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IN-HOSPITAL BNCT TREATMENT SYSTEM: OVERVIEW OF CLINICAL TRANSLATION

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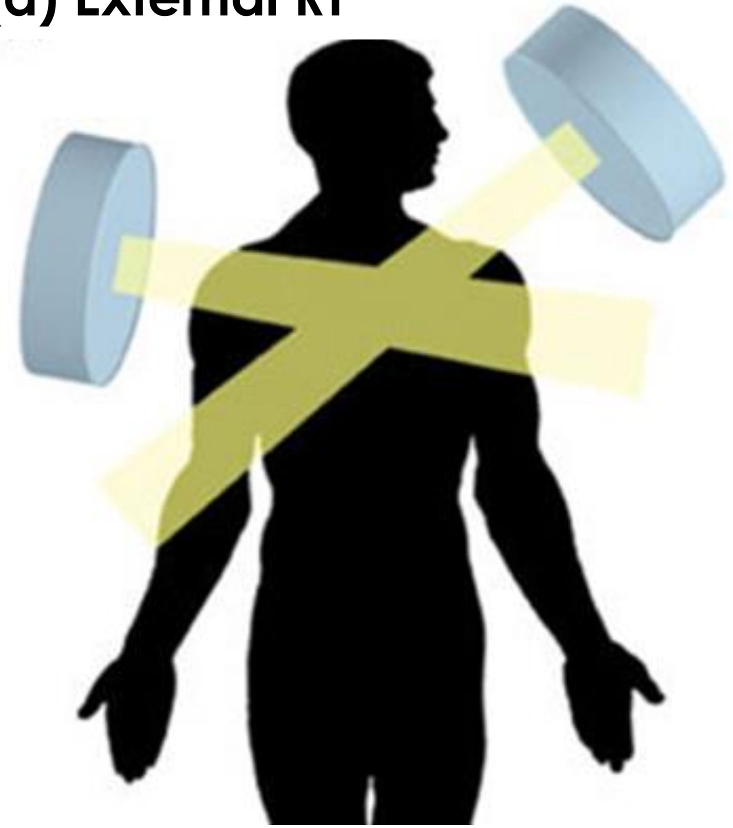
BNCT-PRINCIPLE

EXTERNAL AND INTERNAL RADIOTHERAPY

- Beams travel trough the patient
- They cross at the tumor position
- Unnecessary radiation dose across thebeam path

(a) External RT

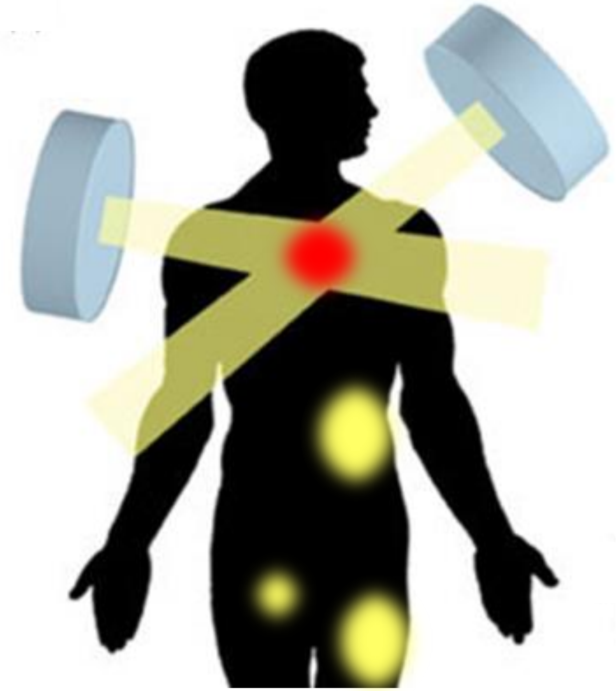


- Patient is given radioactive drug
- Drug accumulates in the tumor, but also in other organs
- Unnecessary radiation dose outside the tumor

BORON NEUTRON CAPTURE THERAPY

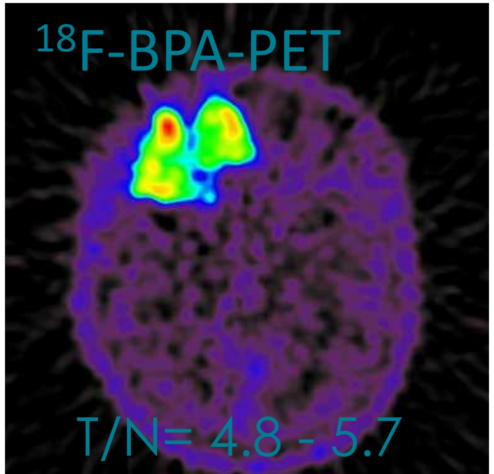
- Boron infusion accumulates in the tumor, but also in other areas of the body
- Tumor area is treated with a neutron beam, which interacts with boron in the treated area and produces high radiation dose to the target

(c) Biologically targeted RT

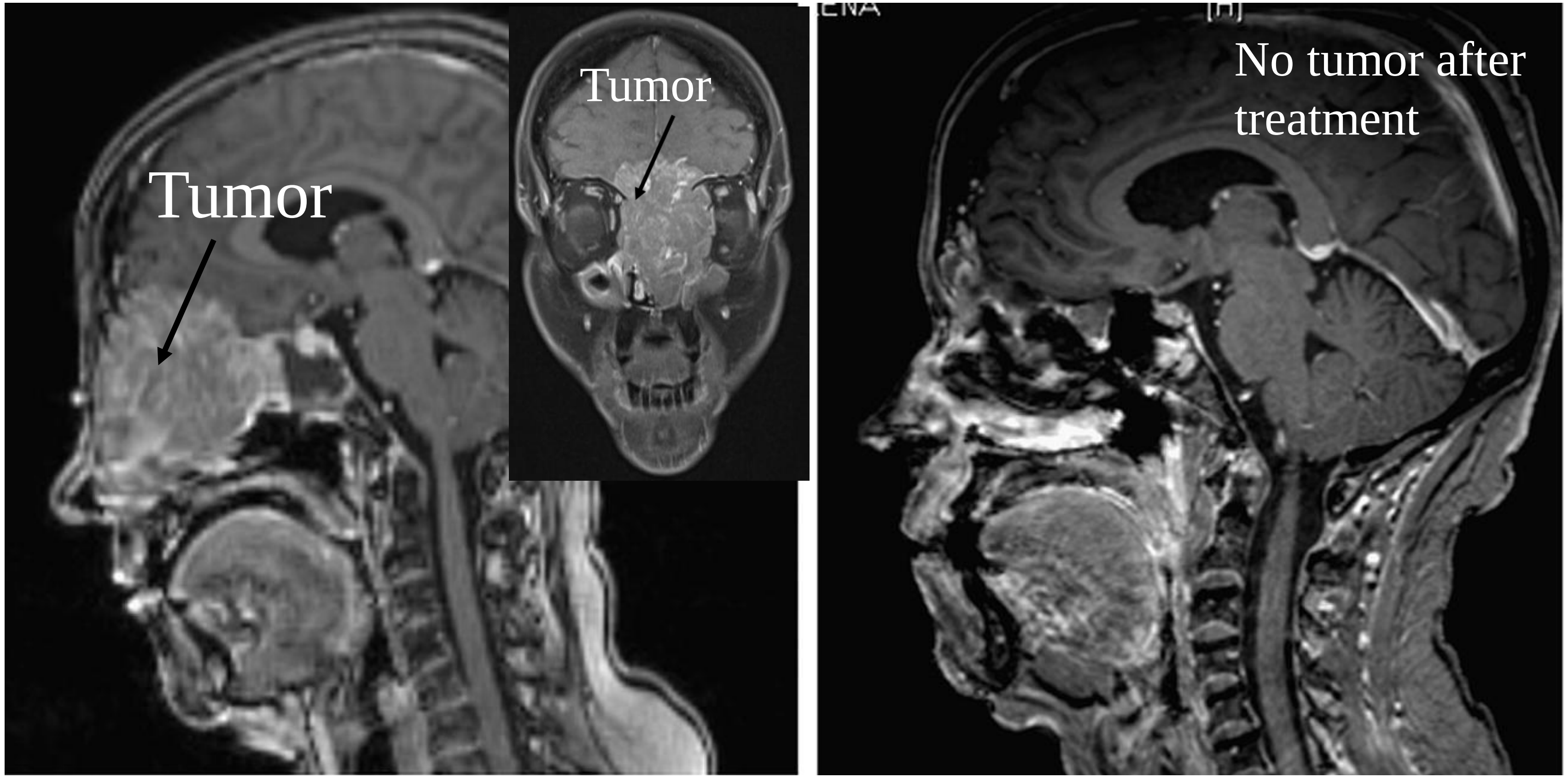


ADVANTAGES OF BNCT

- High dose gradient between cancer cells and healthy tissues
- Cancerous tissue is more sensitive to BNCT than healthy tissue
- Biological targeting allows the treatment of tumors with diffuse edges
- Can be administered:
  - After high-dose radiotherapy
  - Near or within radiosensitive tissues (brain, spinal cord, optic nerve, liver or lung etc.)



Kouri M. *et al* Rad. and Oncol, 72, 2004



Newly diagnosed poorly differentiated large squamous cell carcinoma

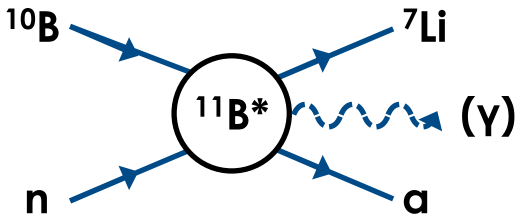
Treated with BNCT: GTV dose 31 Gy (W), optic nerve dose only 4 Gy (W)

4 weeks later **fractionated IMRT** 44 Gy (2 Gy/d) plus stereotactic fractionated booster dose 6 Gy. Weekly **cetuximab** plus **cisplatin** 40 mg/m^2 during photon RT.

Kankaanranta et al. Radiother Oncol 2011;99:97-100

BNCT IN A NUTSHELL

The dominating reaction:



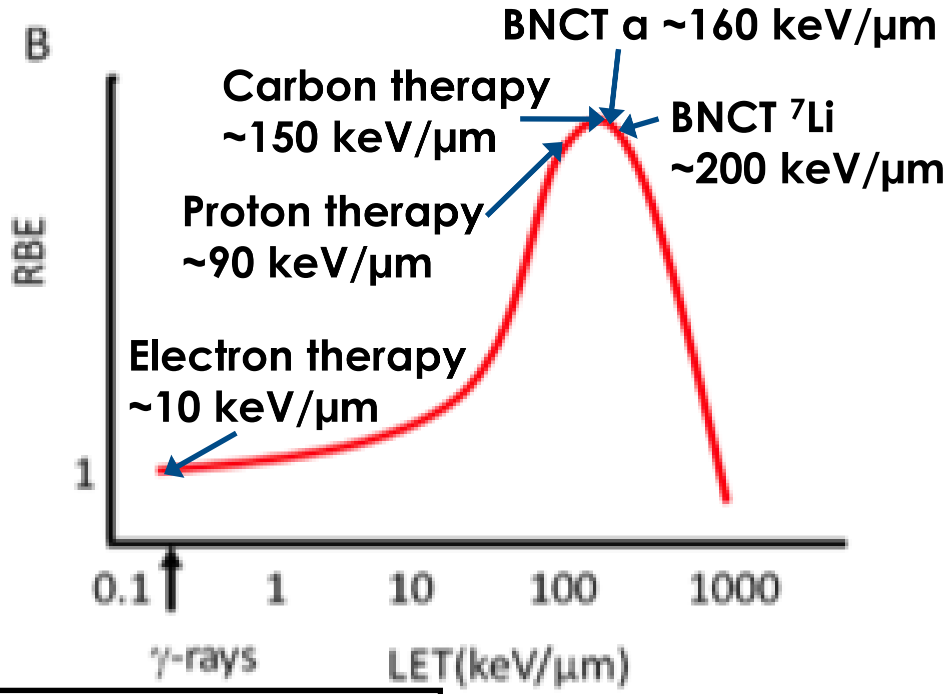
$$^{10}B + n \rightarrow {}^{11}B^* \rightarrow \begin{cases} 6\%: {}^{7}Li(1.02\ MeV) + \alpha(1.77\ MeV) \\ 94\%: {}^{7}Li(0.84\ MeV) + \alpha(1.47\ MeV) + \gamma(478\ keV) \end{cases}$$

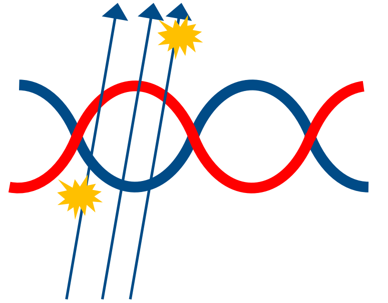
Biologically targeted radiotherapy:

- Patient is administered a boron carrier (BPA) by infusion
- The carrier agent has a high uptake to cancer cells but a low uptake to normal cells
- ^{10}B in the boron carrier has a high cross section for capturing thermal neutrons
- Patient is subjected to an epithermal neutron field
- The ^{10}B isotopes capture thermalized neutrons and produce highly ionizing secondary particles whose range is <10 μm
- The energy released in the reaction is absorbed mostly within the cell that took up the boron carrier

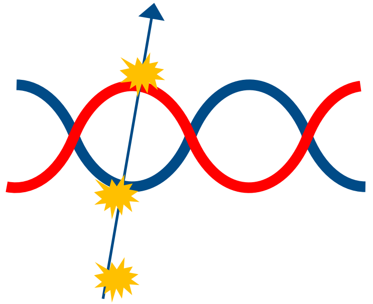
FROM PHYSICAL DOSE TO BIOLOGICAL DOSE

- Linear energy transfer (LET): how much an ionizing particle/ion deposits energy locally along its path per unit of length
- LET correlates with the relative biological efficiency (RBE)
- Comparison point: ^{60}Co irradiation (RBE=1)
- The probability for DNA double strand break increases as function of RBE; beyond RBE_{max} higher LET is "wasted" because the overkill effect
- BNCT: alphas and ^{7}Li nuclei close to RBE_{max}

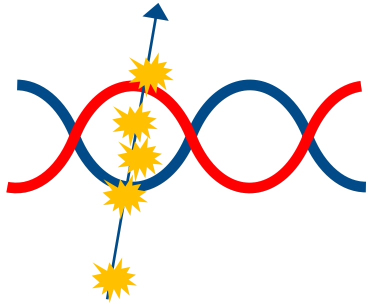




LET < 10 keV/µm
RBE = 1
p(SSB) >> p(DSB)



LET ~ 100 keV/µm
RBE = RBE_{max}
p(DSB) ~ 1 ; p(SSB) ~ 0



LET > 100 keV/µm
1 < RBE < RBE_{max}
p(DSB) ~ 1 ; p(SSB) ~ 0

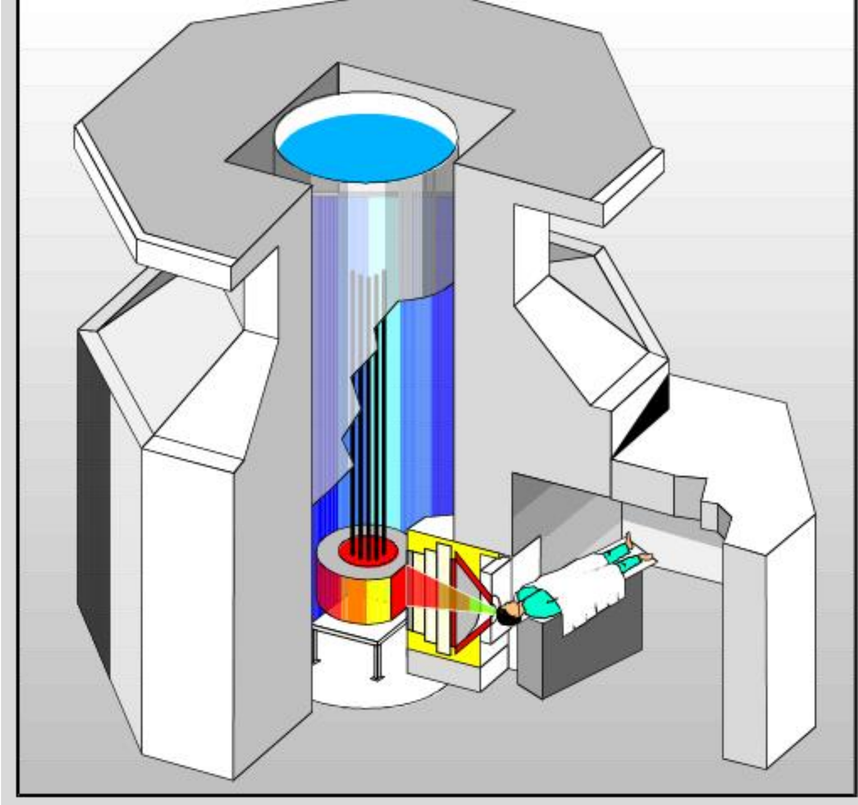
BNCT – IN PRACTICE

BNCT IN FINLAND

Research reactor FiR 1

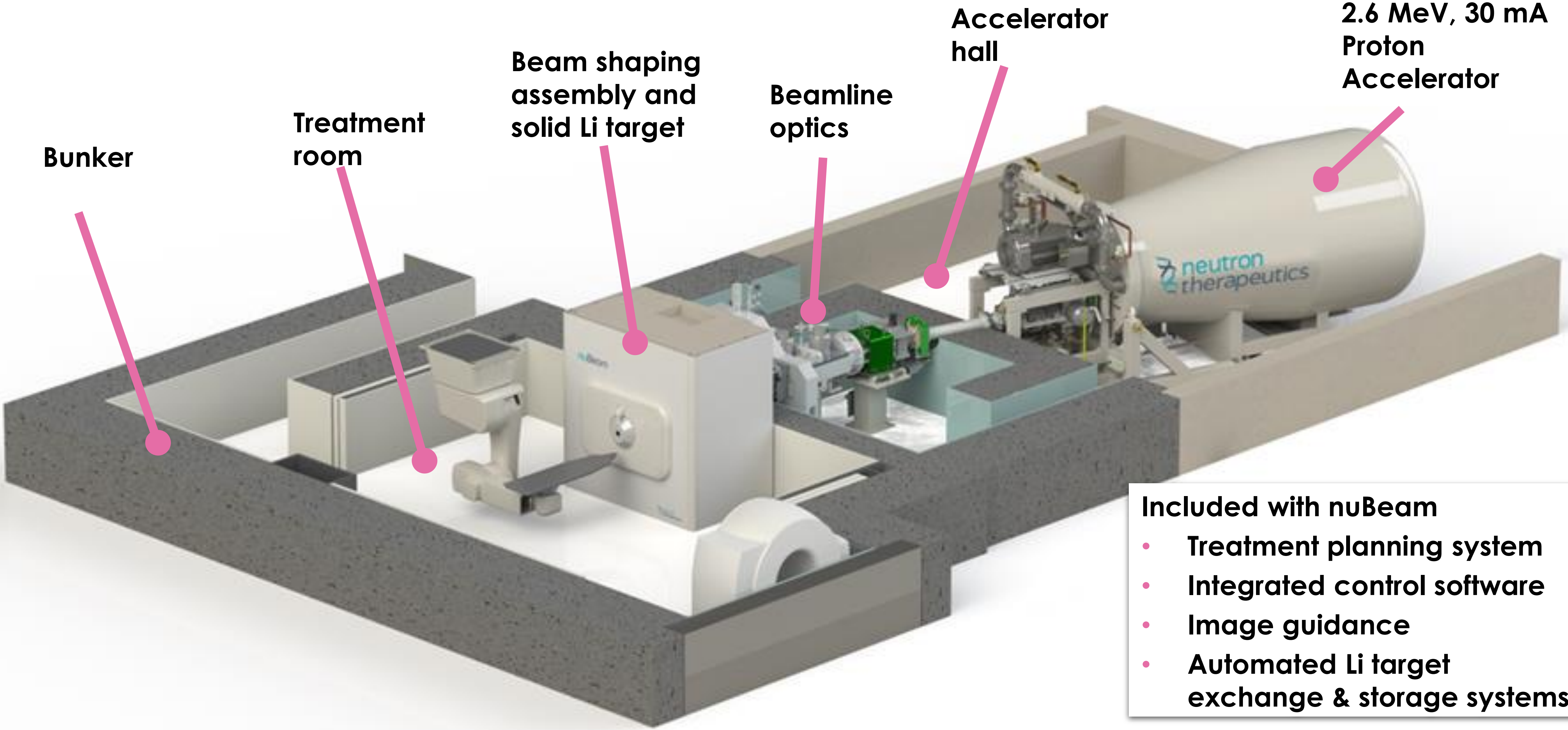
- 250 kW TRIGA Mark II
- Epithermal neutron beam $>10^9$ n/cm^2/s
- Closed 2/2012

- Patient treatments 1999–2012
- 249 patients >300 treatments
  - 101 patients within clinical trials
  - Patients from Finland, Sweden, Norway, Estonia, Italy, Monaco, Japan and Australia
  - Boron phenylalanine (BPA) as ^{10}B carrier
  - Brain cancer
  - Head&Neck cancer



NUBEAM BNCT SUITE BY NEUTRON THERAPEUTICS

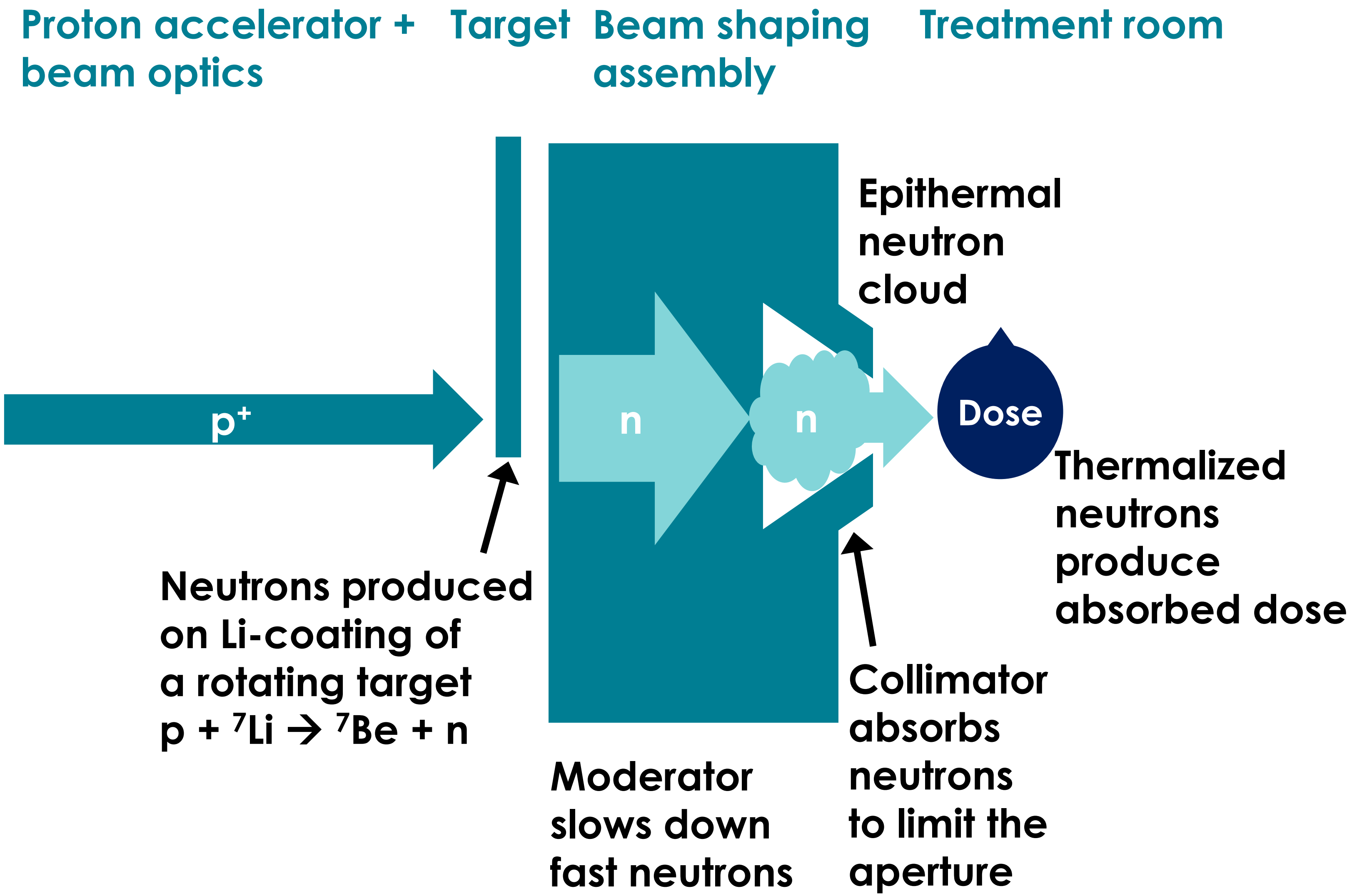
neutron therapeutics HUS



Included with nuBeam

- Treatment planning system
- Integrated control software
- Image guidance
- Automated Li target exchange & storage systems

FROM PROTON BEAM TO NEUTRON CLOUD



WHAT IS NEEDED FOR A BNCT TREATMENT

Neutron source

- nuBeam neutron source at the hospital
    - Beam dosimetry and QA
- Images for planning the treatment
    - CT / MRI / (F18-BPA -)PET
        - Target definition
        - *Boron distribution in the patient*
- Boron carrier
    - HUS-pharmacy: Boron phenylalanine (BPA)-infusion

Blood boron concentration

- ICP-OES (induced coupled plasma optic emission spectrometer)

Treatment planning

- Radiation dose in the target and organs nearby

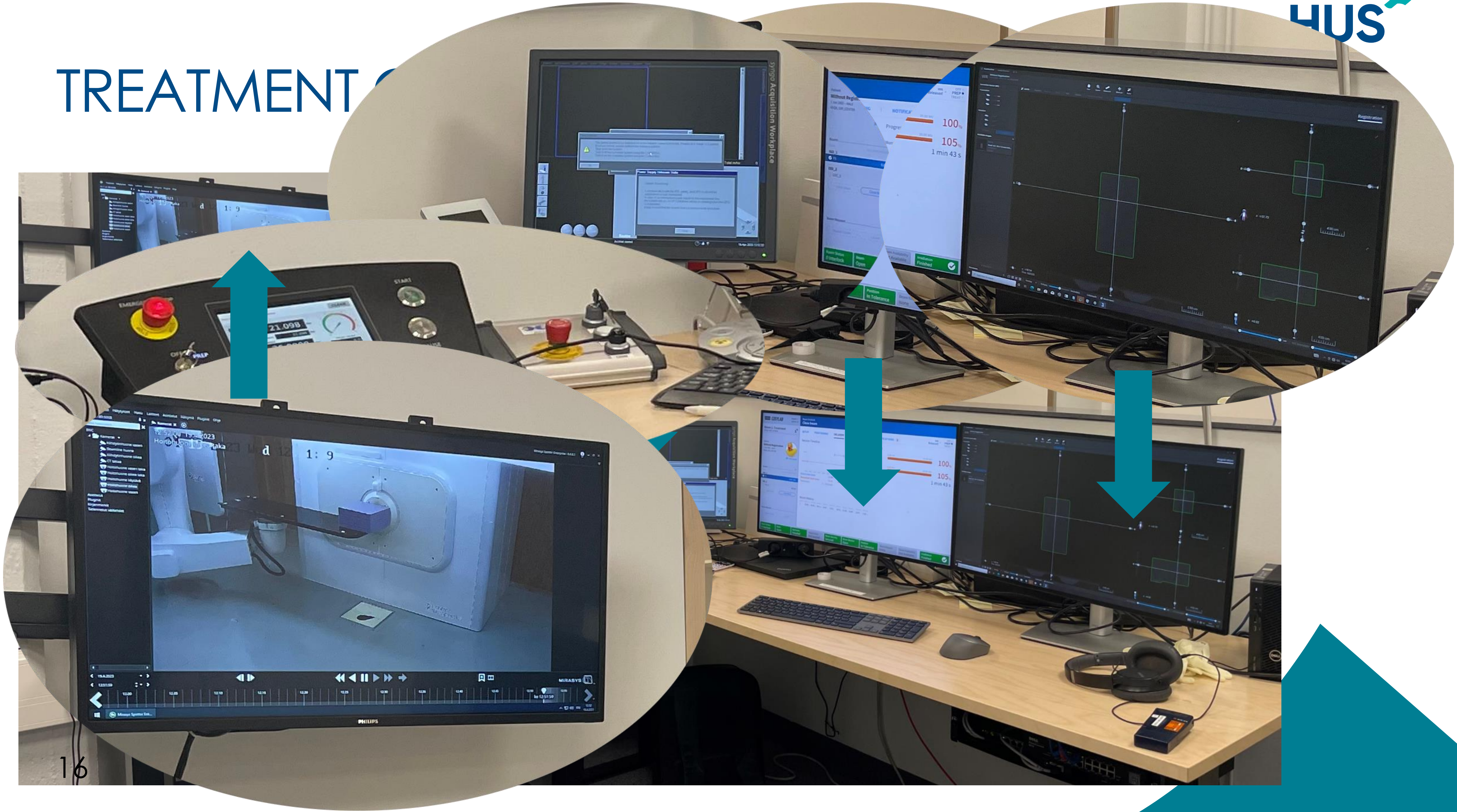
- Hospital personnel

HUS BNCT FACILITY

BNCT TREATMENT ROOM

- Beam shaping assembly and a lead shield
- Robotic couch that allows patient positioning and CT imaging
- In-room sliding gantry CT
- The room is covered with non-activating material

TREATMENT C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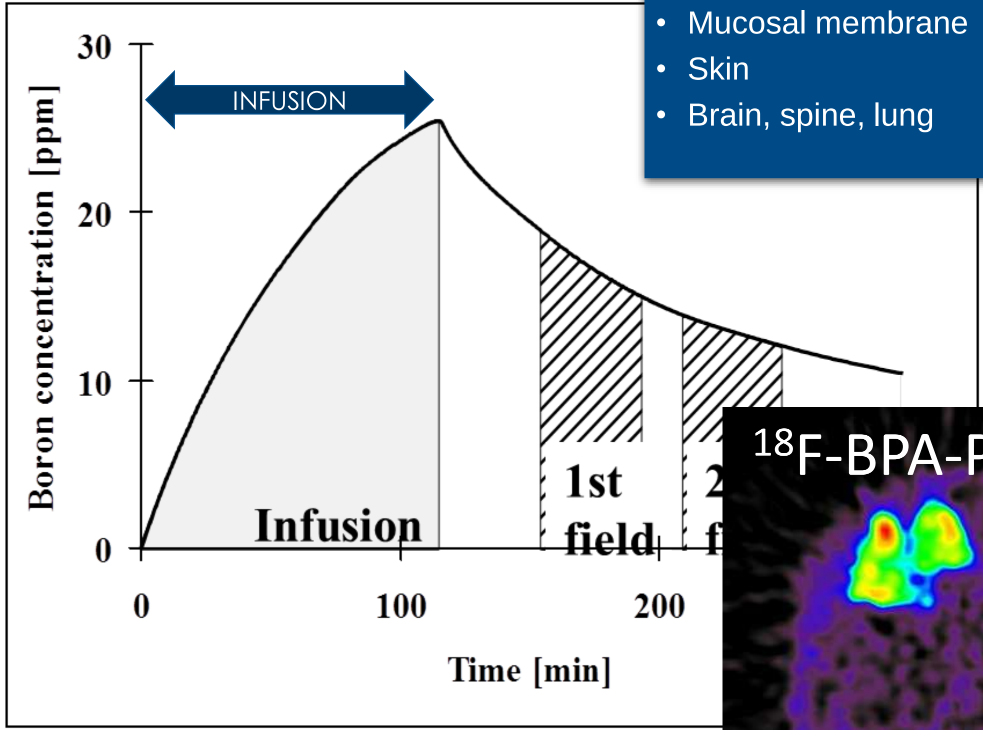
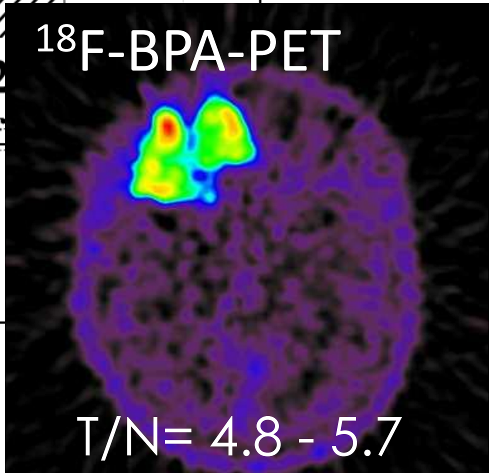
BORON CARRIER INFUSION AND ANALYSIS

- BPA-F (400 mg/kg) intravenously over 2 hours
- Blood samples taken every 20 minutes
- ^{10}B concentration measured with inductively coupled plasma optical emission spectrometry (ICP-OES)

Tissue-to-blood ^{10}B

- Cancer cells 3.5
- Mucosal membrane 2
- Skin 1.5
- Brain, spine, lung 1





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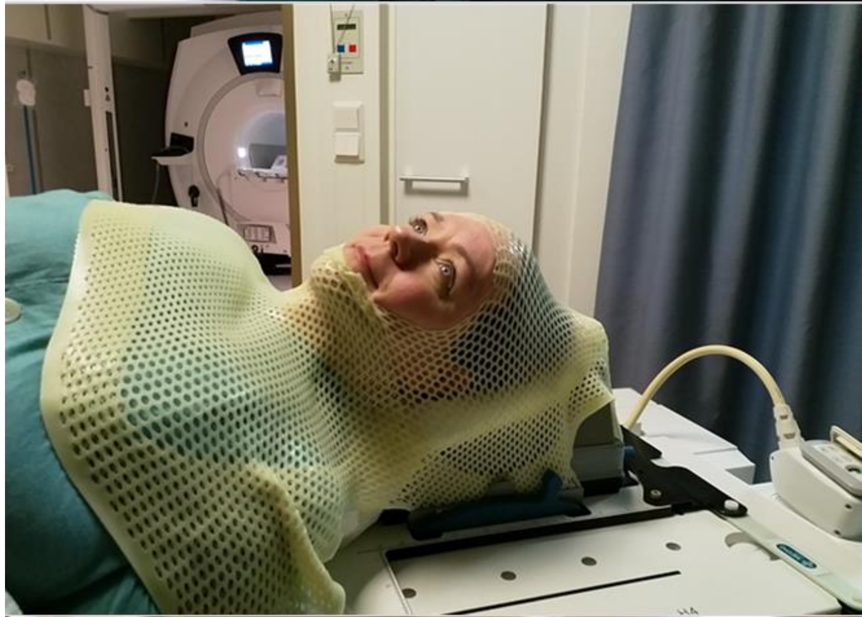
PATIENT POSITIONING ON ROBOTIC COUCH

Since the neutron beam is stationary, patient position needs to be optimized by fixation

- Triangular pillow
- Vacuum pillow
- 5 point facial mask

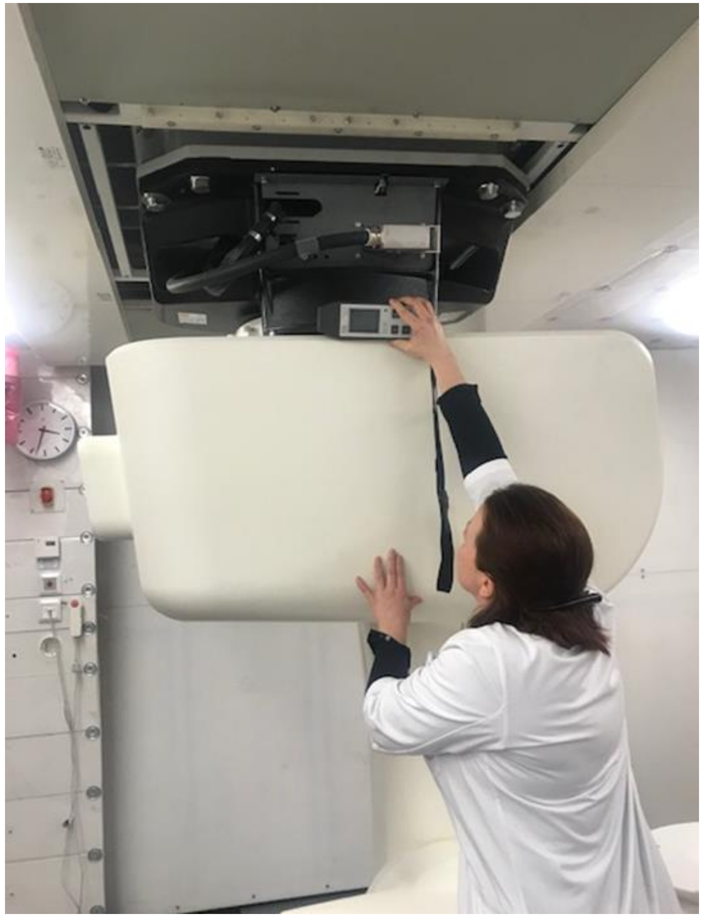
Robotic couch is used for CT imaging and treatment positioning of the patient

First BNCT facility with image-guided treatment



RESIDUAL ACTIVITY IN THE TREATMENT ROOM

- Treatment room has shielded with lithiated and borated plastic
- Room residual radiation is monitored with gamma probe
- Warning lights at the treatment room door
- Lead shield can be used in front of collimator
- Material of possible implants and other material in patient



DOSIMETRY AND QUALITY CONTROL

- **Aim:** ensure that:
  - 1) Measured neutron and photon fields are in line
  - with treatment planning caclucations
  - 2) Patient positioning during treatment is in toleranse
  - with planned position
- **Methods:**
  - Neutron activation
  - Ionization chambers
    - Depth dose / profiles
    - Beam components
    - Spectrum
  - Phantoms
    - Water tank
    - PMMA cylinder
    - Antomorphic phantom

Activation foils in a holder. Photo: LW

Couch position test with a patient load. Photo: LP

Ionization chamber scan. Photo: LW

CURRENT STATUS AND FUTURE PLANS

CURRENT PLANS WITH ACCELERATOR-BASED BNCT

- Recurrent head & neck cancer
  - First in a study protocol, then as accepted standard treatment
- Expand to other tumor types
- Multicenter trials
- To test novel boron carriers
- Combination treatments
- Randomized trials
- Basic and translational research

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Et al…