Investigating the application of glial activation imaging using [18F]-FEPPA PET following cranial irradiation to guide radiotherapy treatments

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Take a photo to learn more about glial activation imaging in breast cancer brain metastases

MOTIVATION

❖ Breast cancer brain metastasis is a challenging disease to treat, despite high recurrence rates (~50% in 1yr), stereotactic radiosurgery alone is the preferred treatment[1]

❖ Whole brain radiotherapy (WBRT) following stereotactic radiosurgery improves metastases control at the cost of cognitive decline and is thus usually delayed[2]

❖ Cognitive decline has been linked with chronic inflammation in the brain[3] which is initiated by the radiation-induced activation of glial cells

What if…

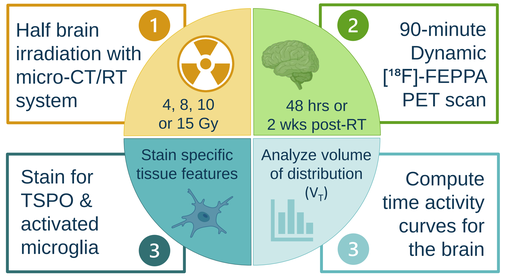
WBRT was only applied to the more vulnerable microscopic disease?

Would a much lower dose be able to control the disease with minimal inflammation and side effects?

OBJECTIVE

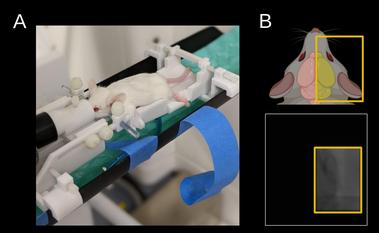
Investigate the application of glial activation imaging using [18F]-FEPPA PET imaging with half brain irradiation in BALB/c immunocompetent mice

METHODS

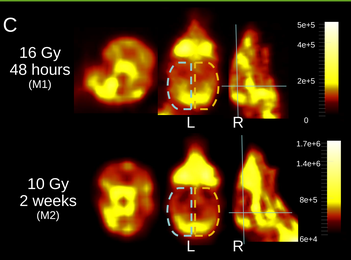


RESULTS

Micro-CT/RT



[18F]FEPPA PET



Volume of Distribution (V_T)

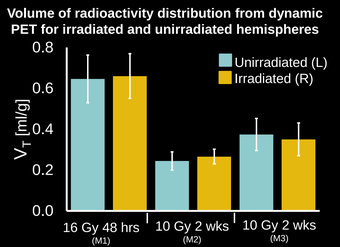


Figure 1. Diagrams and images for half-brain irradiation. A) Mouse setup on 3D printed animal holder on micro-CT bed prior to imaging. B) Diagram (top) and x-ray image (bottom) taken with micro-CT showing the irradiated hemisphere. C) Normalized [18F]-FEPPA PET [Bq/cc] images averaged over last 15 minutes of 90 minute dynamic PET scan for mice receiving half brain irradiation; representative ROI drawn to show the irradiated (yellow) and non-irradiated (blue) brain hemispheres.

Histology

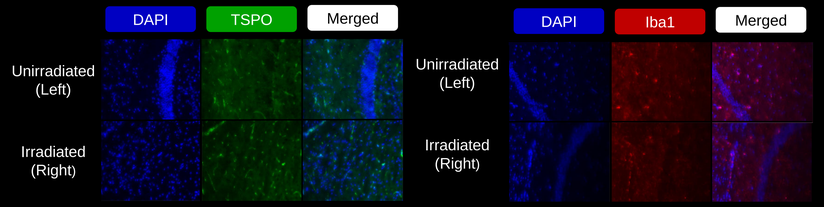
Approximate areas imaged
Cortex
Hippocampus
Midbrain

Figure 2. Diagram showing approximate slice of mouse brain in histological analysis, adapted from Allen Mouse Brain Atlas[4]

Integrated Density: Sum of the values of the pixels within a selection.

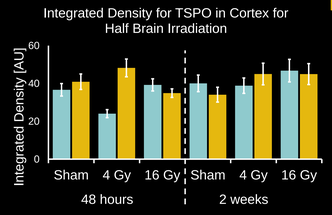
Threshold used: Only values higher than the experimentally determined background signal were included in integrated density.

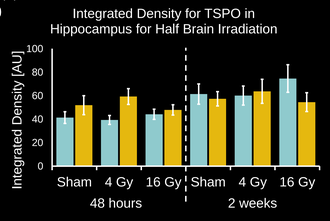
Hippocampus

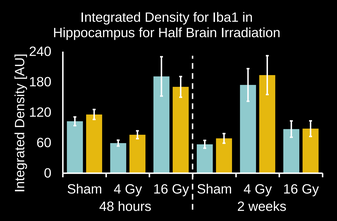


Cortex

Legend for all graphs
Unirradiated (L)
Irradiated (R)







DISCUSSION

[18F]-FEPPA PET showed:

❖ Tracer uptake following half brain irradiation was similar between both sides of the brain within 2 weeks

❖ Visibly higher tracer uptake was evident in areas of the brain respectively represented by the central cerebral cortex and the cerebellum in all mice

❖ Notable differences in volume of distribution for high dose levels at short time points

Investigated further with histology and included lower dose level 4 Gy.

Histology showed:

❖ All regions exhibited an increase in integrated density for TSPO in irradiated hemisphere at 48 hours for 4 Gy

❖ Consistent with PET, 16 Gy generated similar integrated density values for both hemispheres at 48 hours with slight changes at 2 weeks

FUTURE DIRECTIONS

❖ Acquire [18F]-FEPPA PET for sham, 4 Gy and 16 Gy dose levels at longer time points

❖ Investigate glial activation response to whole brain radiotherapy to map the dose-response and examine implications to late cognitive functions

ACKNOWLEDGEMENTS

References:[1] C.Fritz et al. Frontiers in Oncology, 8 (Nov), 2018. [2] P.Brown et al. Journal of the American Medical Association, 316(4), 2017. [3] D.Greene-Schloesser, Clinical Cancer Research, 19(9), 2013. [4] Allen Mouse Brain Atlas, mouse.brain-map.org .