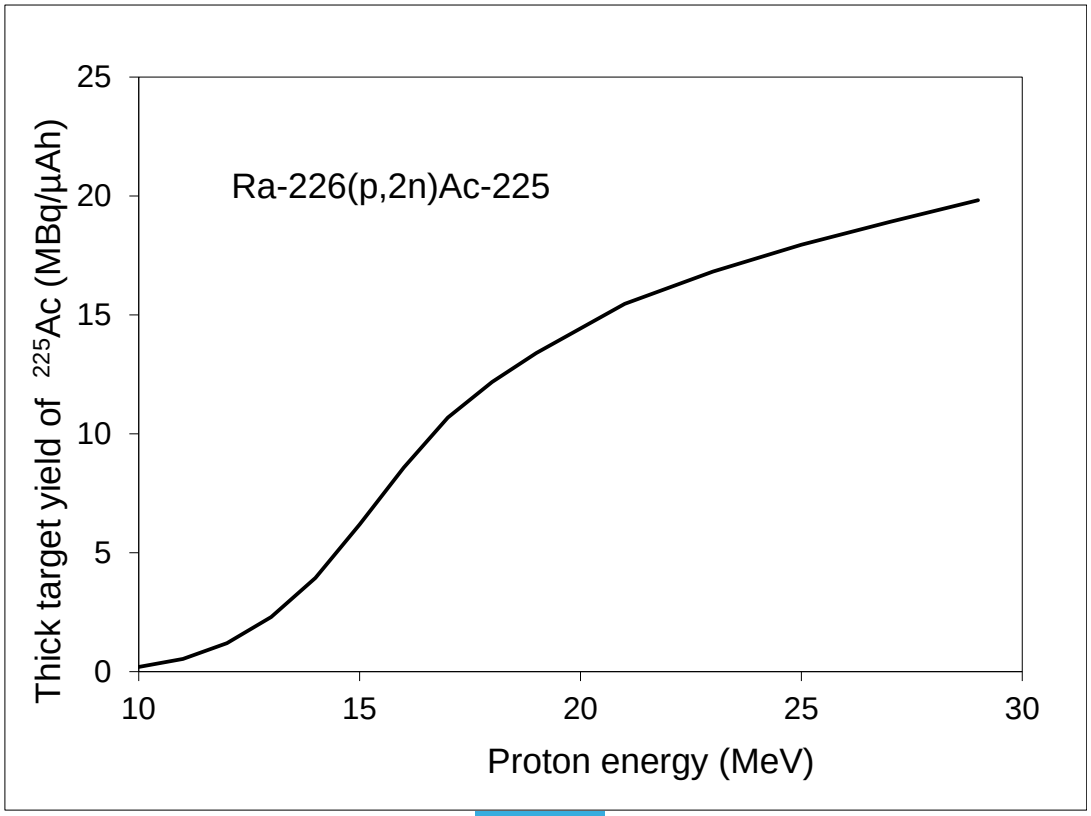
Production of ^{225}Ac / ^{213}Bi

- To date: Radiochemical extraction from ^{229}Th sources
- 3 suppliers available worldwide (ITU, ORNL, IPPE)
- Yearly supply (approx. 60 GBq) sufficient for treatment of up to 200 patients

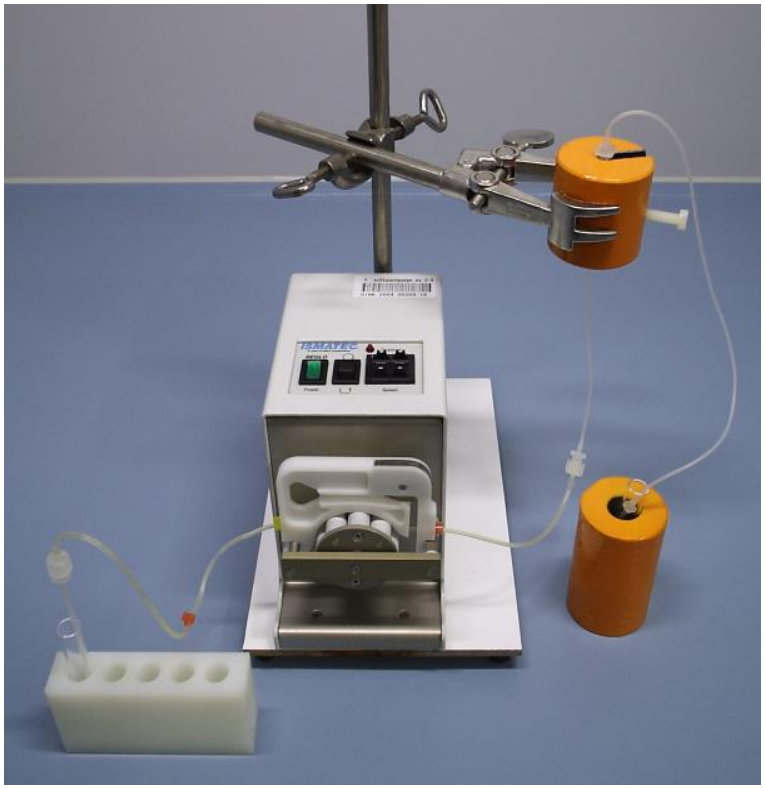


The future: Accelerator driven production of ^{225}Ac / ^{213}Bi

- Proton irradiation of ^{226}Ra in medium energy cyclotrons
  $^{226}Ra(p,2n)^{225}Ac$
- Thick target yield: 18 MBq/µAh at 25 MeV
  => basis for widespread commercial application



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



Today: semi-automated generator operation and radioconjugate synthesis

Future: fully automated generator operation and radioconjugate synthesis

(image courtesy of Dr. R. Knopp, Eurotope)

ITU´s pre-clinical and clinical collaborations

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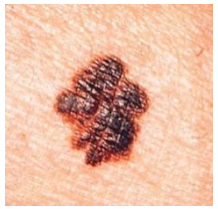
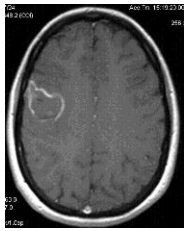
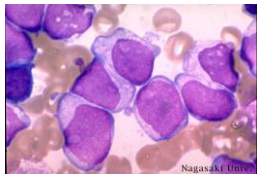


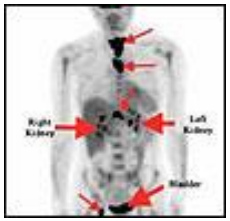
Melanoma Phase I
(Sydney)



Glioma Phase I
(Basel, Warsaw)

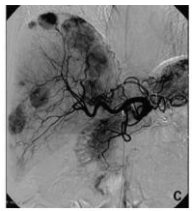


Leukemia phase I/II
(New York)

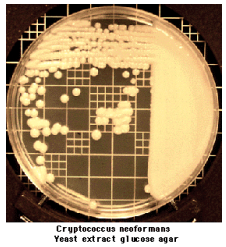


Breast Cancer
(Baltimore)

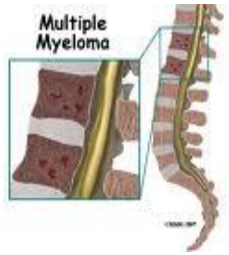
ITU
α-emitting
isotopes



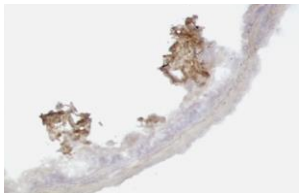
Neuroendocrine Tumors
(Heidelberg, Mainz, Rotterdam)



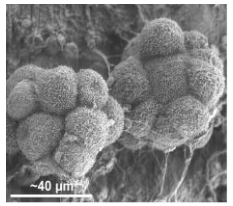
Infectious diseases
(New York)



Multiple myeloma
(Nantes)



Bladder carcinoma
(Munich)



Ovarian Cancer
(Gothenburg)

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^{213}Bi-DOTATOC therapy of NETs

- Therapeutic options for metastatic NET refractory to beta-radiation PRRT (^{90}Y/^{177}Lu) are limited

- Alpha-emitters have been shown to break radioresistance to beta- and gamma-radiation as well as resistance to chemotherapy *in vitro**

  => NET patients refractory to beta therapy might benefit from peptide receptor alpha therapy

- Drugs labeled with the short-lived alpha emitter ^{213}Bi ($T_{1/2}$ = 46 min) require rapid tumor targeting

- Intra-arterially administration of DOTATOC accelerates and increases tumor-uptake

Clinical testing – Methods

- Patients: 21 patients with unresectable NET refractory to standard therapies, including beta-emitter labeled DOTATOC, received ^{213}Bi-DOTATOC as experimental therapy
- Mode of administration: Intra-arterial injection into the main tumor feeding vessel
- Kidney protection: amino acid co-infusion, gelofundin
- Response assessment: MRI, ^{68}Ga-DOTATOC-PET/CT, Digital subtraction angiography, contrast enhanced ultrasound, Chromogranin A

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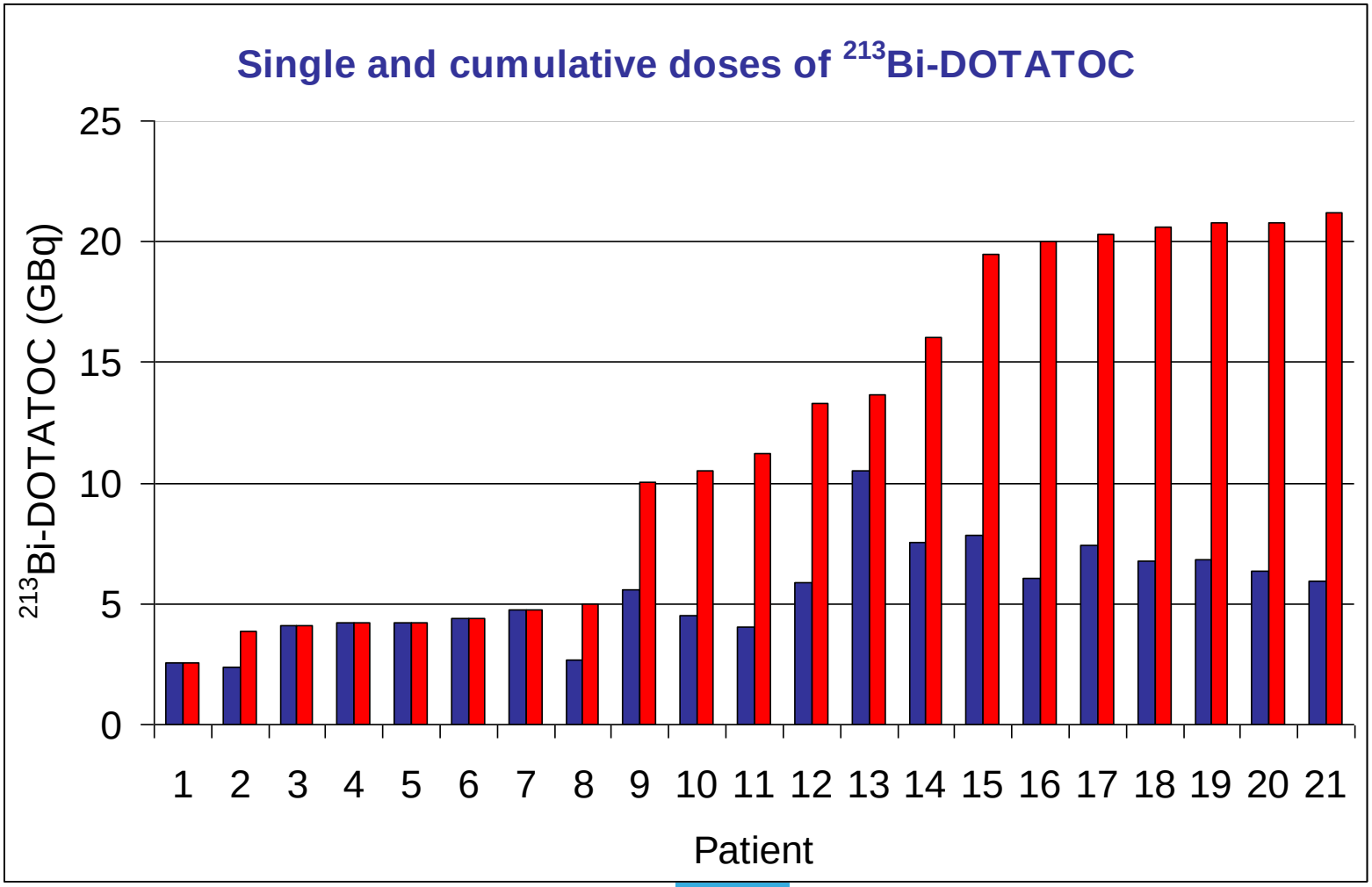
Dose escalation:

Single dose: ≤ 10.5 GBq Cumulative dose: ≤ 21 GBq



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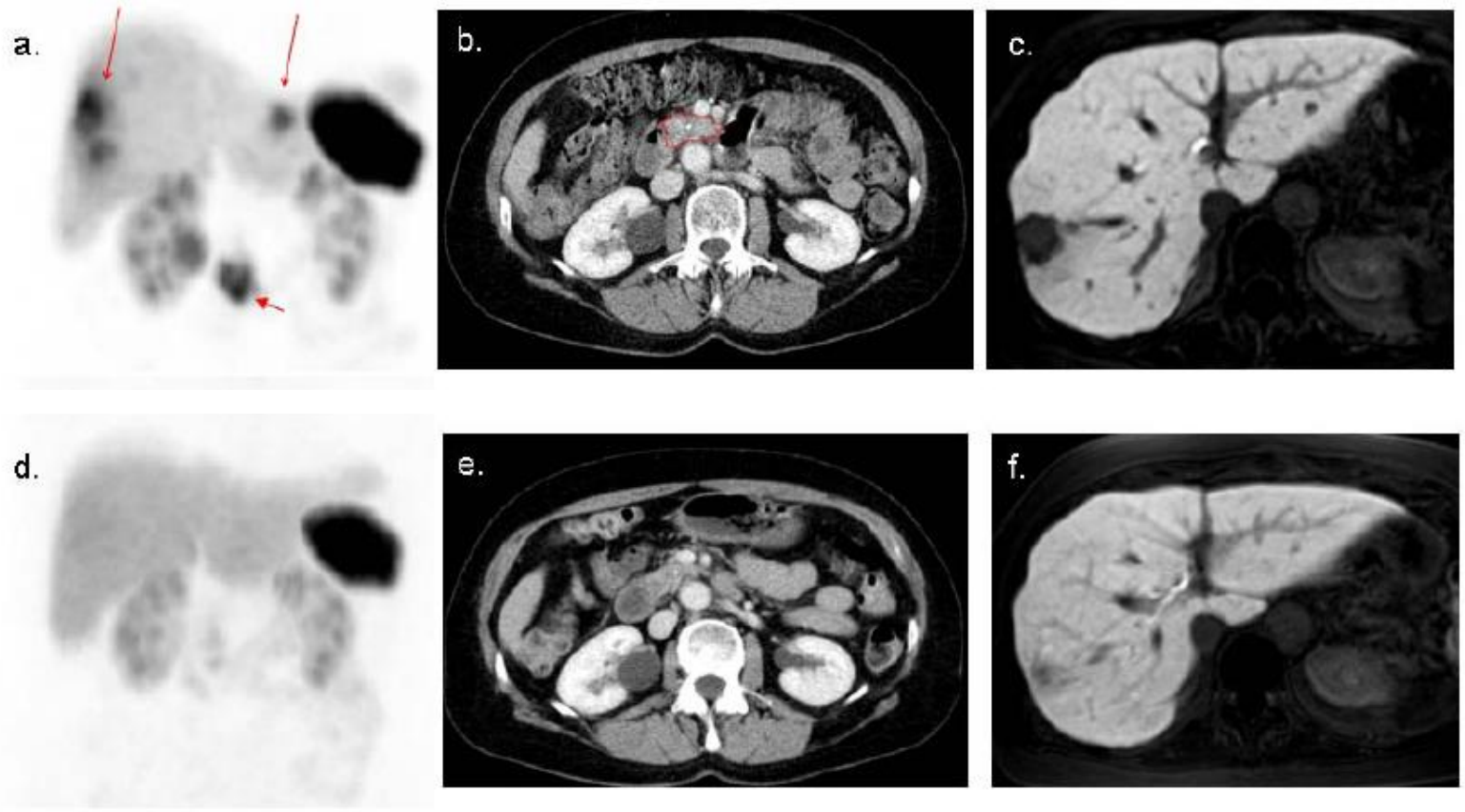
Toxicity (1.5 – 3 years follow up):

- 2 cases of Radiation induced pneumonitis
  10.5 GBq single dose (1/1) => dose escalation halted
  15 GBq in 3 cycles within 16 weeks (1/7)
  mild symptoms, outpatient treatment with good response to steroids
- 1 case of AML with typical radiation induced chromosomal aberrations 2 years after initiation of ^{213}Bi-DOTATOC (pre-treatment 3 x 4 GBq Y-90-DOTATOC, 4 x 2 GBq Y-90 + 4 GBq Lu-177-DOTATOC, 8 GBq Lu-177-DOTATOC)
  Death 5 months later
- Temporary hair loss > 6 GBq single dose (4/7)
- Grade 1-2 kidney toxicity (4/21)

Case (61y, f)

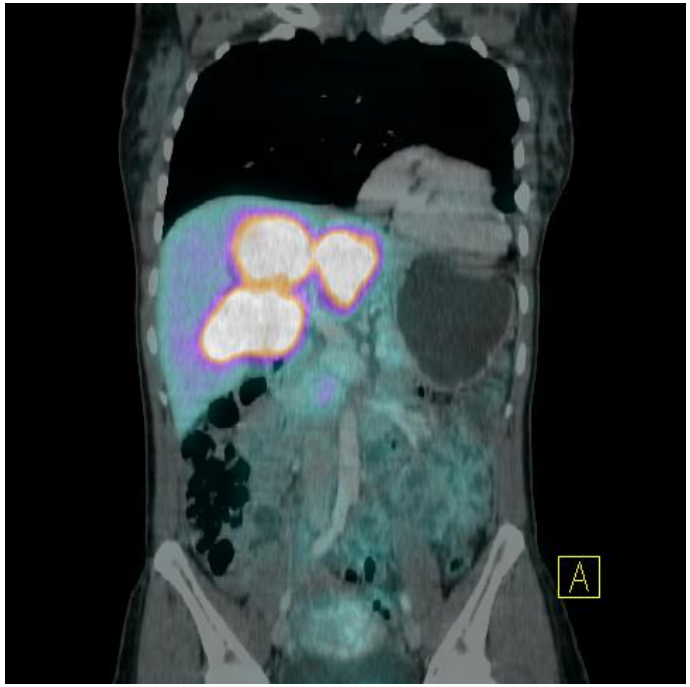
Partial response to 3 cycles of ^{90}Y-DOTATOC, then refractory



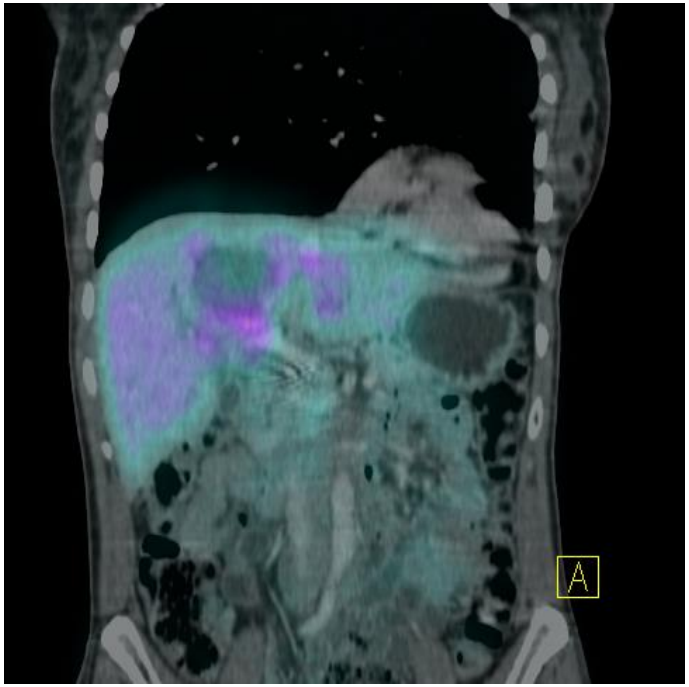
13 GBq

=> CR in liver lesions and primary tumor (ongoing, 37 months)

Case: (40y, f) pulmonal carcinoid with hepatic metastases
Pre-treatment: Chemotherapy (carboplatin/vepesid), „cold" octreotide, ^{90}Y-DOTATOC; progressive; risk of occlusion of caval and hepatic vein

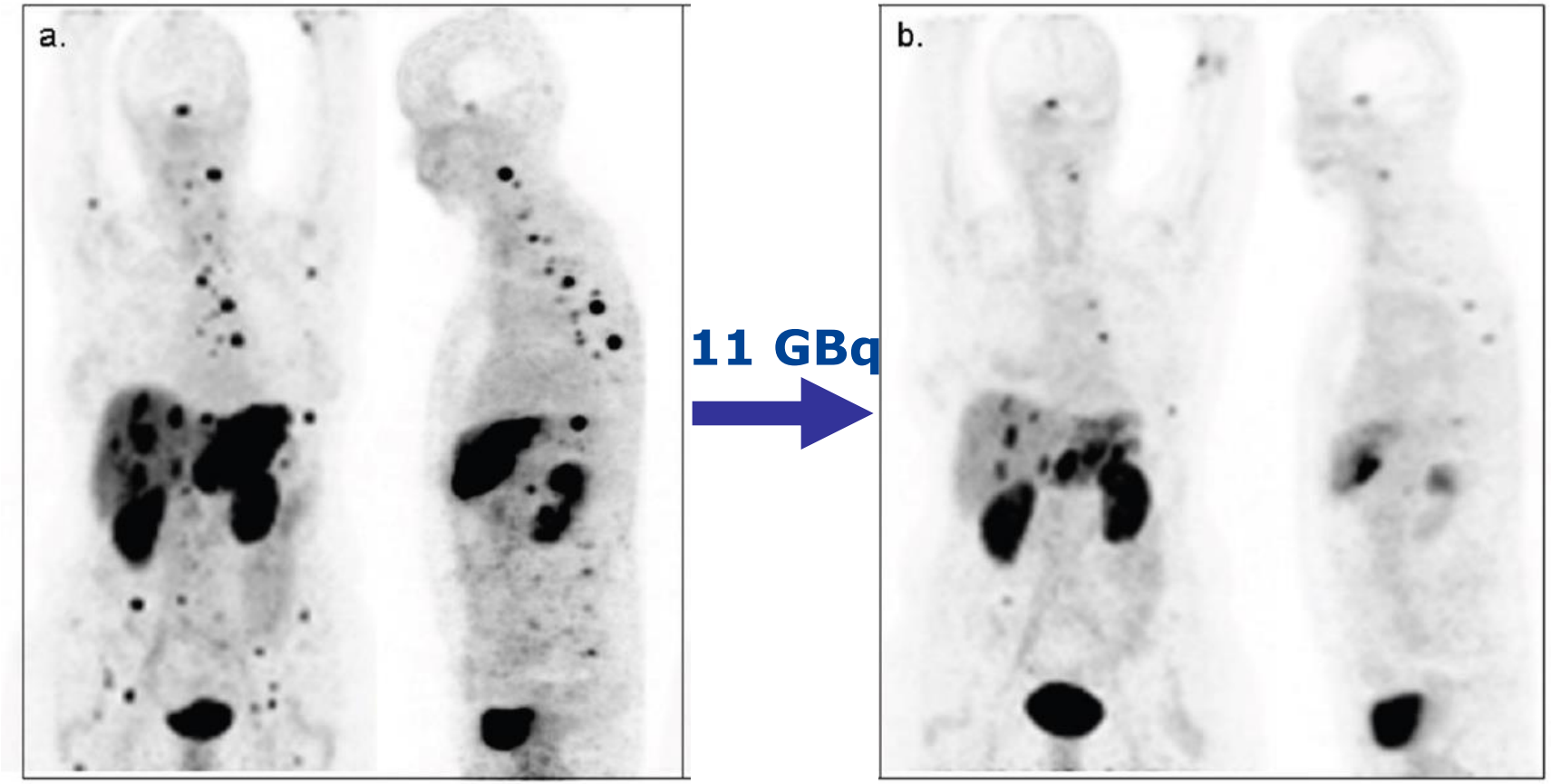


14 GBq



=> PR (ongoing, > 2,5 years)

Case: (60y, f) hepatic and bone metastases history of grade IV hematotoxicity after ^{90}Y-DOTATOC treatment

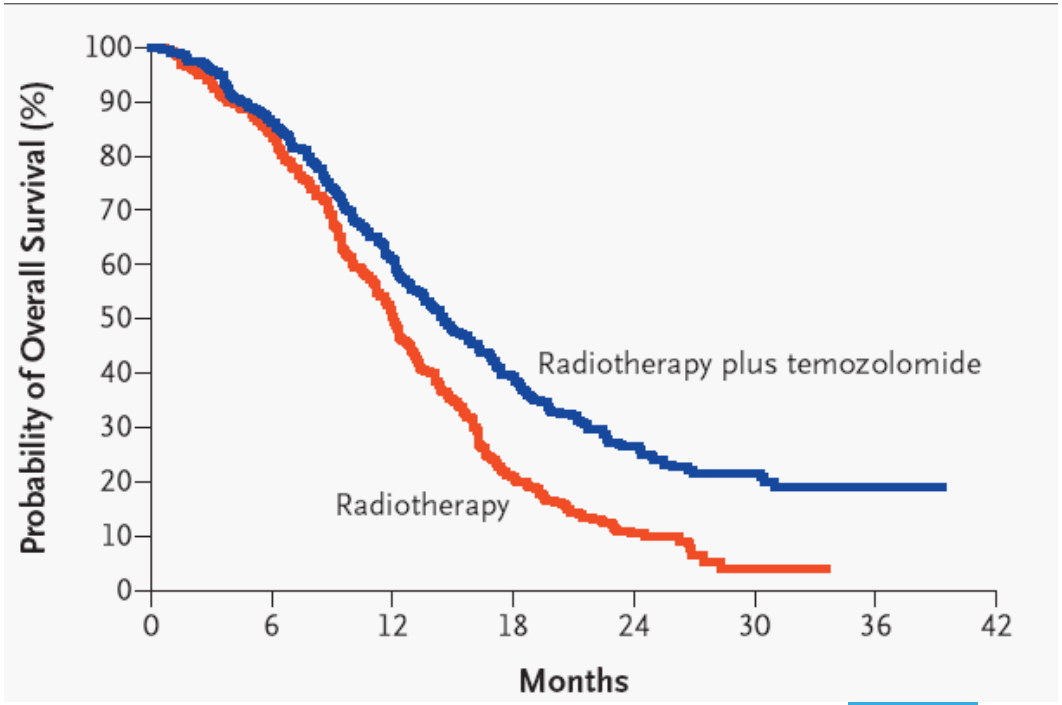


=> PR of liver lesions and bone metastases (lasting > 2 years)

=> *no hematotoxicity*

Peptide receptor alpha therapy of 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



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

Stupp, NEJM 2005

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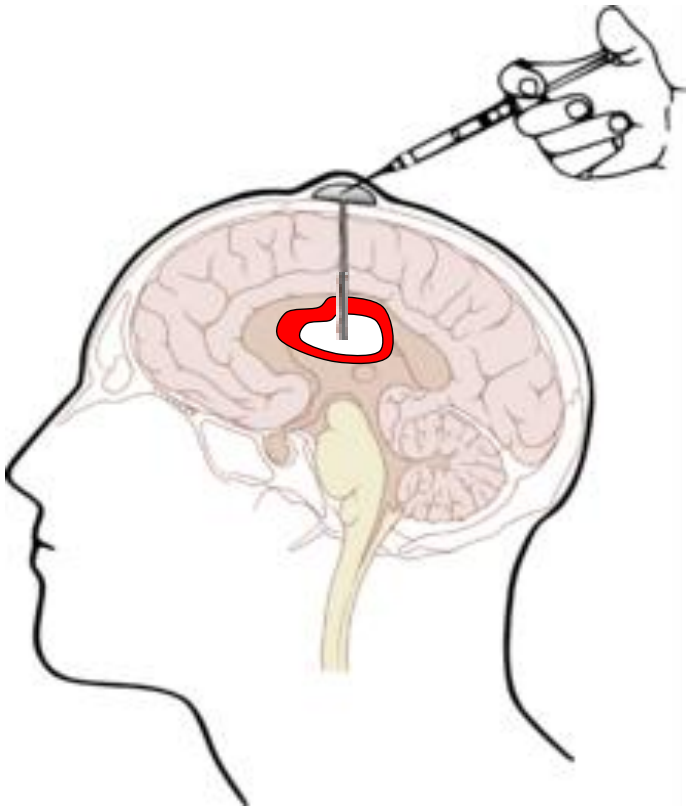
Targeted alpha therapy with ^{213}Bi-DOTA-Substance P

- Targeting vector: DOTA-[Thi^{8}, Met(O_2)^{11}] – Substance P adresses NK1-receptor
- ^{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*)

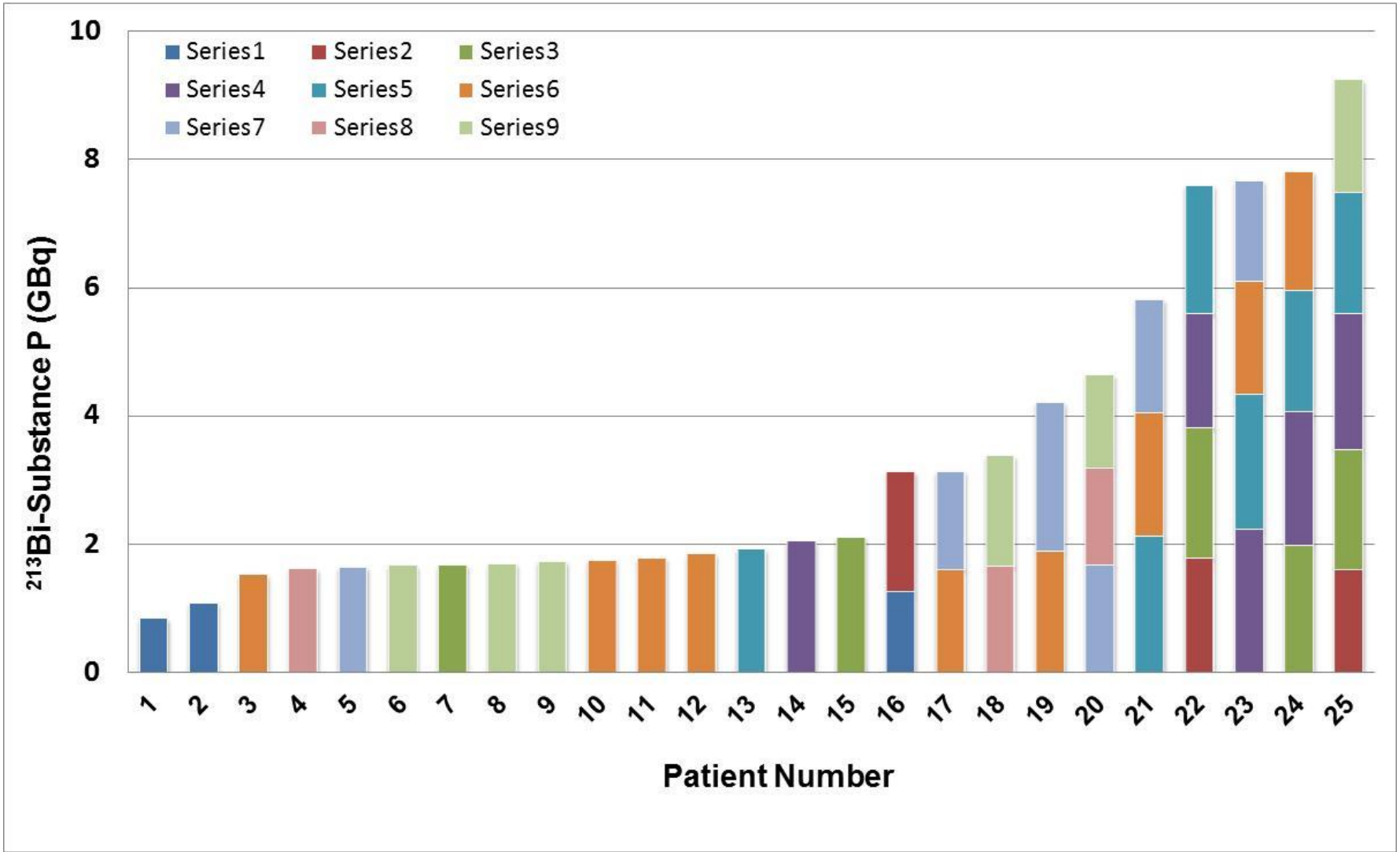
Treatment of recurrent GBM

- All patients receive standard treatment (surgery + radiochemotherapy)
- Recurrence => 2nd resection, placement and testing of catheter
- Intracavitary / intratumoral injection of 2 GBq ^{213}Bi-substance P every 2 months

  => monitoring of toxicity and overall survival
- To date 24 recurrent GBM patients treated 1 to 5 times (since April 2012)



Administered activities of ^{213}Bi-substance P (1-5 cycles)



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Interim results of phase I study

- Current follow up period: 2 to 18 months
- 24 patients with recurrent GBM treated with 1.1 to 9.2 GBq ^{213}Bi-SubstanceP in 1 to 5 cycles
- Intracavitary / intratumoral injection of ^{213}Bi-substance P is tolerated well
- Only mild, temporary adverse effects observed up to 9.2 GBq ^{213}Bi-SP (edema, epileptic seizures, aphasia)
- Co-injection of ^{68}Ga-DOTA-Substance P allows imaging of biodistribution with PET
- Patient recruitment and dose escalation ongoing

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Alternative Radionuclides under development

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U-230 / Th-226 system

- parent nuclide U-230: $T_{1/2}$= 20.8 days => long generator lifetime
- Th-226 emits cascade of 4 alpha-particles of 27.7 MeV cumulative energy
  => high cytotoxicity
- $T_{1/2}$ of daughter nuclides: 164 µs - 38 s => translocation from target site limited
- tetravalent Th(IV) forms very stable complexes
  => straightforward labelling protocols and high *in vivo* stability
- Th-227 ($T_{1/2}$= 18.7 d) for biodistribution studies and
  Th-232 for structural characterisation of chelate complexes

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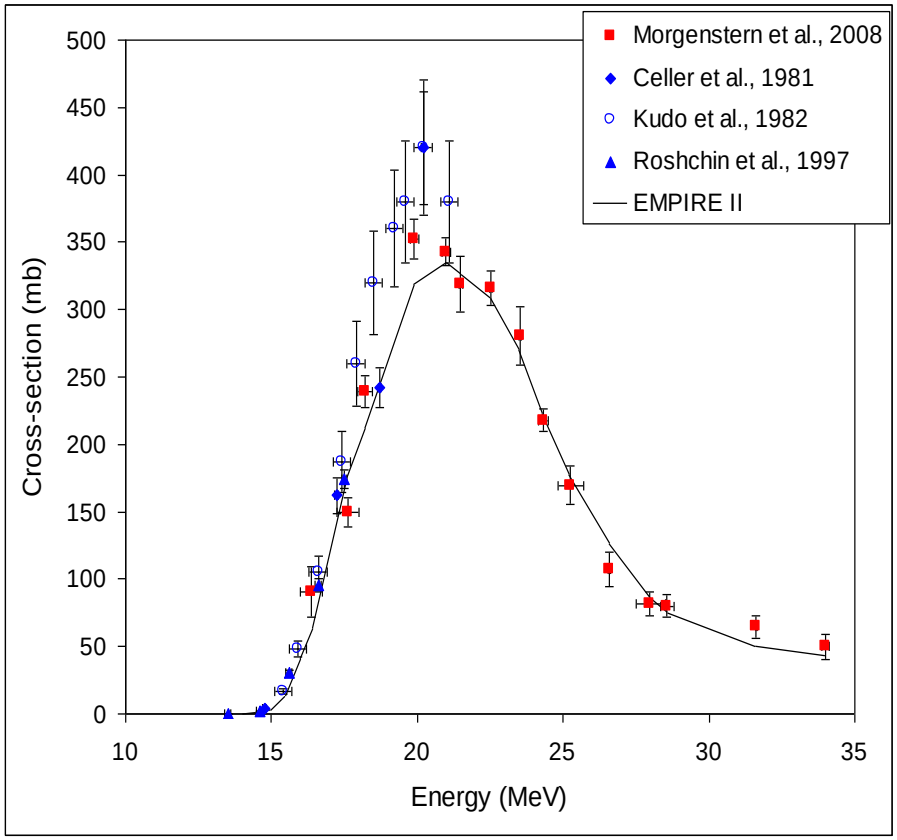
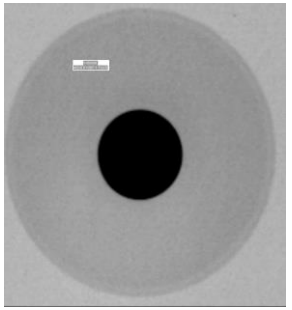
Production of U-230

Th-232 (p,3n) Pa-230 => U-230





X-ray image of Th-232 metal disc in Al envelope

Th-232 target and water cooled high current target holder

+ simple irradiation of low radioactive Th-232 metal
+ isotopically pure U-230 product
- only moderately effective (approx. 0.24 MBq/µAh for thick targets)
- co-production of fission products (Th-232(p,f))

A. Morgenstern et al., Appl. Rad. Isotop. 2008

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