# Investigate the mechanism of proton boron capture therapy

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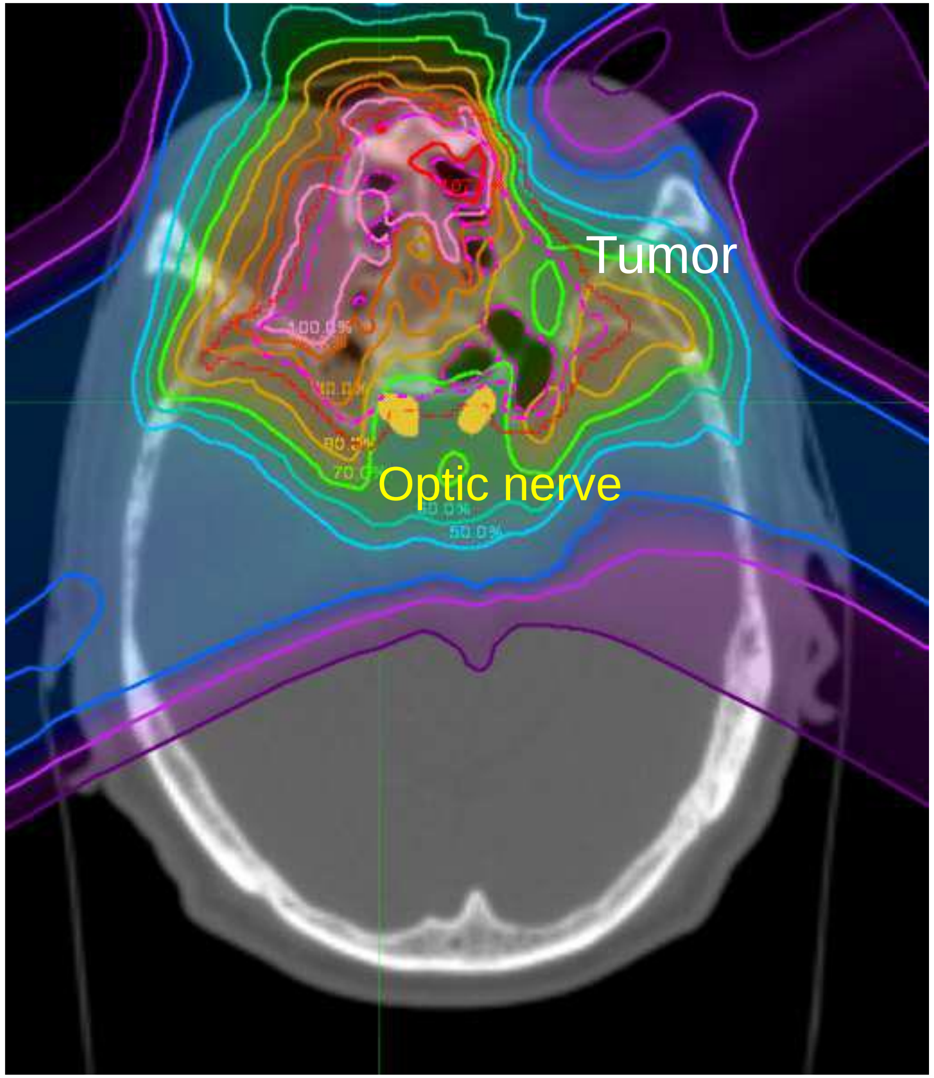
# Radiotherapy

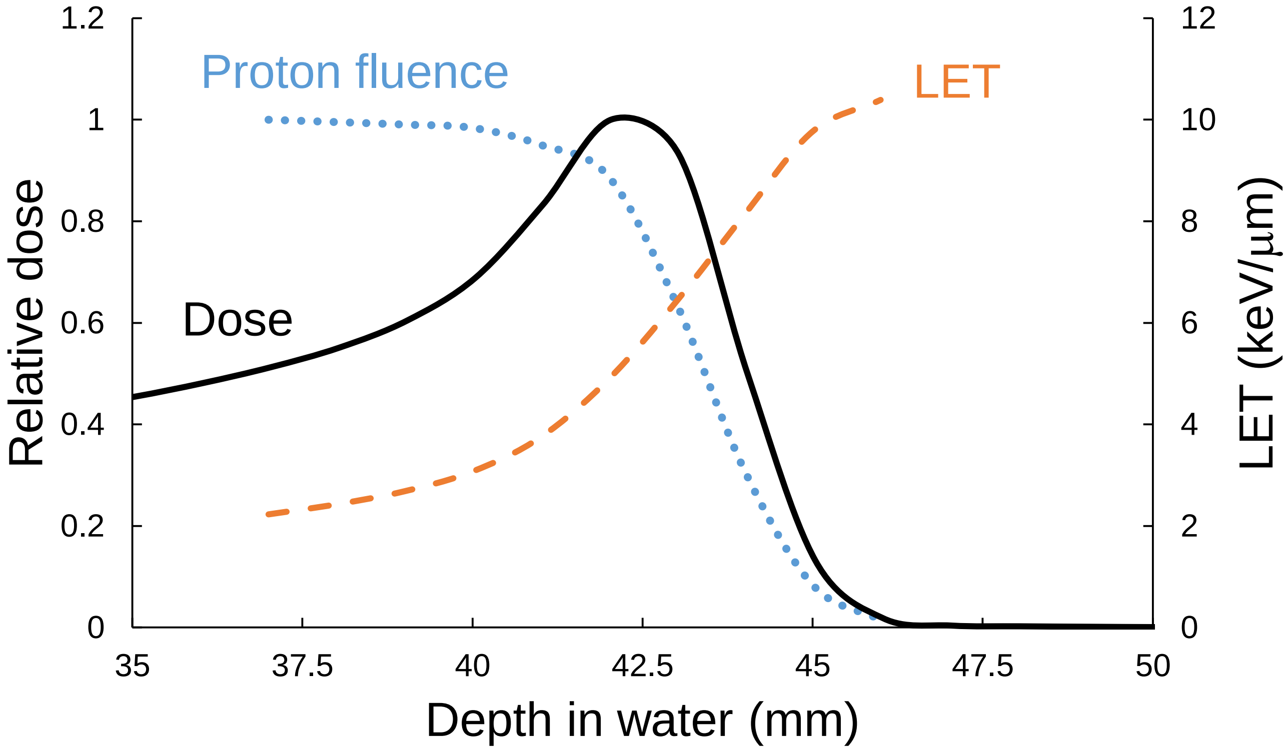
- One of the treatments of cancer
- Radiation destroys cancer cells by inducing DNA breaks
- Deliver a sufficient dose to a tumor region while sparing health tissues

Liu, Med Phys 39 1079 2012



# Proton cancer therapy

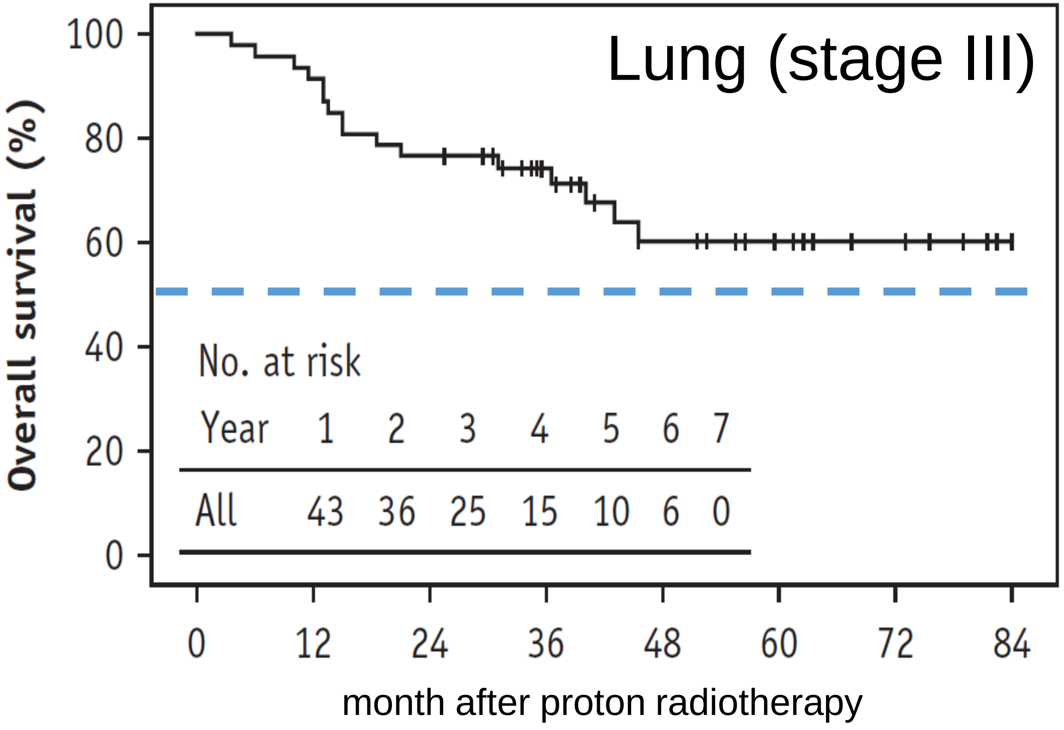
- A kind of radiotherapy with hydrogen nuclei
- Spare normal tissues behind a tumor because of the Bragg peak



# Treatment outcome

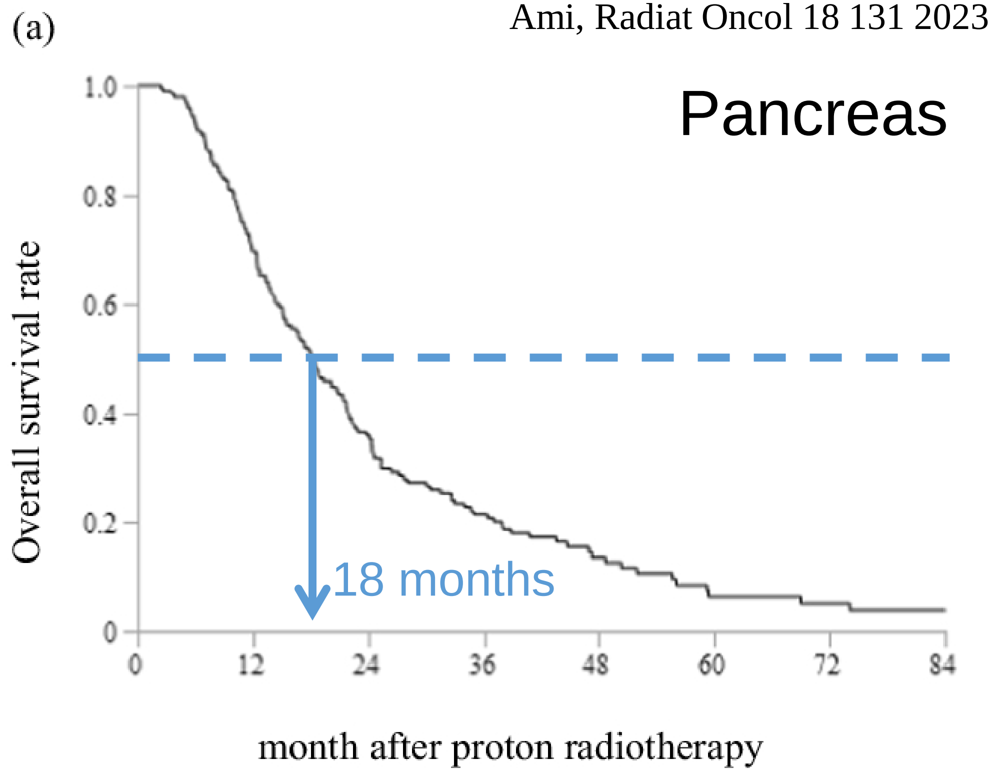
- Poor treatment outcome for radioresistant tumors

Iwata, IJROBP 109 1359 2019




Non-small cell lung cancer

Ami, Radiat Oncol 18 131 2023

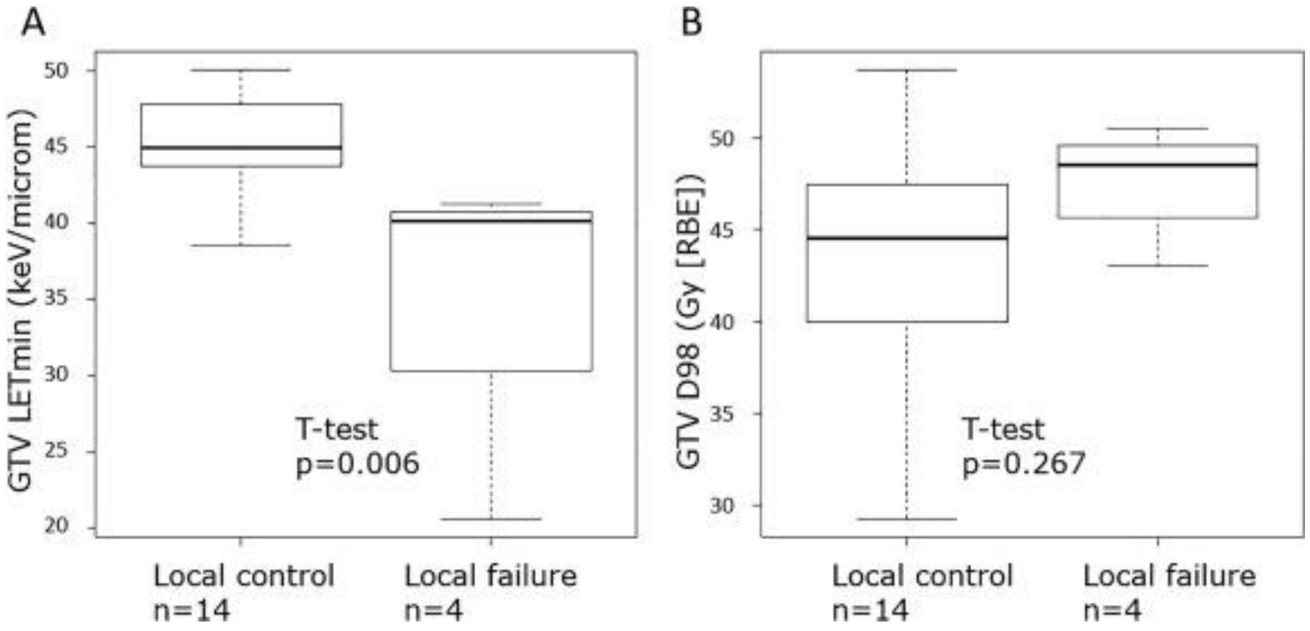



Locally advanced pancreatic cancer

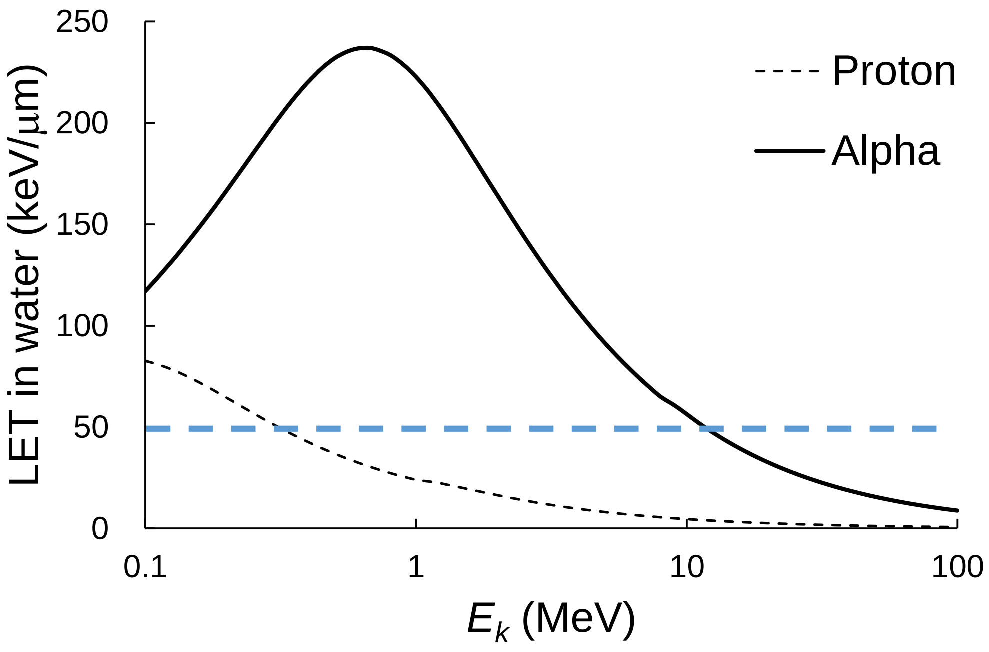
# Linear energy transfer (LET)

- Higher LET might improve the outcome for radioresistant tumors.

Hagiwara, Clin Trans Rad Oncol 21 19 2020




The minimum LET in a tumor region　The minimum dose in a tumor region

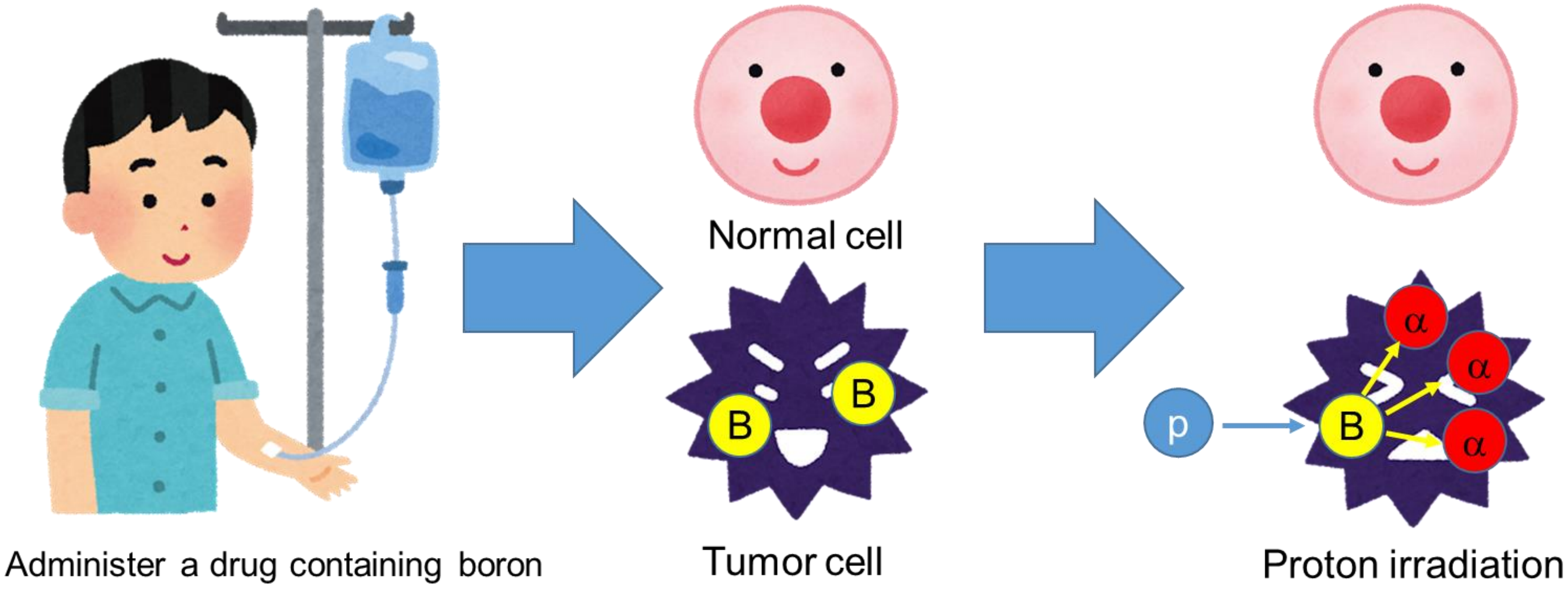


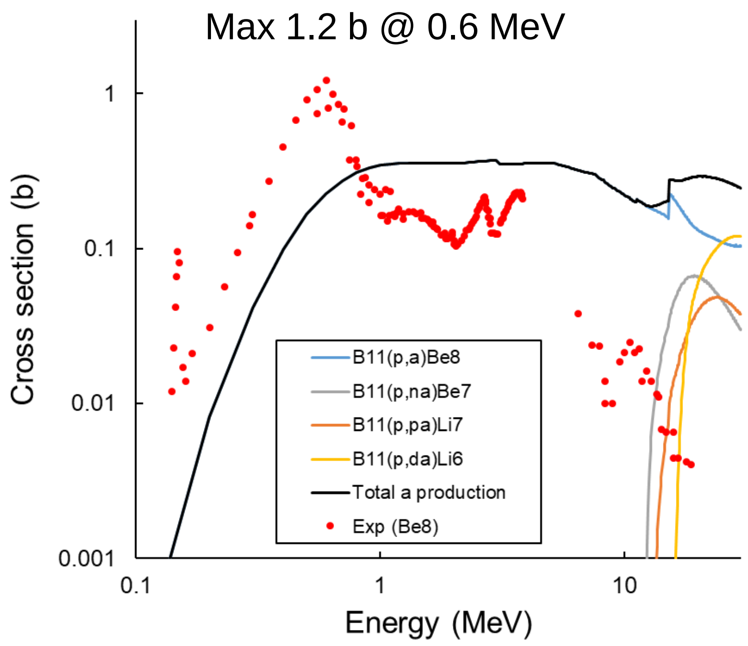

LET in water (SRIM calculation)

# Proton boron capture therapy (PBCT)

- Increase local dose and LET via p +$^{11}$B → 3α

D.K. Yoon et al. Appl Phys Lett 105 223507 2014



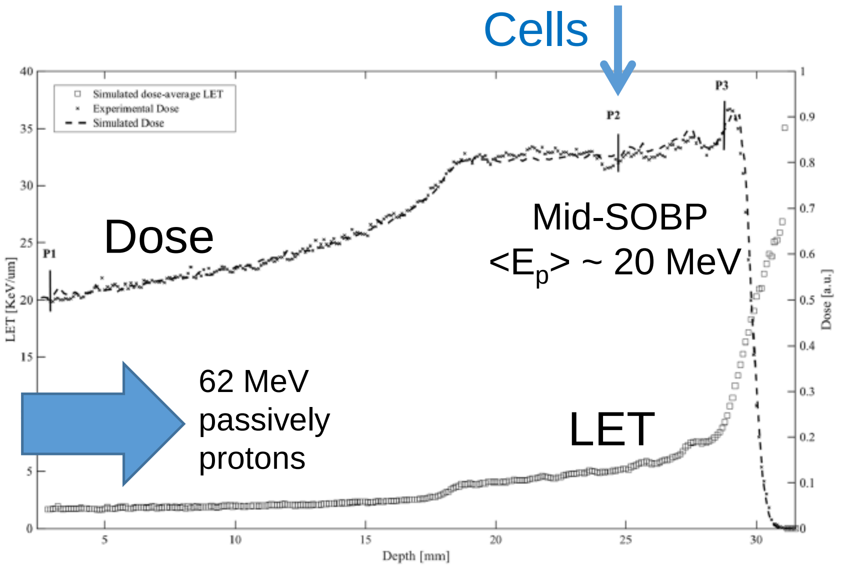

Experimental and theoretical (TALY1.96) cross sections in p + $^{11}$B reaction.

but too small cross section! (e.g. 4 x $10^3$ b for n + $^{10}$B → α + $^7$Li)

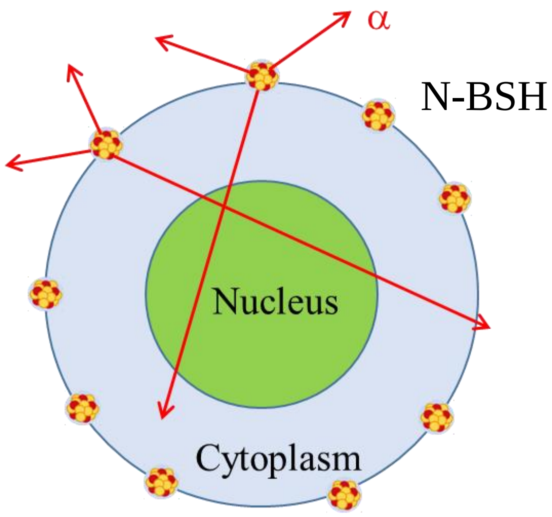
# Experimental proof-of-principle

- Demonstrate the effectiveness of PBCT by a cell experiment

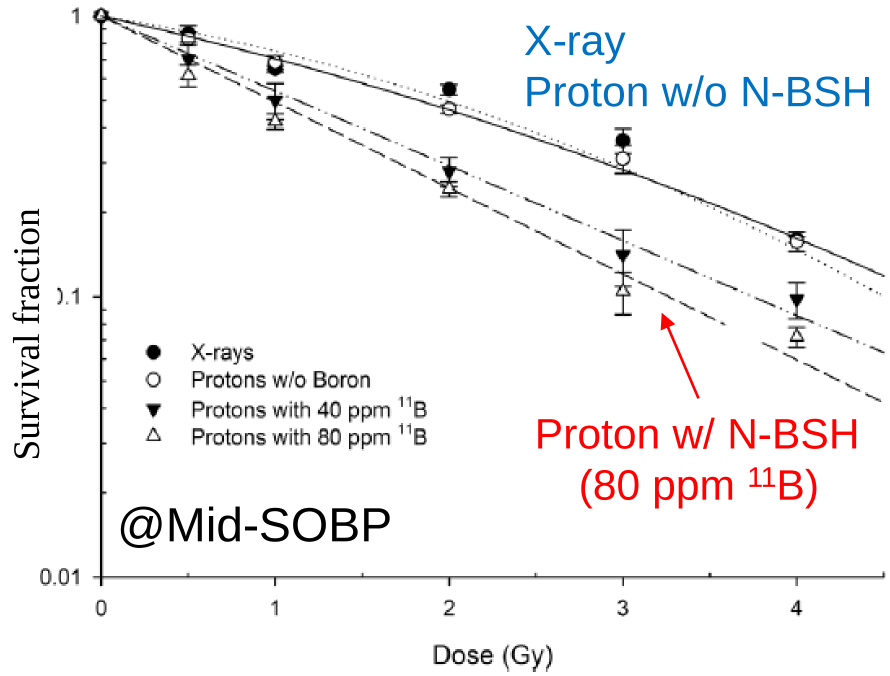
G.A.P. Cirrone et al. Sci Rep 8 (2018)1141




Dose profile and LET distribution




Schematic view of accumulated positions of BSH




Survival rate of prostate cancer cell line DU-145

## Dose modifying factor (DMF) = 1.46 @ Mid-SOBP

*Derived from 10% survival fraction

# $\alpha$ yield calculation

- Physics data can scarcely account for the biological effects
- $\alpha$ yield estimated from the cell experiment

  - $D_\alpha = \Phi_\alpha \text{ x } (S_{col}/\rho)_\alpha = \Phi_\alpha \text{ x } 886 \text{ MeV cm}^2/\text{g} = 0.47 \text{ x } D_p$

    $\Phi_\alpha = 1.7 \text{ x } 10^7 \text{ cm}^{-2} = 1.7 \text{ x } 10^5 \text{ mm}^{-2}$

  Stopping power in water of 5 MeV $\alpha$ (astar, NIST)

  *assume that the biological effectiveness was induced by $\alpha$ dose deposition

- $\alpha$ yield estimated from the physics data

  - $\Phi_\alpha \sim 1.2 \text{ x } 10^1 \text{ mm}^{-2}$

    at 80 ppm $^{11}$B concentration, 1.2 b cross section (Max. @ 0.6 MeV)

We need $10^4$ b cross section to explain the discrepancy!

# Possible causes

- Physics
  - $\alpha$ yield from proton-boron reaction
- Biology
  - reproducibility of the cell experiment

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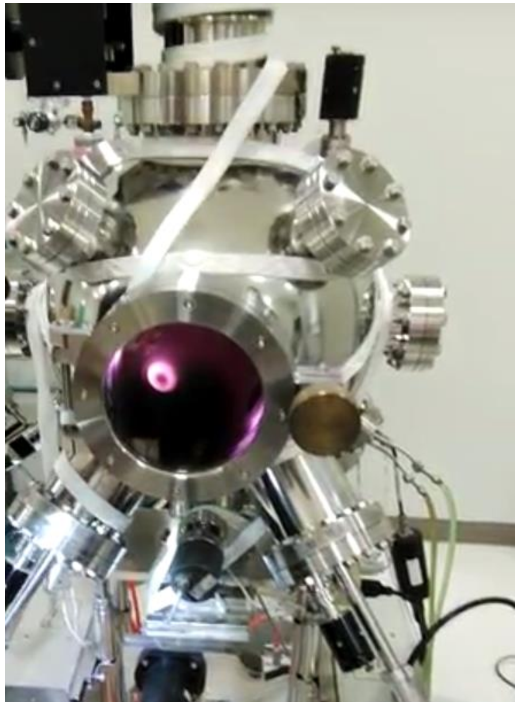
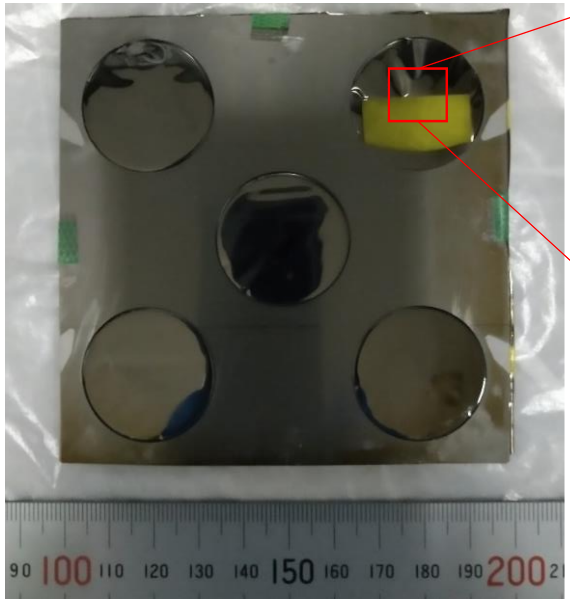
# Boron target production

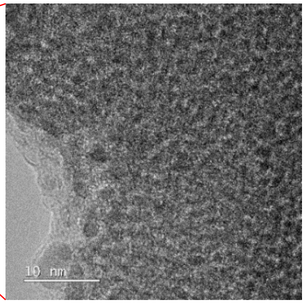
- Produce a boron layer with a RF magnetron sputtering machine



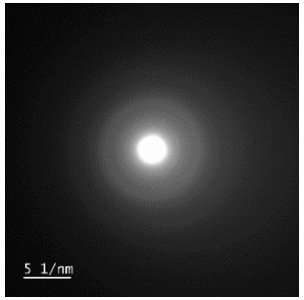
RF magnetron sputtering machine



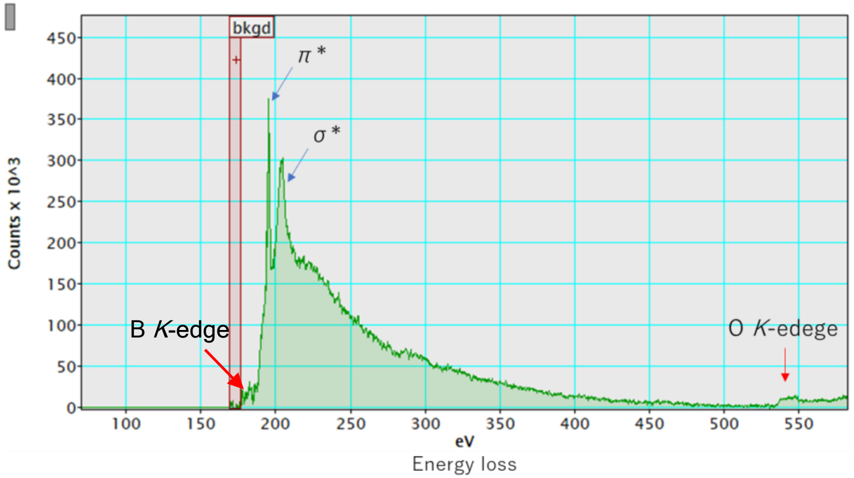

Fabricated boron target




TEM image
(200 kV)




Diffraction image




Electron energy loss spectrometry (EELS) spectrum measured at Nagoya Institute of Technology

Deposit a 0.18 μm thick amorphous boron on a 7.5 μm thick Kapton film

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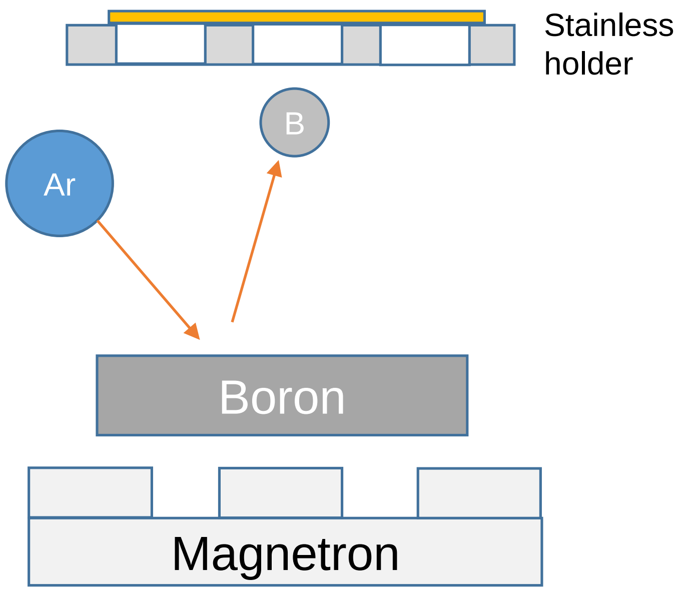
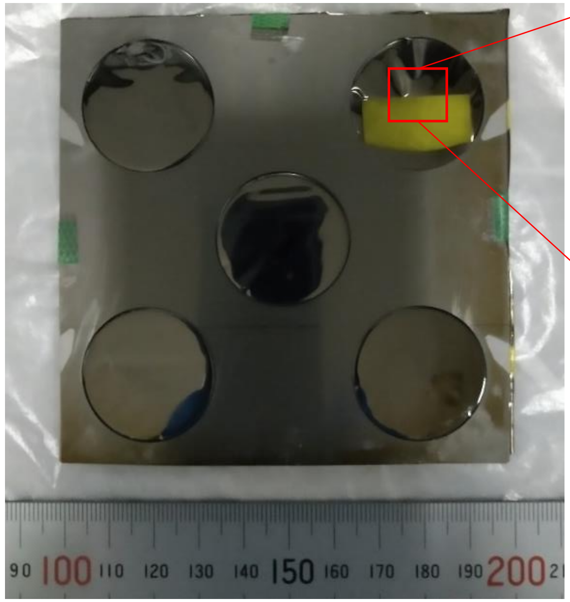



RF magnetron sputtering machine



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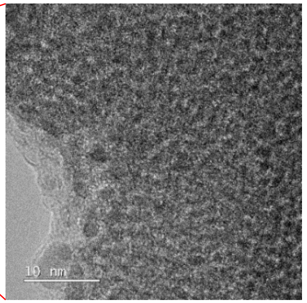


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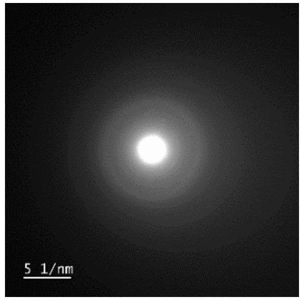


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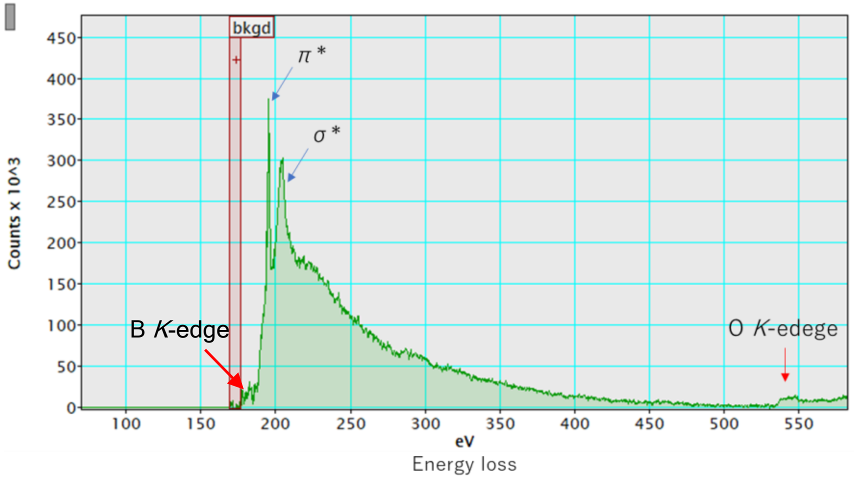


Electron energy loss spectrometry (EELS) spectrum measured at Nagoya Institute of Technology

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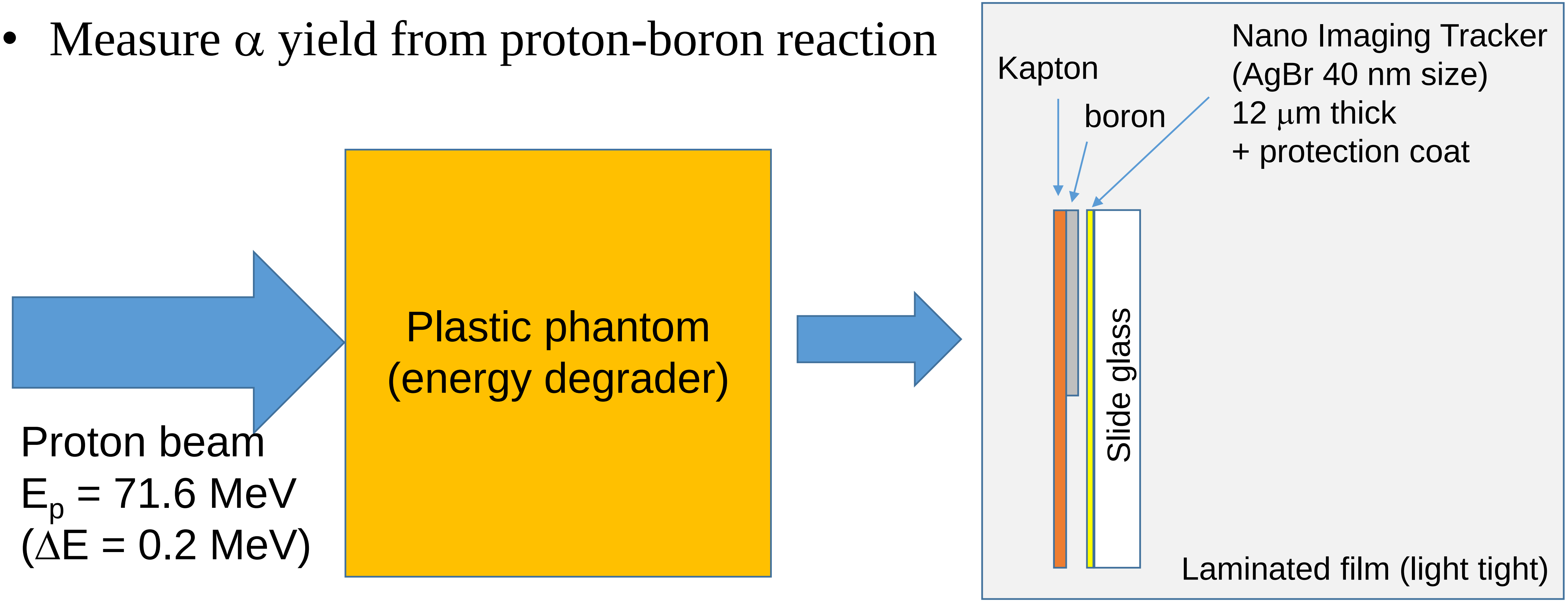
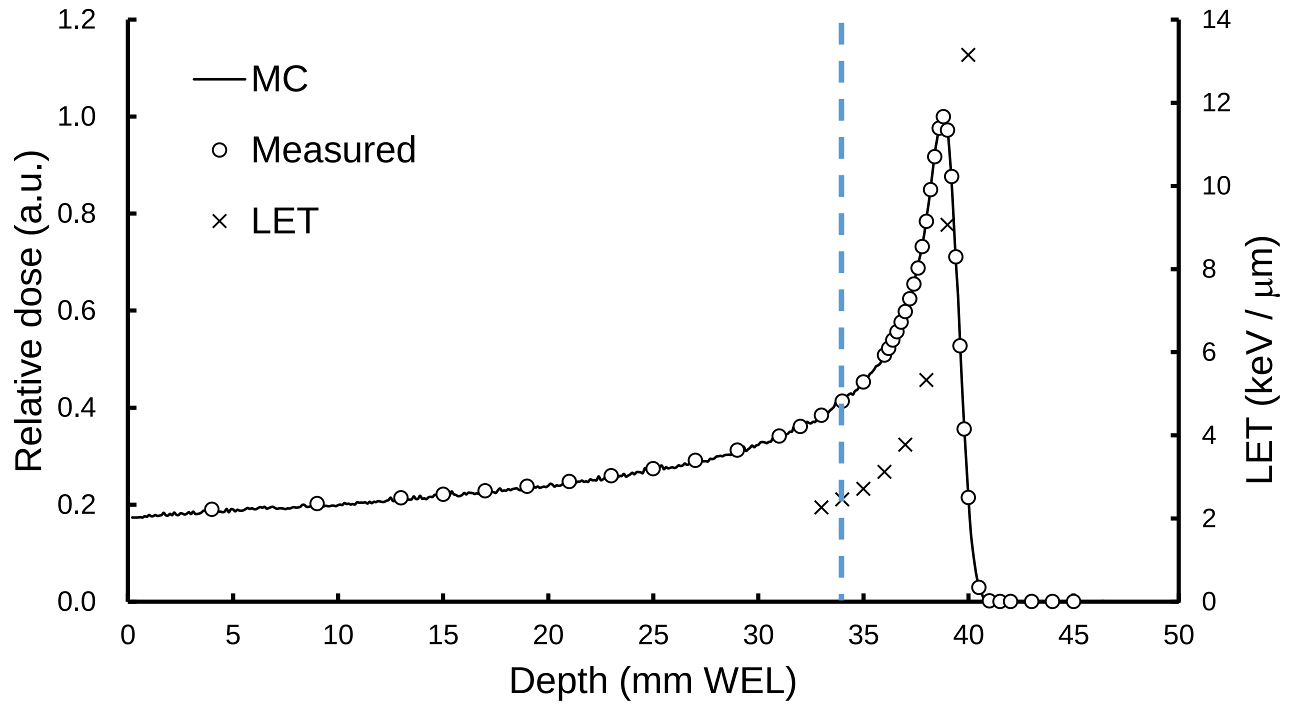
# Experimental setup

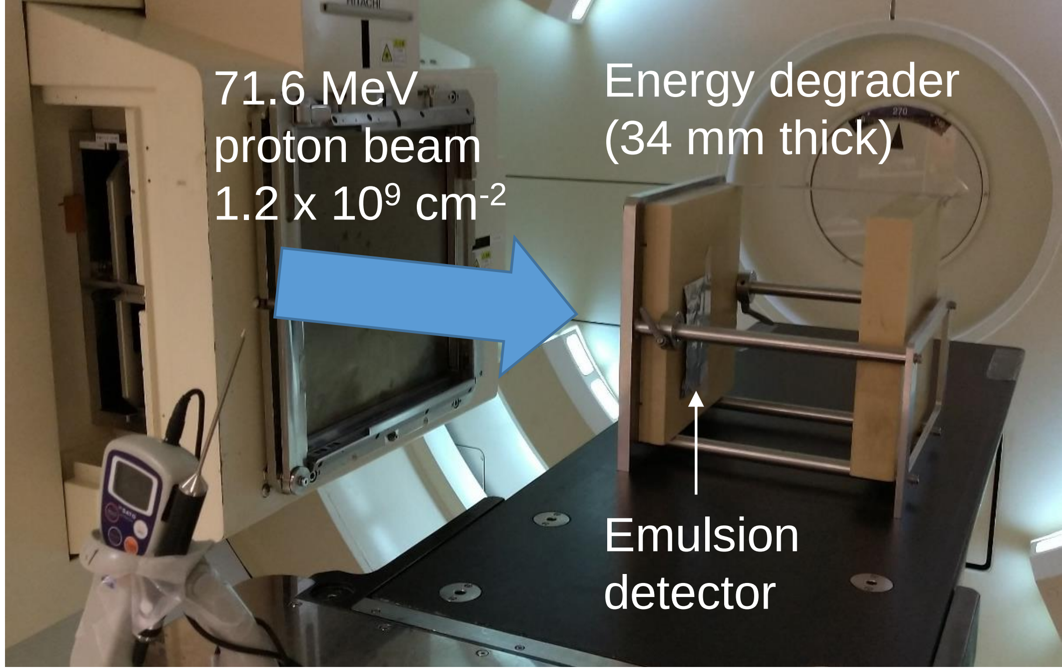
- Measure α yield from proton-boron reaction



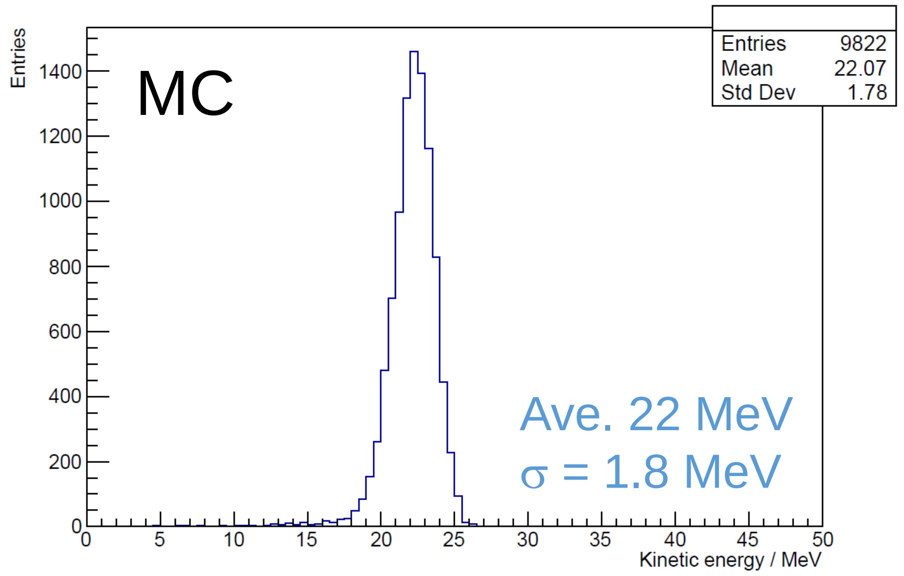
# Proton beam exposure

- Irradiate proton beams at NPTC




G1 beamline @ NPTC




Pristine proton energy at 34 mm depth

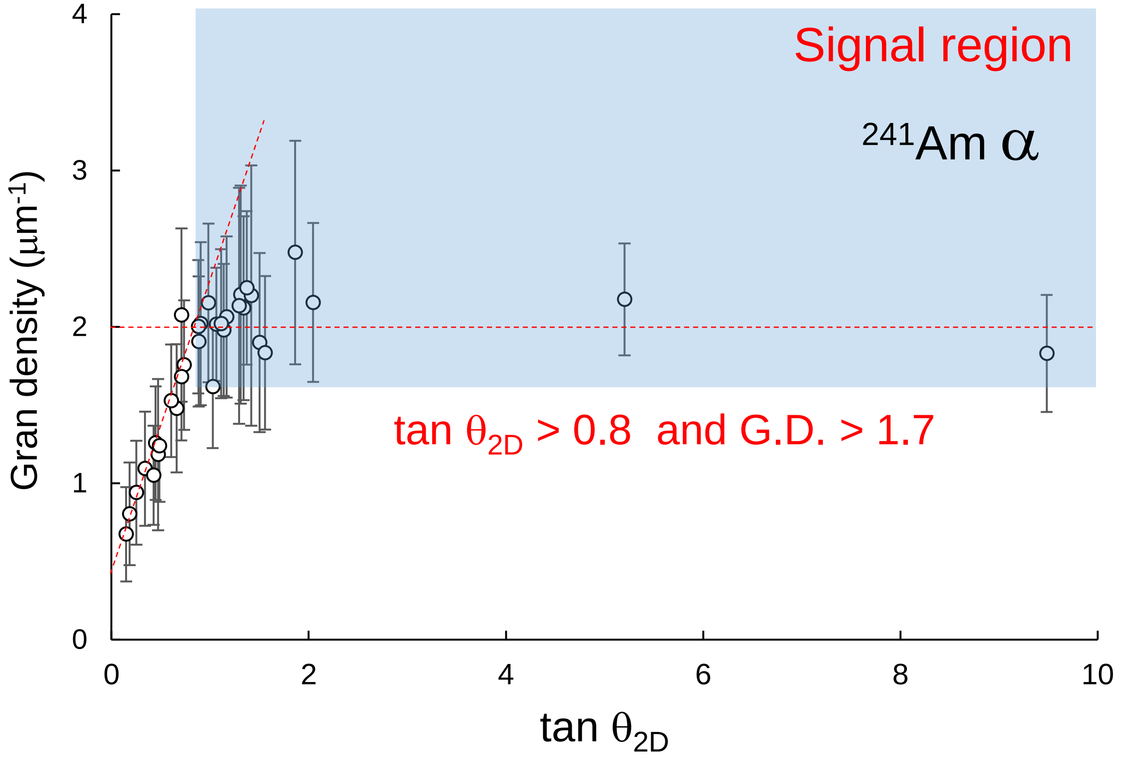
# Development and scanning

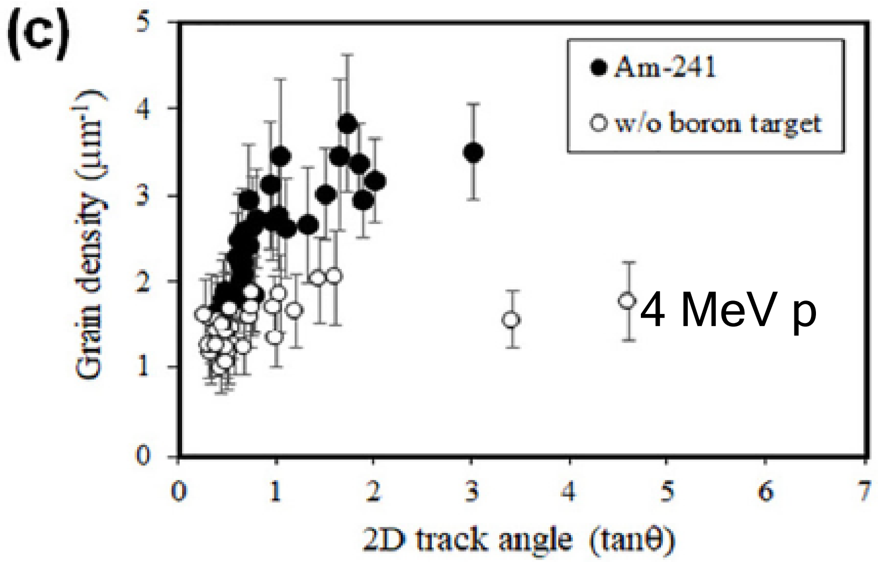
- Prepare a reference sample
  - irradiate $^{241}$Am $\alpha$ ($E_\alpha$ = 5.4 MeV)
- Develop the exposed films at flab, Nagoya Univ.
  - developer: XAA (Fujifilm)
  - dev. time: 5 min @ 20°C
- Scan by PTS-3
  - scanning area: 1 x 1 $mm^2$
  - pixel size: 0.058 x 0.058 $\mu$m
  - z-interval: 0.275 $\mu$m
- Measure positions of grains under ImageJ

Automatic scanning system PTS-3

# Results

- No excess in α tracks from boron




Yoon, Naganawa, Kimura, APL 115 223701 2019

- α track candidate
  - Kapton region: 102 tracks / mm$^2$
  - boron + Kapton region: 110 tracks / mm$^2$

→ α tracks from boron: 8 ± 15 tracks / mm$^2$

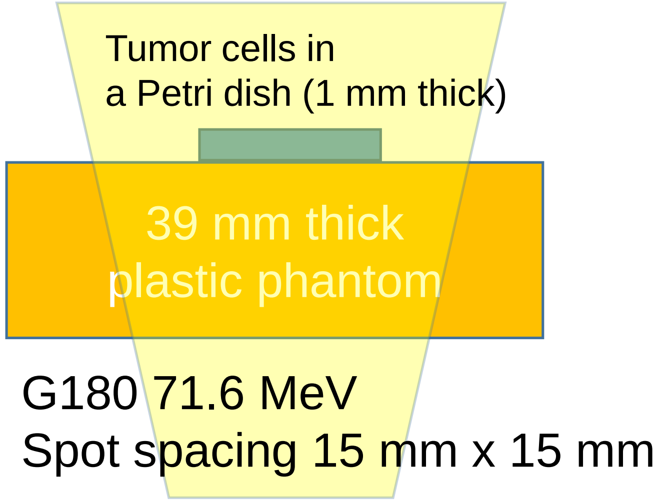
σ < 1.6 b (90% CL) @ 22 MeV

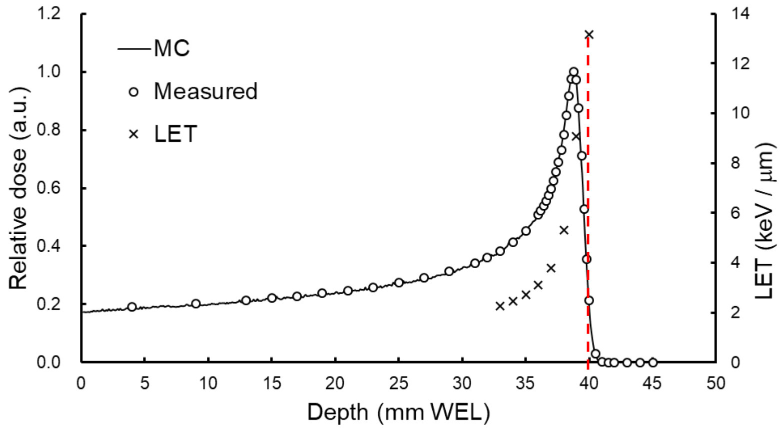
# Possible causes

- Physics
  - $\alpha$ yield from proton-boron reaction
- Biology
  - reproducibility of the cell experiment

# Reproducibility check of the cell experiment

- Measure the cell viability w/ and w/o the boron agent N-BSH




- Procedure

  - use human lung cancer A549 cell line
  - administer a medium containing 640 ppm $^{11}B$ to the cells at 7 hours before the beam exposure
  - deliver ~ 3.5 MeV proton beams at 0, 2, 4, and 8 Gy
  - wash the exposed cells with phosphate buffer
  - incubate the cells for 1 week
  - stain living cells
  - count the number of colonies by visual inspection

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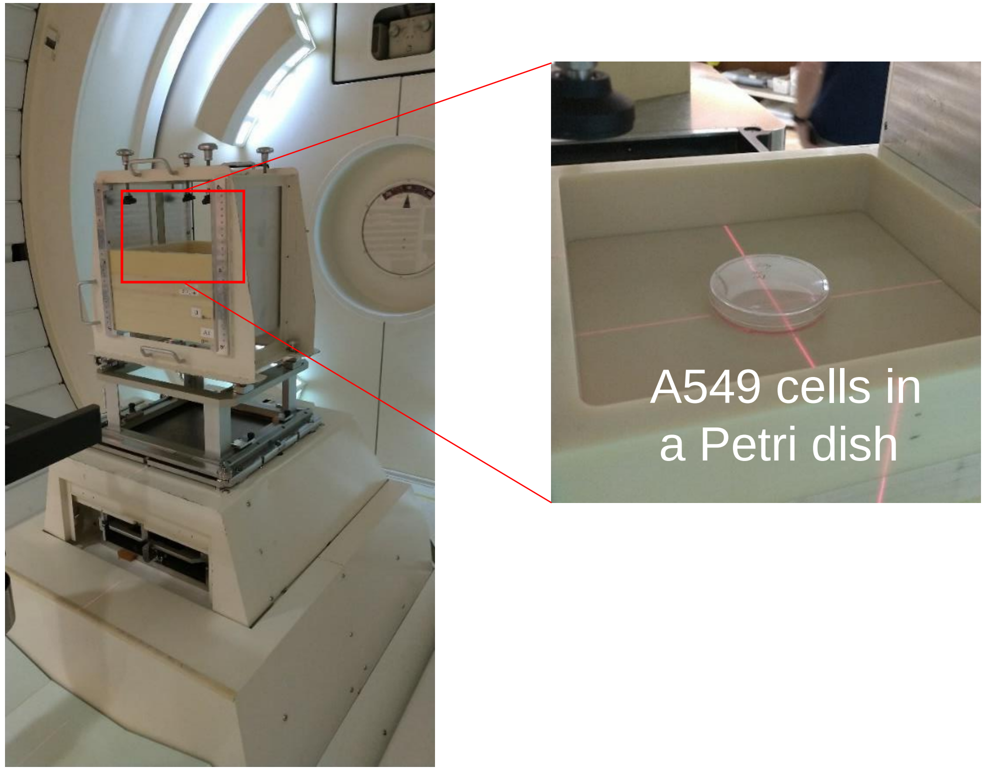


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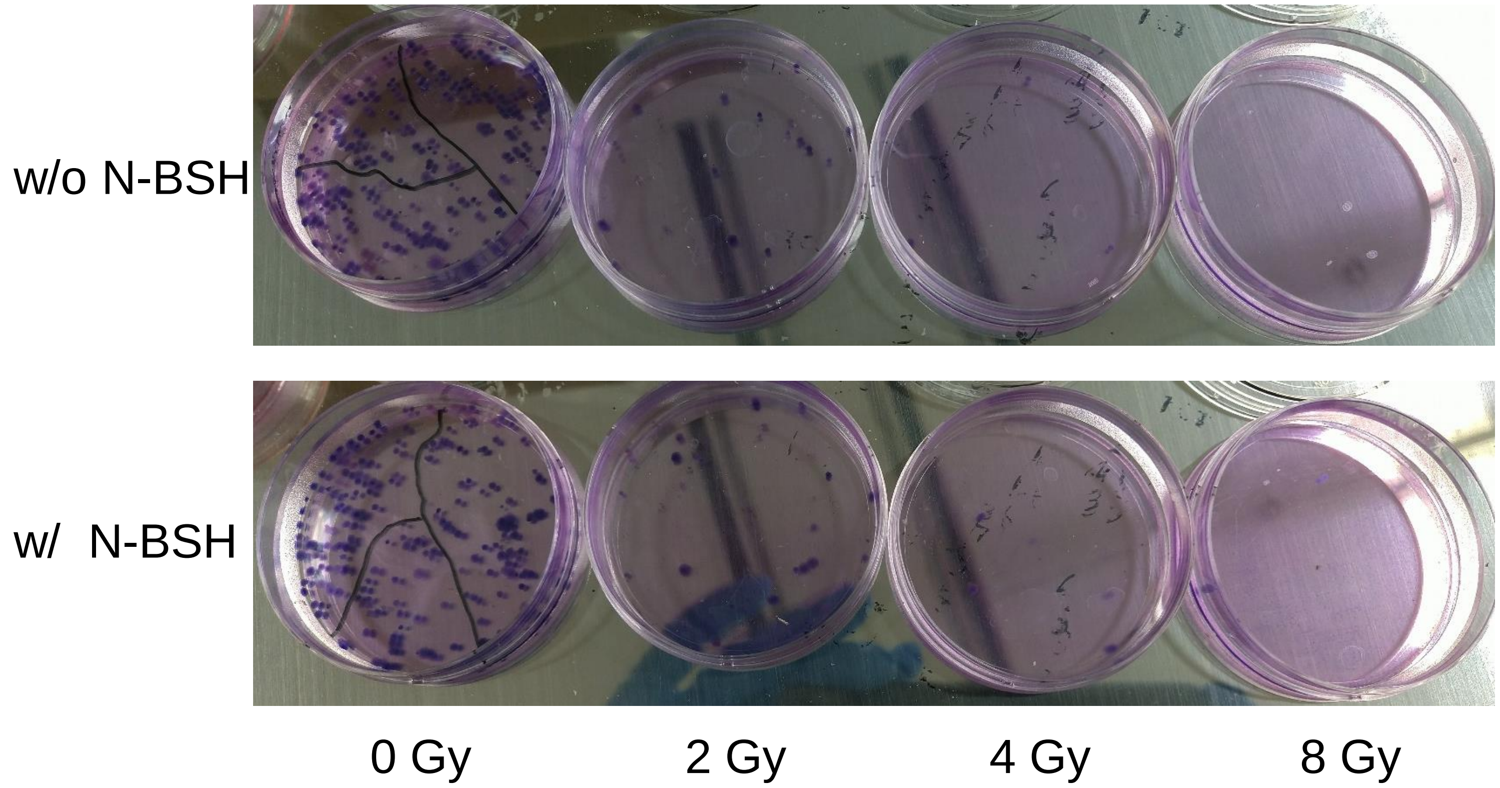
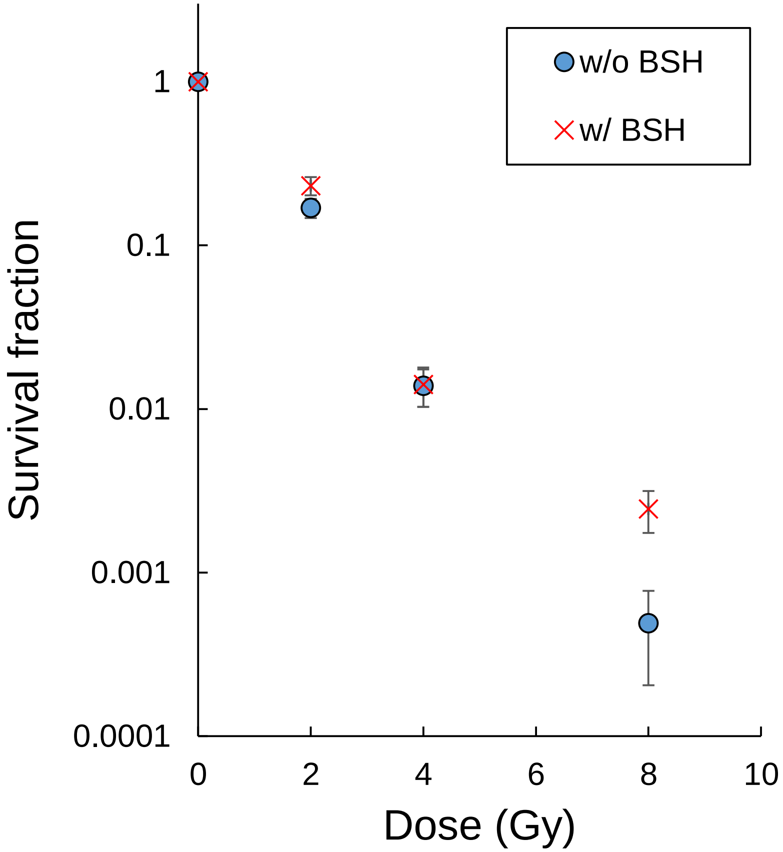
# Results of the reproducibility check

- No significant changes between w/ and w/o N-BSH



# Results of other experiments

- Many cell experiments reported:

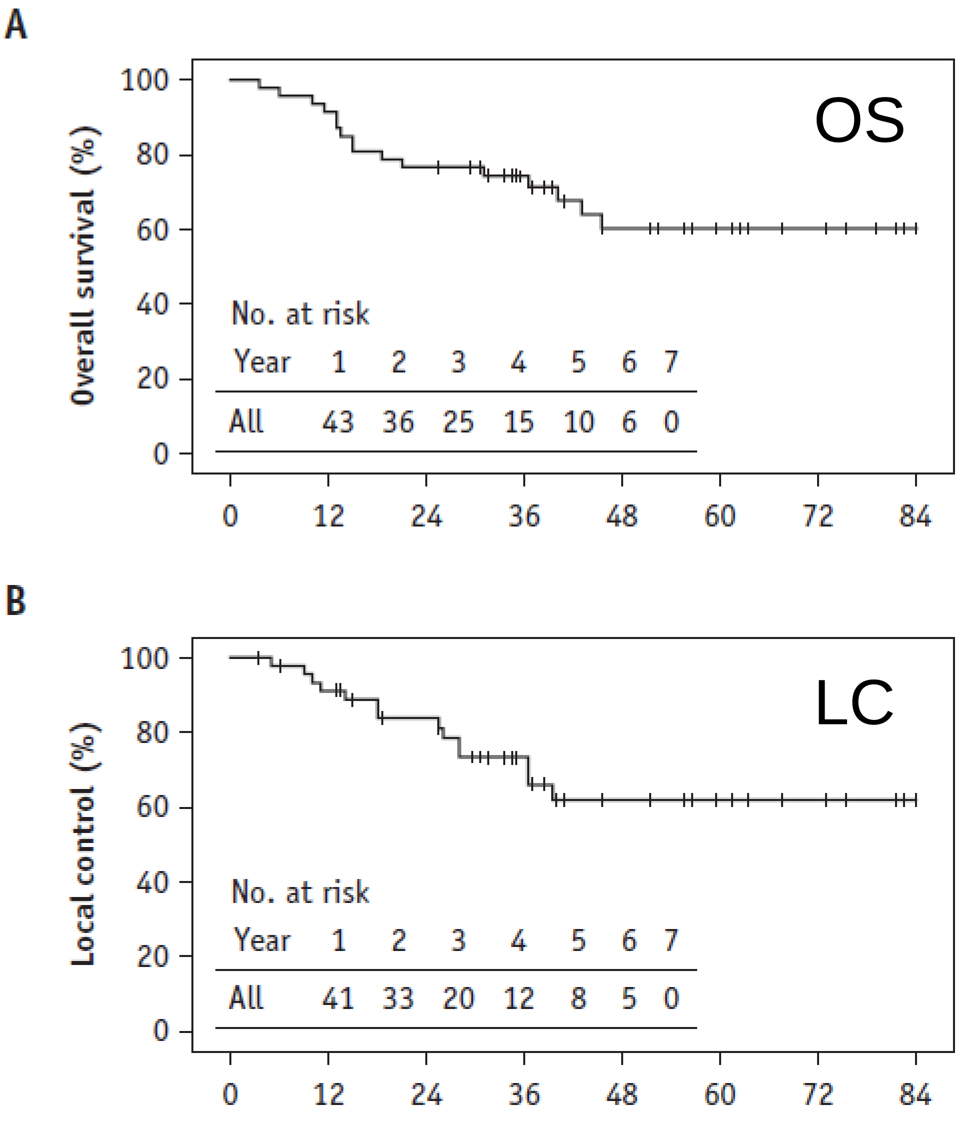
| Agent | Cell line | DMF | Article |
|---|---|---|---|
| N-BSH | DU-145 (prostate) | 1.46 | Cirrone Sci Rep 2018 |
| | DU-145 | No | Manandhar Med Phys 2022 |
| | DU-145, A-172, Gl-Tr (glioma) | No | Shtam Sci Rep 2023 |
| | DU-145, MIA-Paca (pancreas) | No | Hosobuchi NIM 2023 |
| N-BPA | DU-145 | No | Manandhar Med Phys 2022 |
| | DU-145, MIA-Paca | No | Hosobuchi NIM 2023 |
| FESAN | U-87 (glioblastoma) | ~1.4 | Neus-Martinez JMCB 2022, Pinheiro EPJ 2023 |
| 50 nm NP | MNNG/HOS (osteosarcoma) | 1.5-1.7 | Zavestovskaya Nanomat 2023 |
| Bononated porphyrinoid | mouse (in-vivo) | Yes | Miyoshi. JP patent 2014-177421 |

# Conclusions

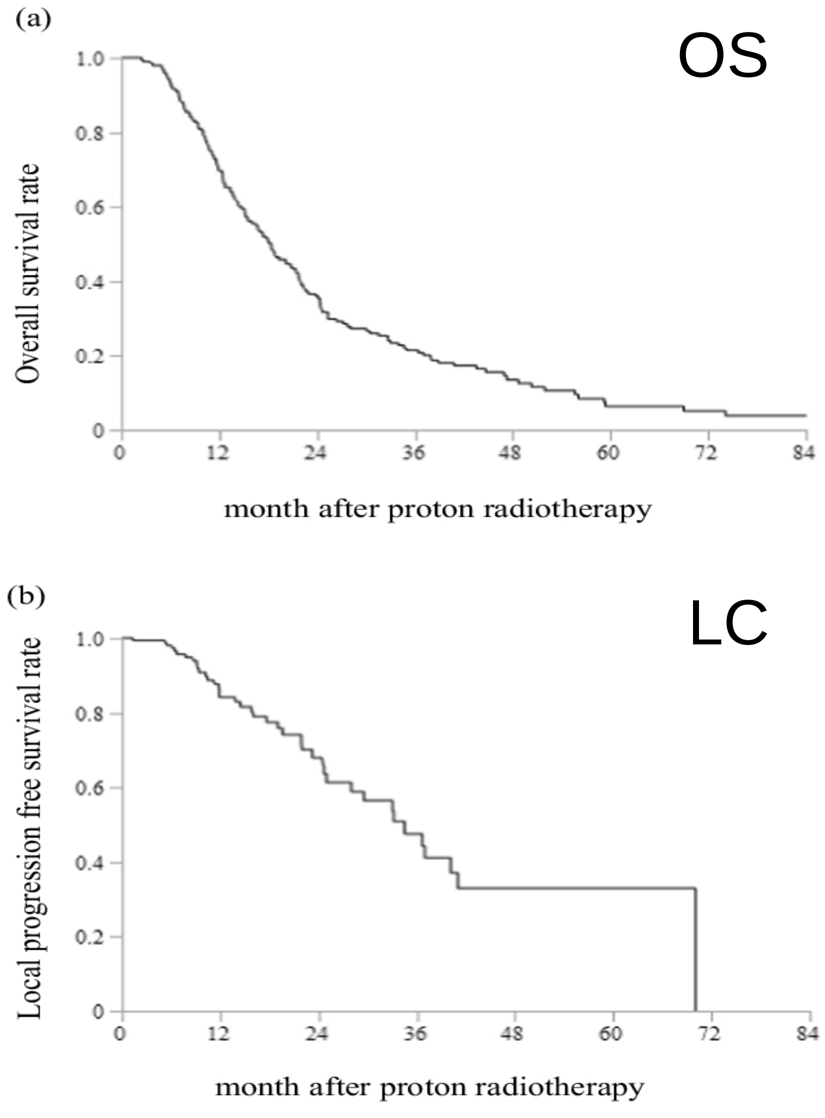
- PBCT was proposed to enhance the biological effects in proton therapy.
- Its biological effects were observed in the cell experiment.
- A discrepancy exists between physical dose and biological dose.
- We checked the $\alpha$ yield and the reproducibility of the cell experiment.
- Treatment with N-BSH had no effects on the biological effectiveness of proton beam.

# Next steps

- Prepare a new boron target
  - 2 μm thick boron layer
  - x10 statistics
- Measure physical density of boron target with X-ray reflectivity (XRR)
  - contribute accurate calculation of cross section




Non-small cell lung cancer (stage III)




Local advanced pancreatic cancer