Radiation Absorbed Dose to Spinal Cord: Therapy of Leptomeningeal Metastasis Using Beta-Emission Radiopharmaceuticals

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Abstract

Approximately 150,000 cancer patients develop leptomeningeal (LM) metastases annually in the US, mainly from breast, lung, melanoma, and central nervous system (CNS) primary cancers. The treatments of LM are limited, with poor prognosis. One common treatment method is the intrathecal administration of therapeutic agents into the CSF for locoregional cancer therapy. In recent years, the beta-emission radiopharmaceuticals, e.g., ^{131}I-antibodies and Rhenium (^{186}Re) Obisbemeda (rhenium-nanoliposomes, ^{186}RNL), have been studied for the treatment of LM. The advantage of this therapy technique is high radiation absorbed doses can be applied to focally eradicate cancer cells in the CSF and on the leptomeninges. However, the radiation absorbed dose and possible toxicity to spinal cord may be a concern. Based on the ^{186}RNL distribution analyzed from an ongoing trial for adult patients with LM, (ReSPECT-LM, NCT05034497) we performed a radiation dosimetry study to understand the radiation absorbed dose to spinal cord to evaluate the safety and possible toxicity to spinal cord for the treatment.

Method: The T2-weighted MRI on C-spine from a patient with LM was segmented into volumes of CSF and spinal cord. With the distribution of beta-emission radiopharmaceutical in the CSF, the radiation absorbed distribution in CSF and spinal cord were calculated using dose voxel kernel and 3D convolution under 0.2 mm voxel dimension. Dose distribution from different beta-emission radionuclides with different beta-energies – ^{177}Lu, ^{131}I, ^{186}Re, ^{188}Re, and ^{90}Y – were calculated, summarized, and evaluated.

Result: Radiation absorbed doses to the spinal cord were associated with beta-energy of radionuclides. The mean doses to spinal cord in the calculated volume was 2.75%, 7.25%, 10.89%, 29.69%, and 37.66% of mean doses in CSF for ^{177}Lu, ^{131}I, ^{186}Re, ^{188}Re, and ^{90}Y, respectively. The radionuclides with lower beta-energy, ^{177}Lu, ^{131}I, and ^{186}Re, can largely spare the spinal cord with much lower radiation doses to spinal cord. The radionuclides with higher beta energy, ^{188}Re and ^{90}Y, give much larger doses to spinal cord, while the dose to spinal fluid is also more heterogeneous.

Summary: Beta-emission radiopharmaceuticals with lower beta-energies are optimal for the treatment of LM. The dosimetry study results provide the guidance for possible doses that may be applied for the safe treatment of LM, including patients with previous external beam radiation therapy to the spine. While large radiation absorbed dose can be used, multidose treatments may be applied for long term effective tumor control.

Leptomeningeal Metastases (LM)

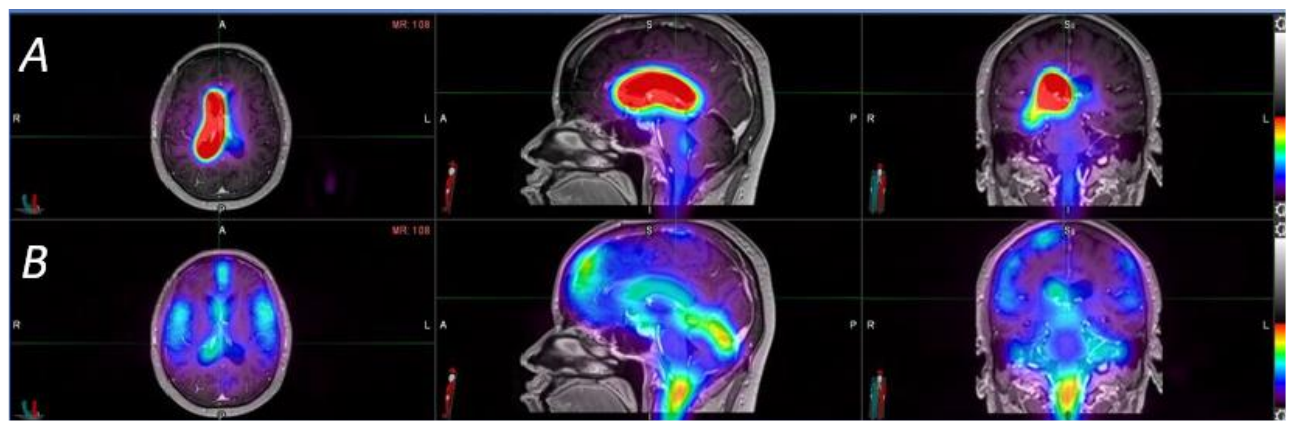
- Leptomeningeal metastases (LM), a devastating complication of primary cancers marked by the spread of tumor cells to the fluid-lined or intrathecal structures of the CNS
- LM occurs in 5-15 % of patients with malignant cancers, including breast, lung, melanoma, and central nervous system primary cancers
- There are approximately 150,000 cases of LM annually in the US
- The average survival of patients with LM metastases is 3-6 months and treatment options are limited

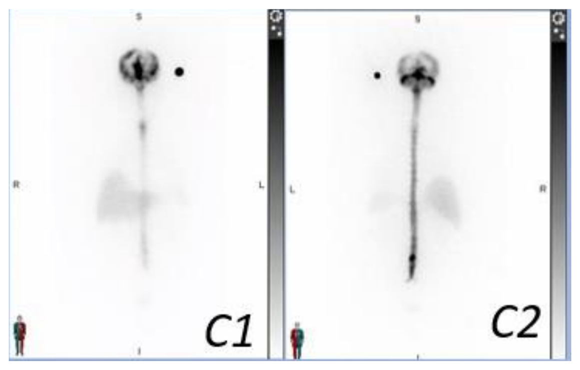
Targeted Radiopharmaceutical Therapy of LM

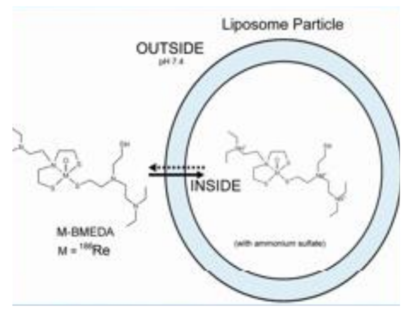
- The use of therapeutic radiopharmaceuticals provides a focused radiation field to eradicate cancer cells in the CSF
- Compared to external beam radiation therapy (EBRT), a higher radiation absorbed dose can be applied for effective control of disease progression
- However, due to the millimeter range of beta-radiation particles, the radiation absorbed dose to spinal cord may be a dose limiting factor
- Beta-radiation from different radionuclides has different radiation energy and different path-lengths
- We studied the radiation absorbed doses to spinal cord with the use of different beta-emission radionuclides
- Therapeutic radiopharmaceuticals have been studied in the treatment of LM via locoregional administration, e.g. ^{131}I-labeled antibodies
- ReSPECT-LM is an enrolling clinical trial using Rhenium (^{186}Re) Obisbemeda (rhenium nanoliposomes, ^{186}RNL) to treat adult patients with LM

	Half Life (hr)	Mean Beta Energy (KeV)	Major Gamma Energy (KeV)	Beta Radiation dose constant (Gy.g/(mCi.hr))
Lu-177	159.53	147.9	112.9 (6.4%); 208.4 (11.0%)	3.14
I-131	192.50	191.8	364.5 (81.7%)	4.05
Re-186	89.24	336.2	137.2 (9.42%)	7.11
Re-188	17.00	779.3	155.0 (15.6%)	16.52
Y-90	64.10	933.1		19.85

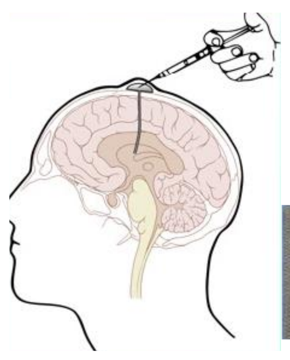
Distribution of Rhenium (^{186}Re) Obisbemeda After Intraventricular (Ommaya Reservoir) Administration





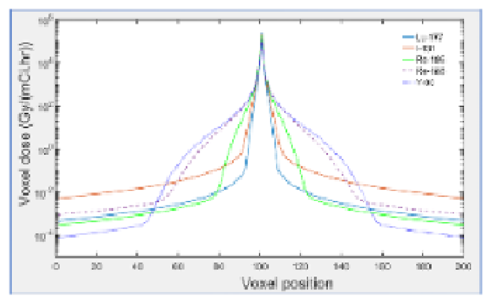


- A: End of Fusion (EOI) SPECT/MRI
- B: 24-hour SPECT/MRI
- C1: AP whole body planar image at 24 hours
- C2: PA whole body planar image at 24 hours



Dose-Voxel Kernel

- Five beta-emission therapeutic radionuclides, ^{177}Lu, ^{131}I, ^{186}Re, ^{188}Re, and ^{90}Y, with different beta-radiation energies were studied
- The dose-voxel kernels with 0.2 mm voxel size were from the data published by Graves SA, et al.
- The dose-voxel kernels from origin of radionuclides were calculated in the range of 20 mm (2cm)



Spinal Fluid — Spinal Cord MR Segmentation

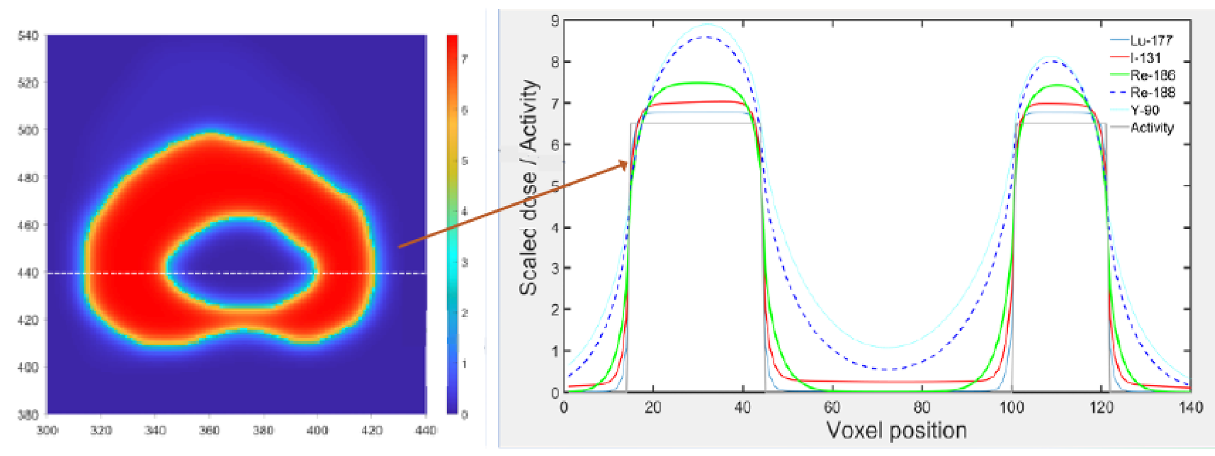
The volumes of spinal cord and spinal fluid at C-spine region were segmented from T2-weighted MR image of a LM patient we treated using MIM software.

- The MR image was re-sampled to 0.2 x 0.2 x 0.2 mm3 voxel size
- The volumes of spinal fluid was segmented using thresholding followed by manual correction
- The volume of spinal cord was determined as the volume in the middle of spinal fluid without gap volume

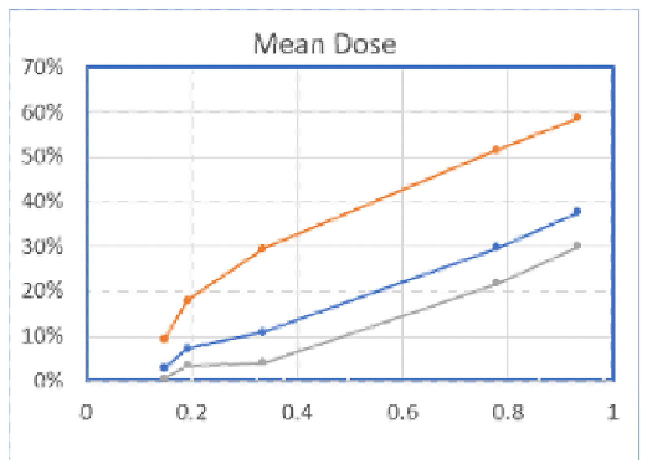
Radiation Absorbed Dose Calculation and Evaluation

- The radiation absorbed dose calculation was based on the radioactivity that distributes in the leptomeningeal and CSF uniformly
- Brain tissue and spinal cord have no radioactivity distribution
- The radiation absorbed dose calculation used dose voxel kernel-radioactivity distribution convolution method using MATLAB software
- Radiation absorbed dose distribution, dose in the volumes, and dose volume histogram (DVH) were analyzed in MATLAB software

Dose Distribution and Dose Profile

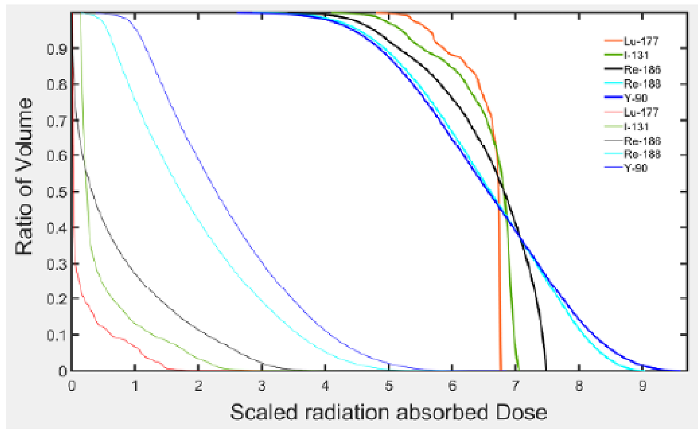


Dose Distribution Statistics

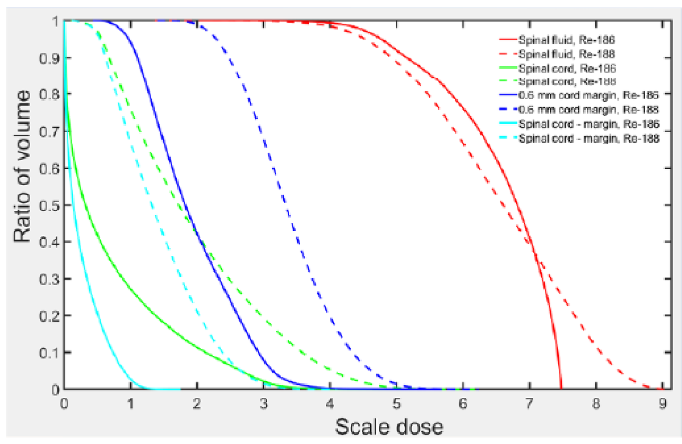


		Spinal Cord			Spinal Cord (0.6 mm margin)			Spinal Cord- 0.6 mm margin		
	Mean Beta Energy (MeV)	Min	Max	Mean	Min	Max	Mean	Min	Max	Mean
Lu-177	0.14792	0.22%	94.07%	**2.75%**	0.56%	94.07%	**9.11%**	0.22%	3.15%	**0.41%**
I-131	0.19184	2.04%	91.17%	**7.25%**	3.65%	91.17%	**17.85%**	2.04%	10.98%	**3.35%**
Re-186	0.33624	0.08%	86.79%	**10.89%**	6.64%	86.79%	**29.55%**	0.08%	26.71%	**4.05%**
Re-188	0.77934	1.56%	95.13%	**29.69%**	21.46%	95.13%	**51.56%**	1.79%	62.60%	**21.70%**
Y-90	0.9331	4.21%	104.55%	**37.66%**	26.60%	104.55%	**58.72%**	4.73%	74.89%	**29.97%**

Dose Volume Histogram (DVH) Spinal Fluid and Spinal Cord



- Thick lines: DVH in spinal fluid
- Thin lines: DVH in spinal cord
- The doses were scaled to the same mean dose in spinal fluid



Summary and Discussion

- Higher beta-energies give higher radiation absorbed doses to spinal cord
- High beta-energy radionuclides such as Re-188 and Y-90, also result in more heterogeneous radiation absorbed dose to the CSF
- To maximize the radiation absorbed dose to treat LM, lower beta-energy radionuclides are preferable to avoid radiation dose to the spinal cord
- Radiopharmaceutical treatment for LM may need to consider both the effective radiation absorbed doses to CSF and leptomeninges
- Re-186 appears to be the optimal radionuclide for maximizing absorbed dose to the areas of interest, while sparing the spinal cord
- This study did not include the chemistry, pharmacokinetics, and the drug distribution throughout the entire subarachnoid space and CSF
- This presentation only reports the radiation absorbed doses to spinal cord at C-spine; however, we believe the findings are applicable to most of the spinal cord region
- Additional studies are ongoing

Disclosure

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- Clinical trial study under Plus Therapeutics, Inc., Austin, Texas
- Ande Bao, William Phillips, and Andrew Brenner are share holders of NanoTx, Inc.
- Norman LaFrance, Melissa Moore, Andrew Brenner, and Marc Hedrick are employees of Plus Therapeutics, Inc.
- Ande Bao and William Phillips are also consultants of Plus Therapeutics, Inc.

Reference

1. Buszek SM, Chung C. Front Oncol 9: 1224: 1-15, 2019
2. Yang J, et al. Neuro-Oncology 23: 134–143, 2021
3. Yerrabelli RS, et al. Eur J Nucl Med Mol Imaging 48: 1166–1177, 2021
4. Barbour AB, et al. Adv Radiation Oncol 9: 101377: 1-10, 2024
5. Bao A, et al. *J Nucl Med* 2003;44:1992–1999
6. Graves SA, et al. Med Phys 46: 5284–5293, 2019

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