Therapy of glioblastoma using locoregional administration of ^{186}Re-nanoliposomes (^{186}RNL)

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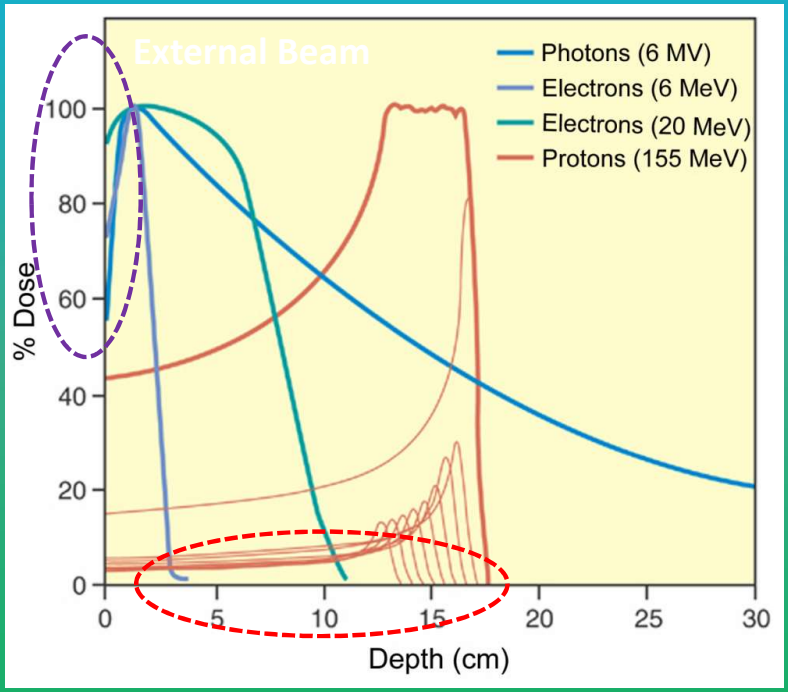
Disclosure

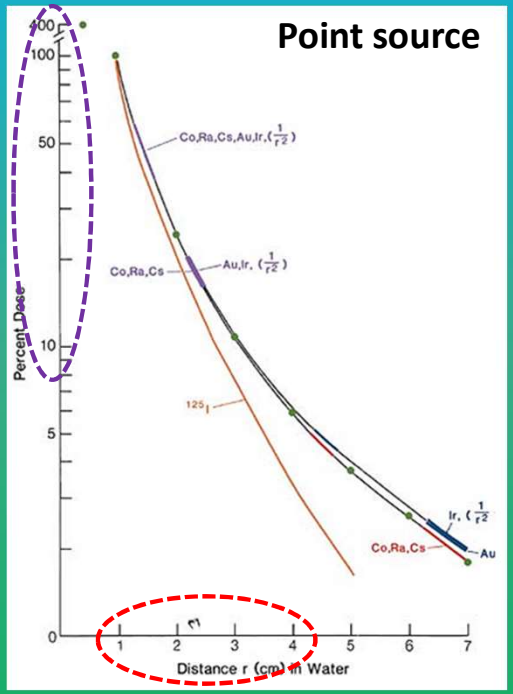
- Ande Bao, Andrew Brenner, and William Phillips are Consultants to Plus Therapeutics, Inc. and shareholders of NanoTx, Inc.
- Norman LaFrance and Marc H. Hedrick are employee of Plus Therapeutics, Inc.

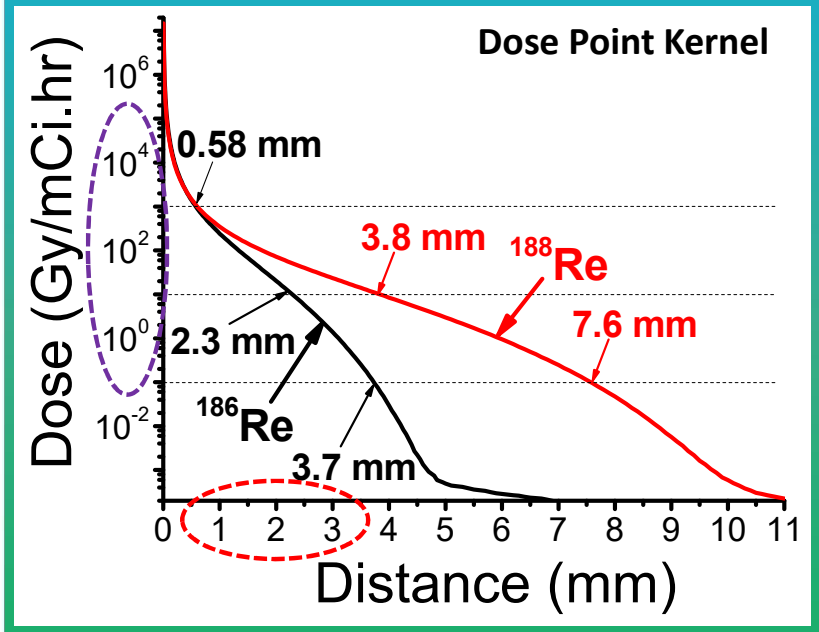
Focused Cancer Brachytherapy

- The focused cancer brachytherapy (radiation therapy) using nanoliposome (lipid nanoparticle)-carried radiation sources
- Nanoparticles, and physics of radiation sources used
- Convection force (CED) mediated infusion delivery of radiation sources into tumor
- Image-guidance, planning, therapy, and evaluation
- Clinical studies
- Perspectives

Radiation Physics – Comparison of different radiation sources

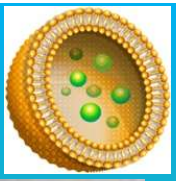


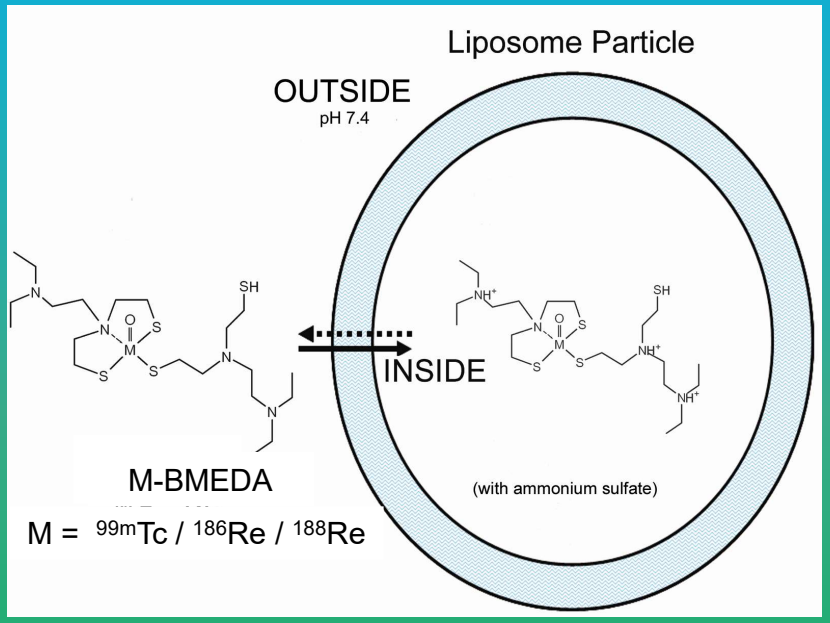


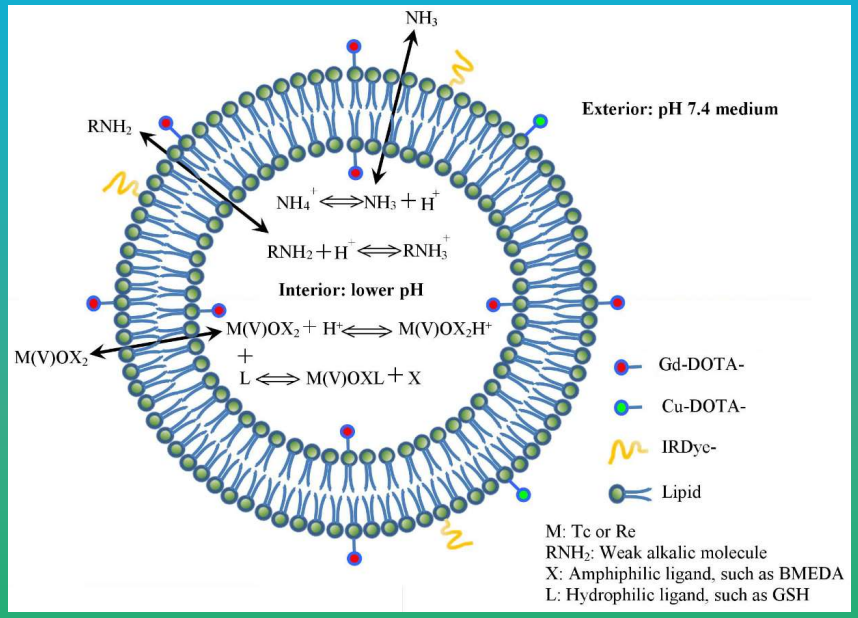


Radiation absorbed doses from β-particles drops for over 100 times within 2 – 4 mm distance from 0. 5 mm.

^{186}RNL / ^{188}RNL: Lipid nanoparticle (nanoliposome)-carried ^{186}Re / ^{188}Re radiation sources





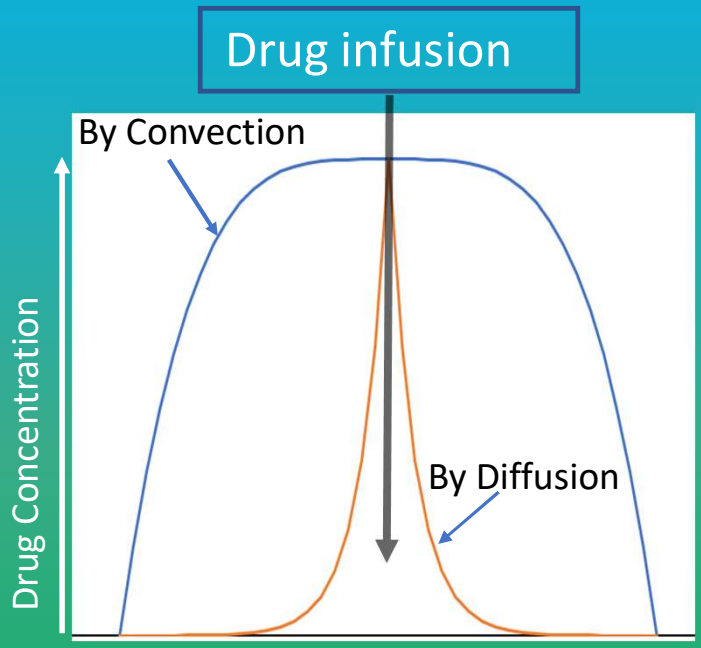


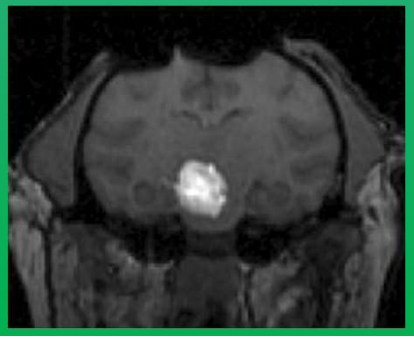
100-nm Diameter spherical shape biodegradable lipid nanoliposomes carrying radiation sources for focused therapy of cancer

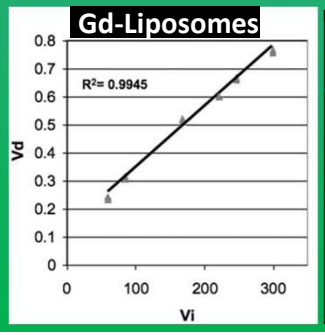
1. Bao, et al. *J Nucl Med* 2003;44:1992–1999
2. Bao, et al. *J Pharm Sci* 2003;92:1893–1904
3. Bao, et al. *J Pharmacol Exp Ther* 2004;308: 419-425
4. Goins, et al. *Methods Mol Biol* 2017;1522:155-178
5. Li, et al. *Bioconjugate Chem* 2012;23:1322–1332

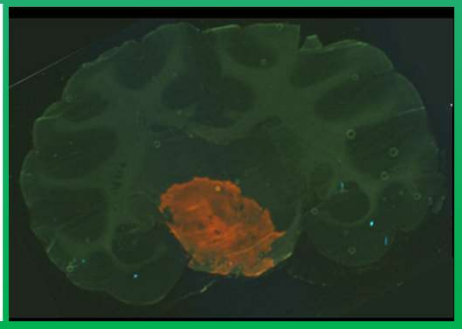
Convection-enhanced drug delivery (CED)

- To overcome drug delivery problem for the treatment of CNS diseases, CED technique has been proposed.
- CED involves continuous positive-pressure infusion of a solute containing a therapeutic agent for delivery to the CNS. The bulk flow mechanism is created by a constant pressure gradient from a pump that pushes solute through the volume at the location to be treated.
- In years, CED delivery of chemotherapeutic agents into tumor interstitial space for the treatment of brain cancer in patients have been studied.
- The planning and image-guided intervention technique have also been developed.



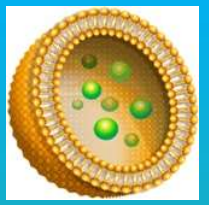




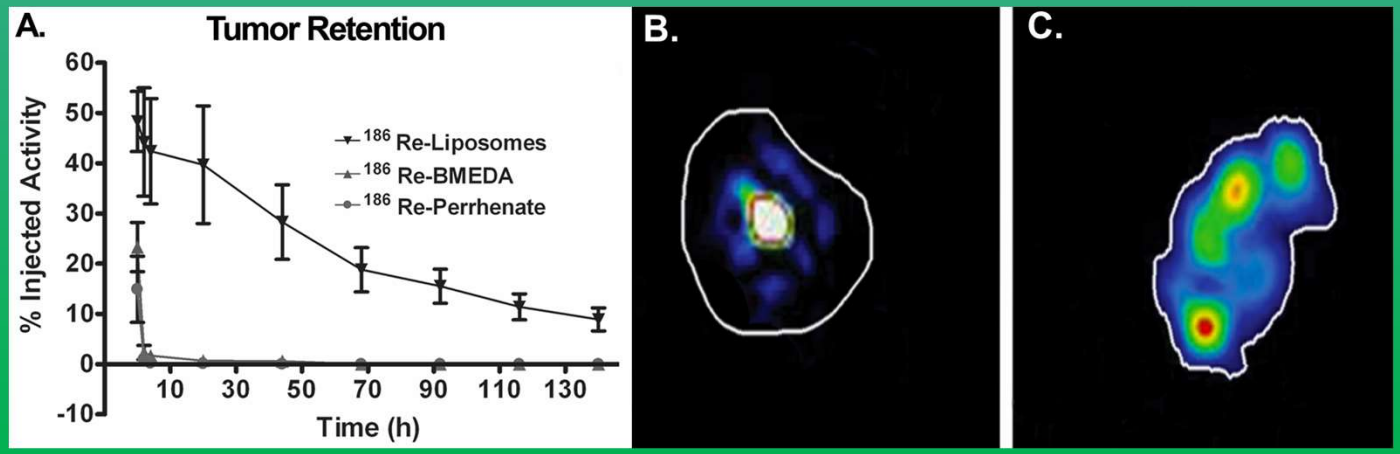


1. Raghavan R, et al. *Neurosurg Focus* 2006; 20 (3):E12: 1-13
2. Vogelbaum MA and Aghi MK. *Neuro-Oncology* 2015; 17(S2), ii3–ii8
3. Krauze MT, et al. *Exp Neurol* 2008; 210(2): 638–644

Cancer therapy using nanoparticle-carried radionuclides

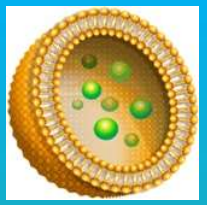


- Liposomal nanoparticle carriage enables dispersion of radiation sources throughout tumor tissue mediated by convection force – Convection-Enhanced Delivery (CED)
- After delivery, the nanoparticles retained radiation sources inside the tumor for focused cancer radiation therapy (focused brachytherapy)



1. Bao, et al. *Int J Pharm* 2006;316:162–169
2. French, et al. *J Vasc Interv Radiol* 2010; 21:1271–1279

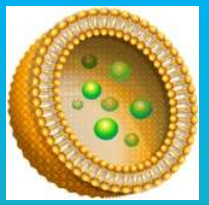
Cancer therapy using nanoparticle-carried radionuclides

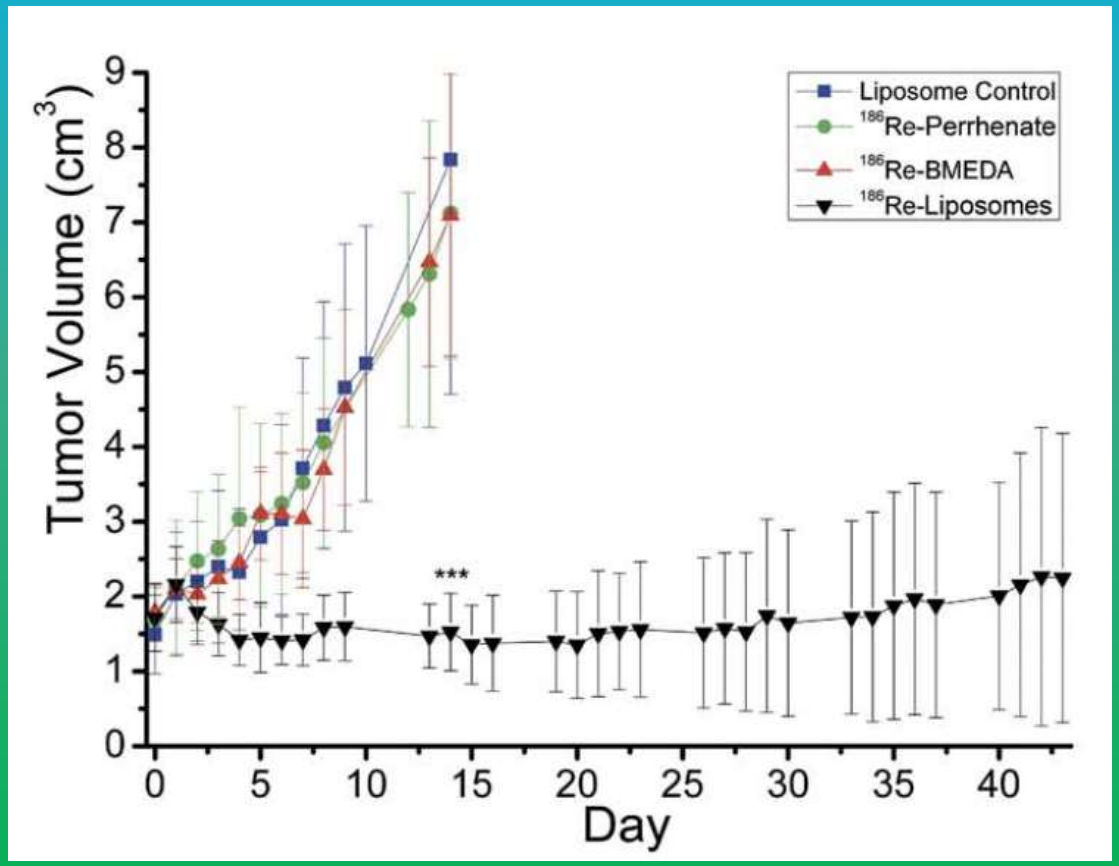


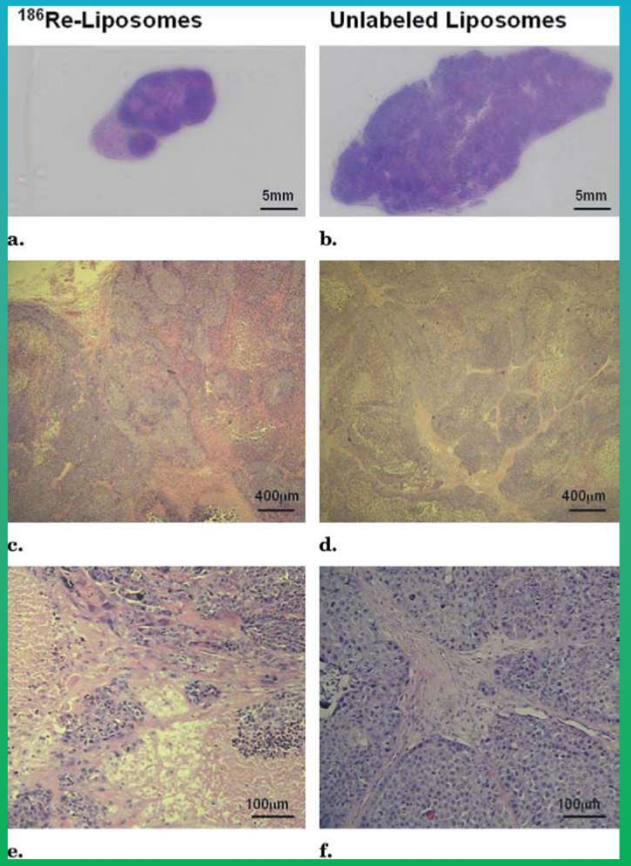
Important message:

- ✓ *Mediated by convection force, nanoparticulate radiation sources behaved large range of distribution throughout the tumor, followed by sustained locoregional retention.*
- ✓ *These double effects form the basis of using nanoparticle-based radiation sources for focused cancer radiation therapy.*
- ✓ *In contrary, small molecules had limited distribution volume from the same delivery protocol, followed by rapid locoregional clearance.*

^{186}RNL had significant tumor therapy effect from CED delivery





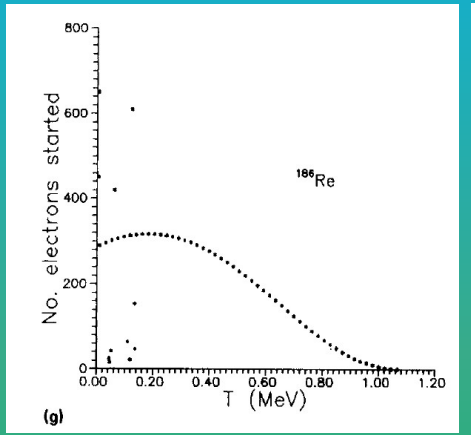


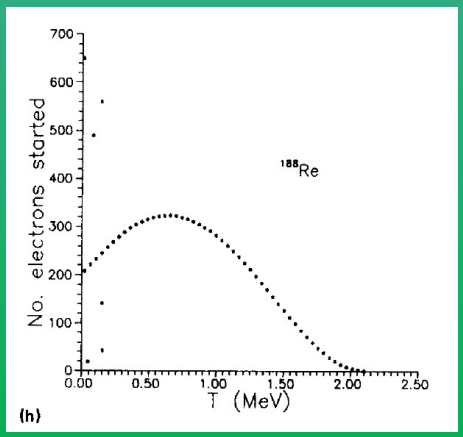
French, et al. *J Vasc Interv Radiol* 2010; 21:1271–1279

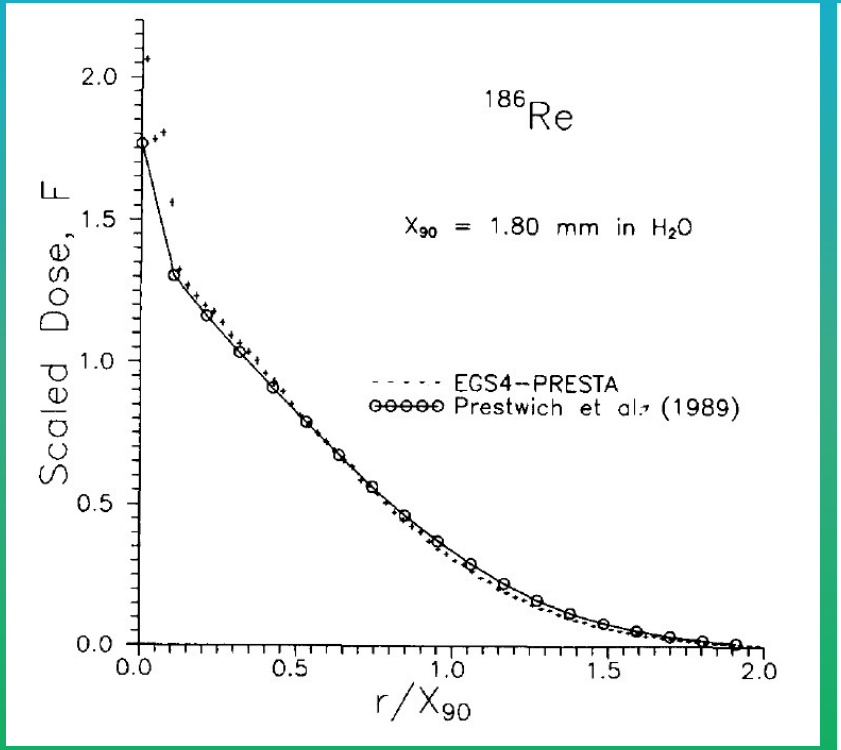
Physics of ^{186}Re, ^{188}Re, and ^{125}I

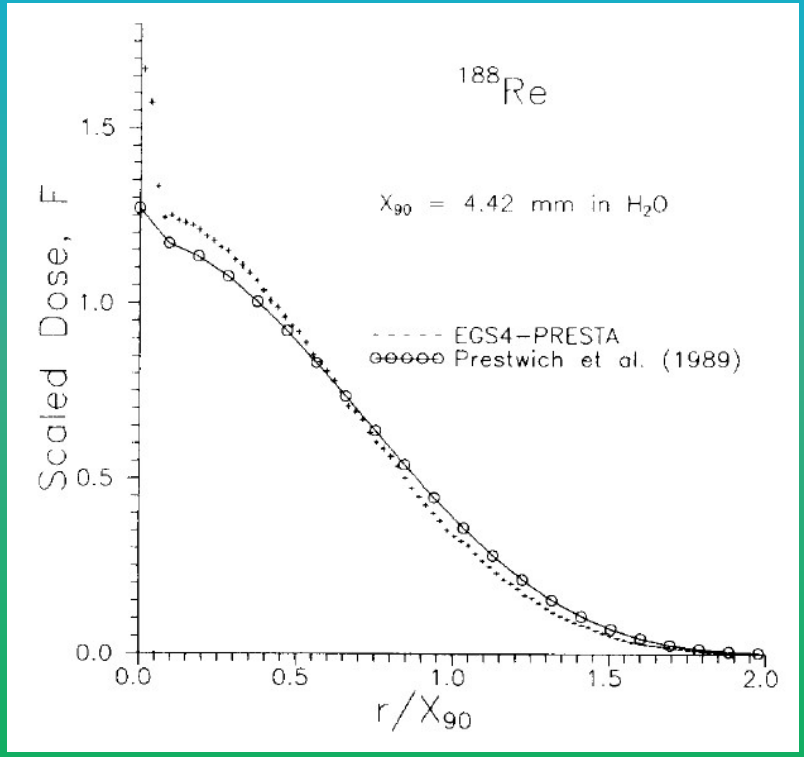
Nuclide	^{186}Re	^{188}Re	^{125}I
$T_{1/2}$	89.24 h	17.00 h	59.40 d
Decay Mode	β^-, EC	β^-	EC
Average β-Energy (KeV)	306 (21.5%); 359 (70.9%)	729 (26.3%); 795 (70.1%)	
Average β-Range (mm)	1.8	3.5	
Major γ-Ray (KeV)	137 (9.42%); 122.6 (0.603%)	155 (15.6%)	22.67 – 35.49 (186%) (γ- & x-ray)
β^- / γ-Energy Ratio	16.21	12.81	
Production	Reactor: $^{185}Re(n,\gamma)$ Accelerator: $^{186}W(p,n)$	Reactor: $^{187}Re(n,\gamma)$; Generator: ^{188}W ($T_{1/2}$: 69.78 d)-^{188}Re	
Therapeutic Radiation and Dose Rate Constant (Gy.g/(mCi.hr))	β-, 7.13	β-, 16.5	Low energy photon, 0.91

β-radiation energy spectrum and dose point kernel





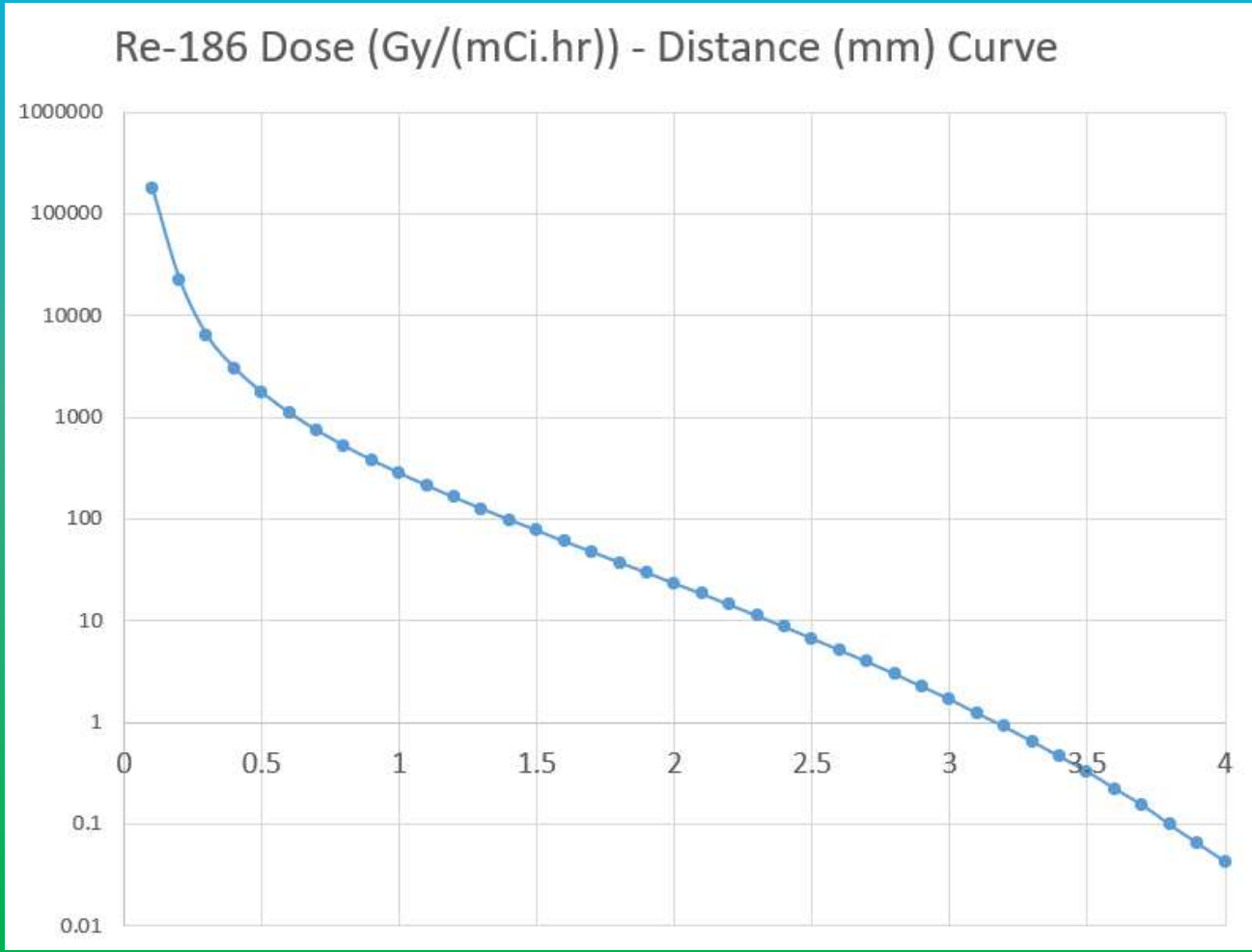




$$F(r/X_{90}) = \frac{\delta E(r)/T_o}{\delta r/X_{90}}.$$

1. Simpkin DJ & Mackie TR. *Med Phys* 17:179-186, 1990
2. Graves SA, Flynn RT, & Hyer DE. *Med Phys* 46:5284-93, 2019

β-radiation energy spectrum and dose point kernel

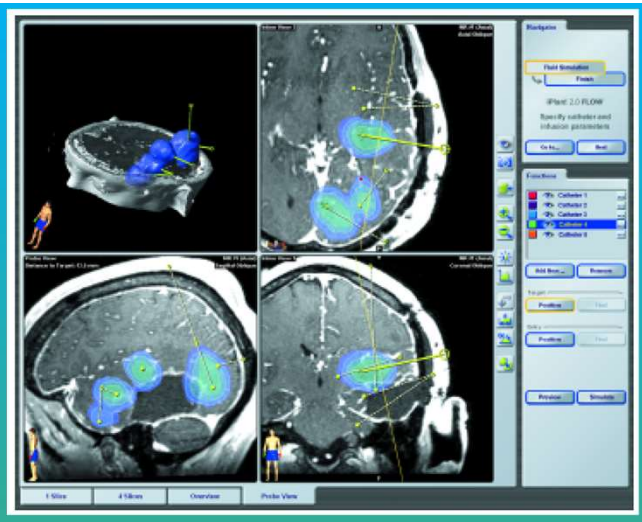


summary of physics

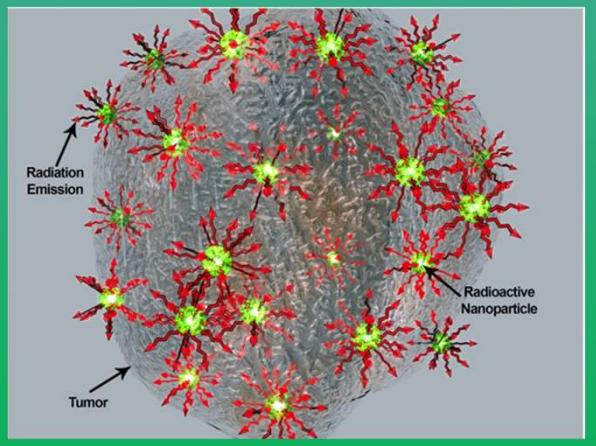
- Lipid nanoparticle (nanoliposome)-carried β-emission radionuclides provide a much higher dose rate at tumor site comparing with low energy photon sealed source brachytherapy.
- The short mm-range β-particle radiation provides a highly focused radiation therapy, which enables further increased radiation doses focused to a small volume to be treated, while the nearby tissue can be largely spared with minimal radiation absorbed doses.
- The accompanied γ-radiation provides a tool of non-invasive imaging on *in vivo* radioactivity distribution for radiation dosimetry and tumor therapy prediction (theranostics).

Summary: Nanoparticle-based focused cancer brachytherapy

- Through intratumoral administration and mediated by convection force, lipid nanoparticle (nanoliposome)-based therapeutic radiation sources have been dispersed throughout the entire tumor volume providing a focused cancer radiation therapy. – Nanotechnology-based focused brachytherapy.



iPlan Flow planning

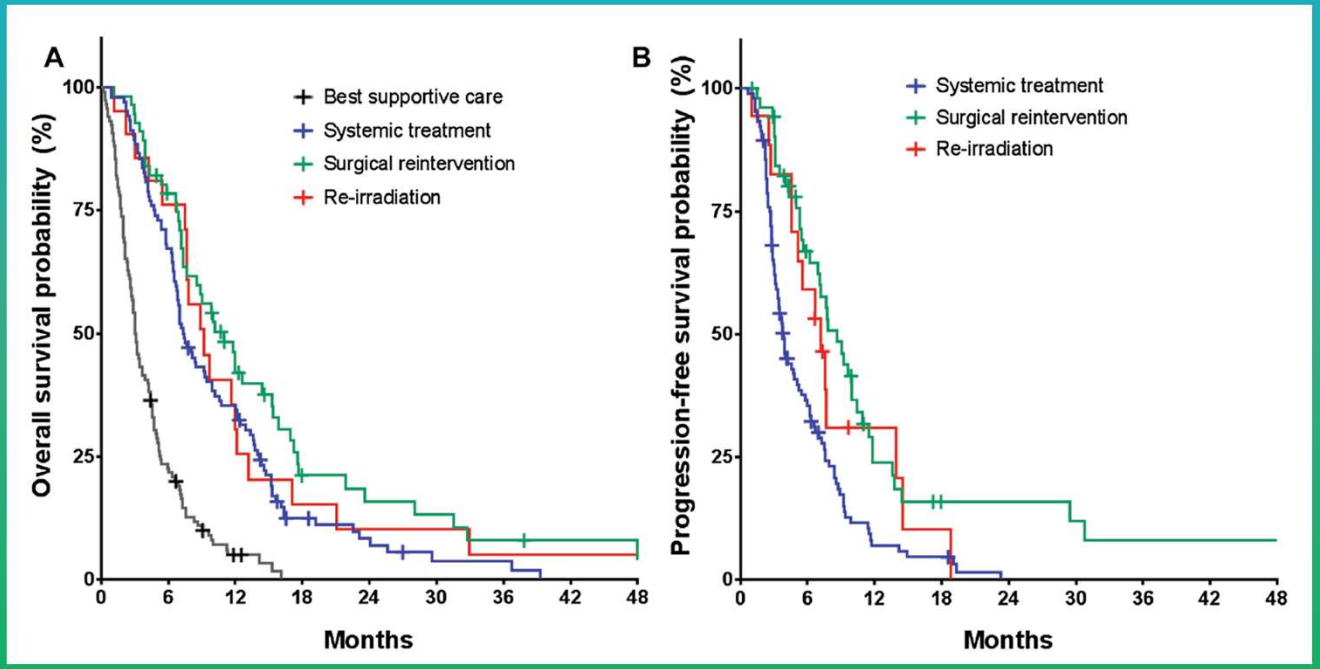


Focused radiation cross-fire tumor eradication

Recurrent Glioblastoma (GBM)

Overall survival

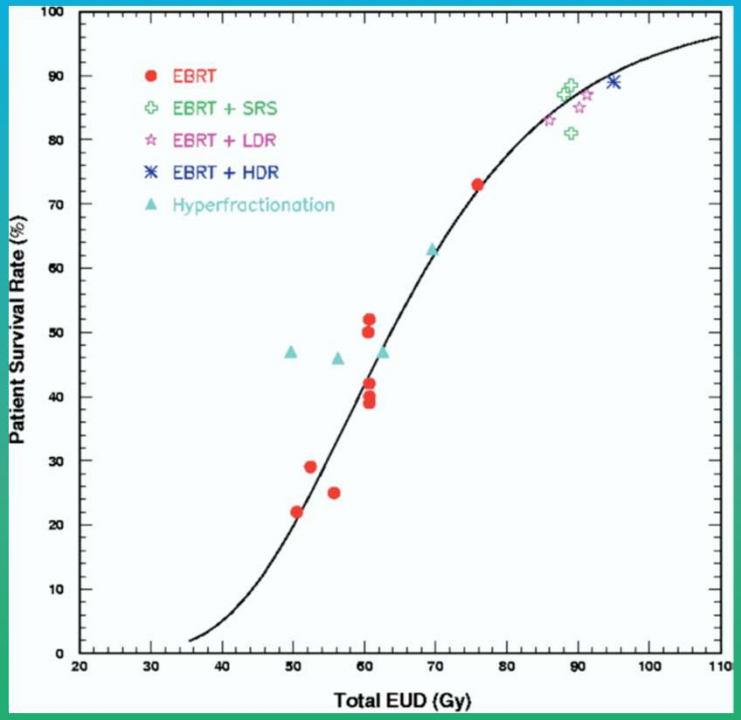
Progression-free survival



- Mean survival: 6-8 months
- Challenge with drug delivery
- Highly radiation resistant

van Linde, et al. *J Neurooncol* 2017; 135:183–192

Brain Cancer Therapy: Challenges in tumor dose and toxicity



1-Year survival improves with higher EUD

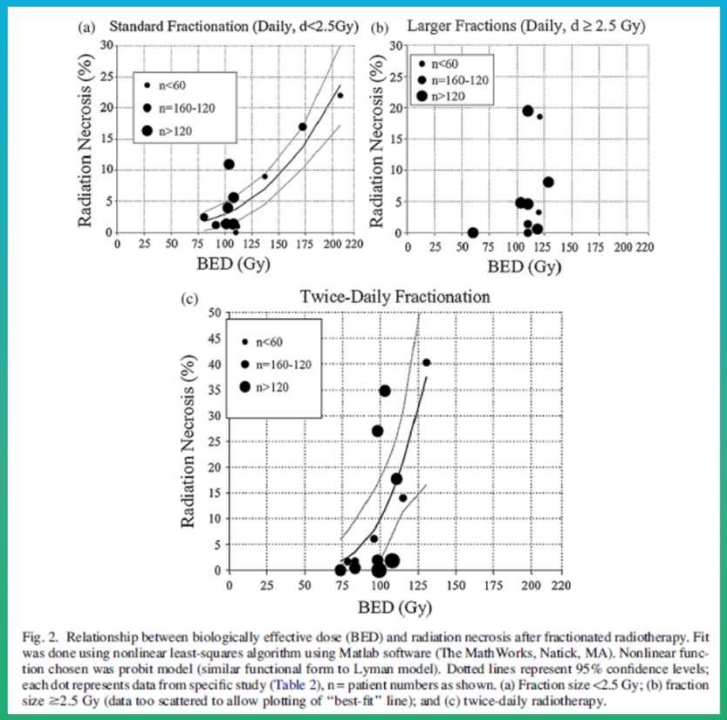
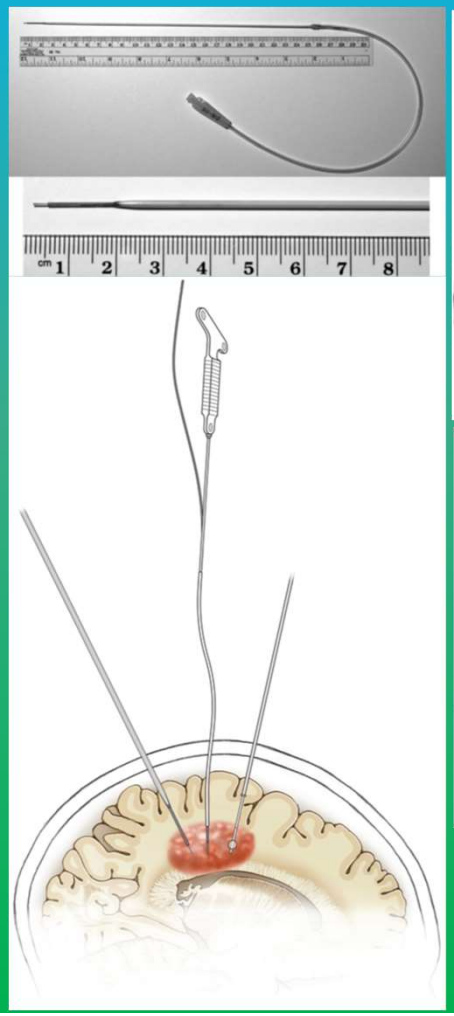


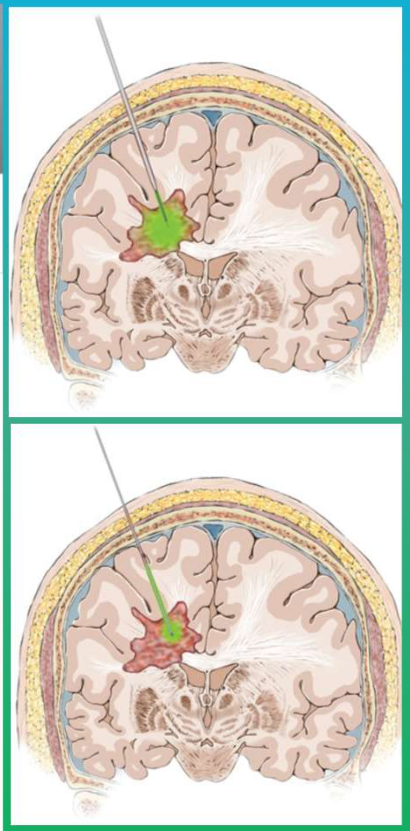
Fig. 2. Relationship between biologically effective dose (BED) and radiation necrosis after fractionated radiotherapy. Fit was done using nonlinear least-squares algorithm using Matlab software (The MathWorks, Natick, MA). Nonlinear function chosen was probit model (similar functional form to Lyman model). Dotted lines represent 95% confidence levels; each dot represents data from specific study (Table 2), n = patient numbers as shown. (a) Fraction size <2.5 Gy; (b) fraction size ≥2.5 Gy (data too scattered to allow plotting of "best-fit" line); and (c) twice-daily radiotherapy.

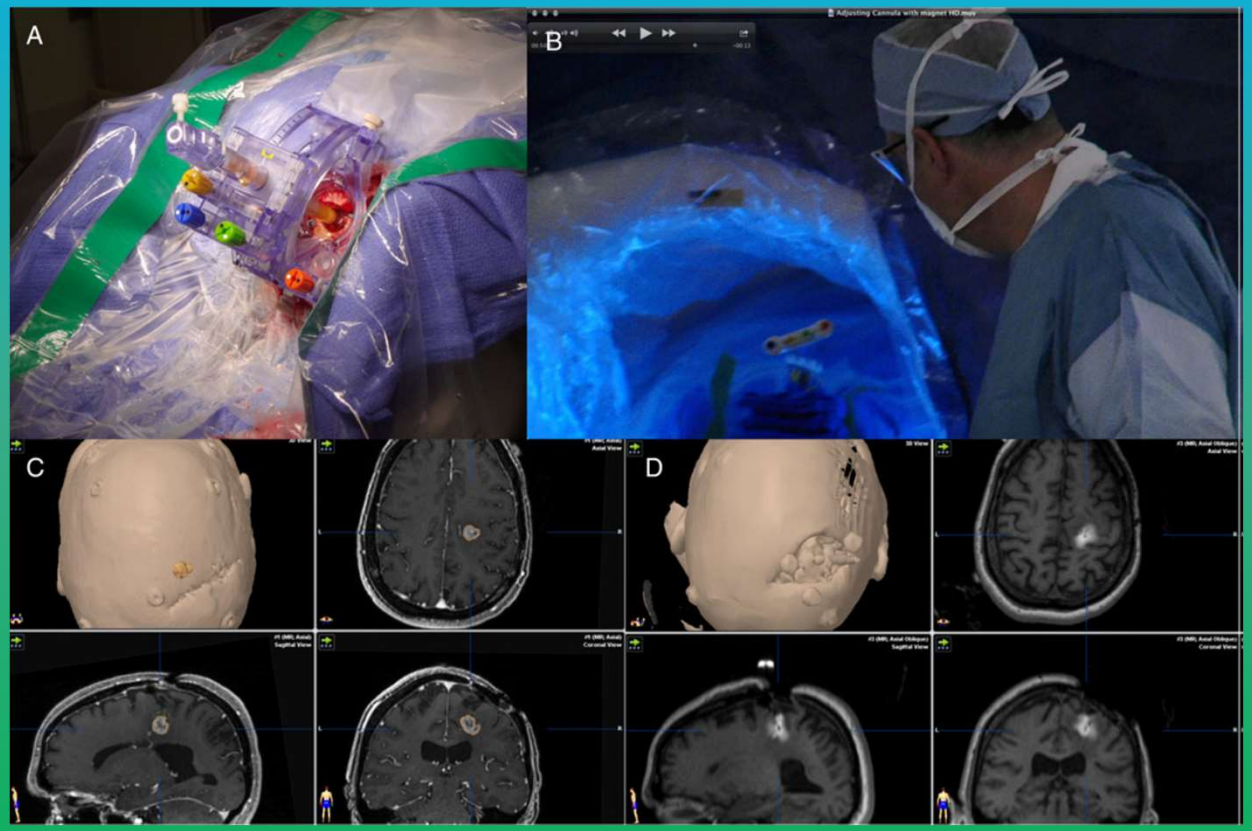
Rapidly increased ratio of necrosis when BED went To ~ 100 Gy

1. Qi XS, et al. *Int J Radiation Oncol Biol Phys* 64: 1570-80, 2006
2. Lawrence YR, et al. *Int J Radiation Oncol Biol Phys* 76: 520-7, 2010

Brain cancer therapy: CED drug delivery in clinic

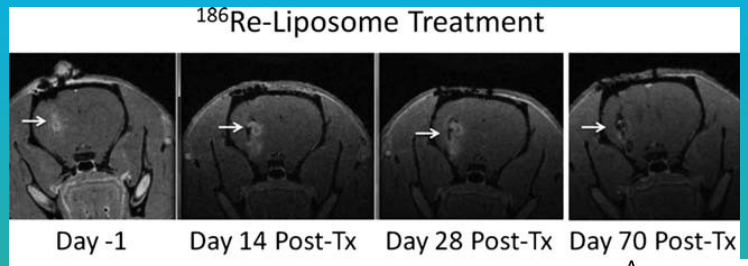


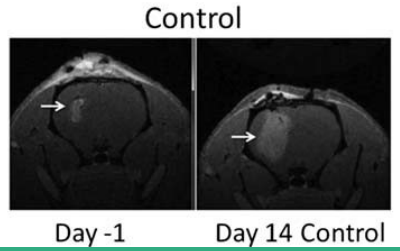


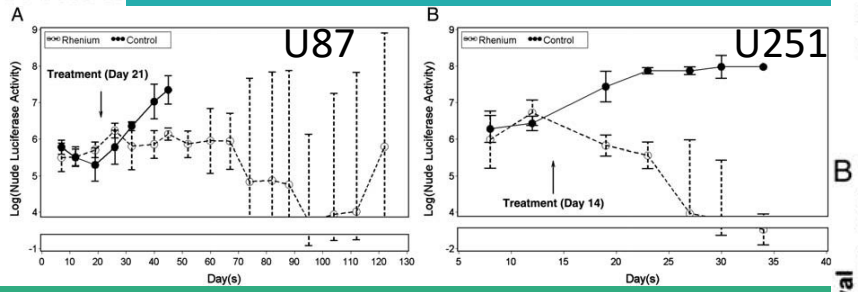


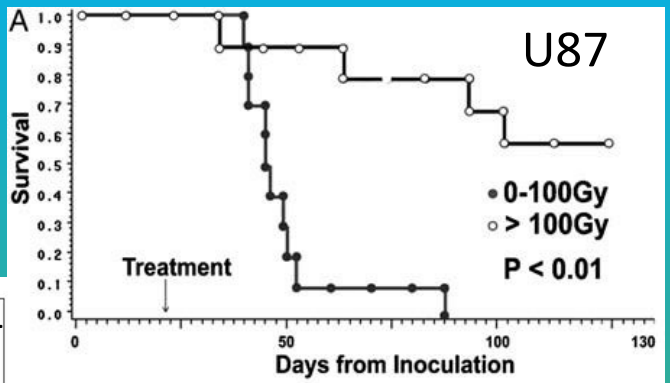
1. Vogelbaum MA and Aghi MK. *Neuro-Oncology* 17(S2), ii3–ii8, 2015
2. Jahangiri A, et al. *J Neurosurg* April 1, Page 1-10, 2016

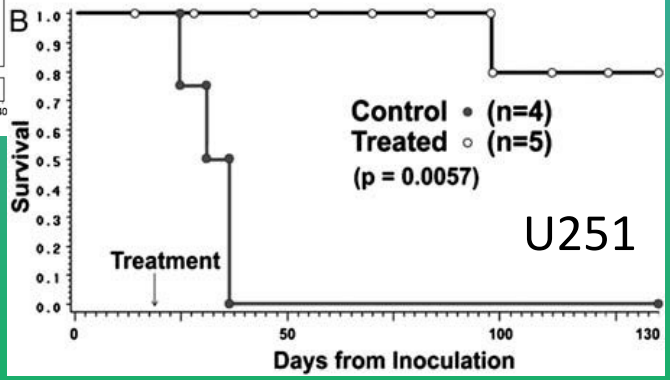
Brain Cancer Therapy with Liposomal Radiation

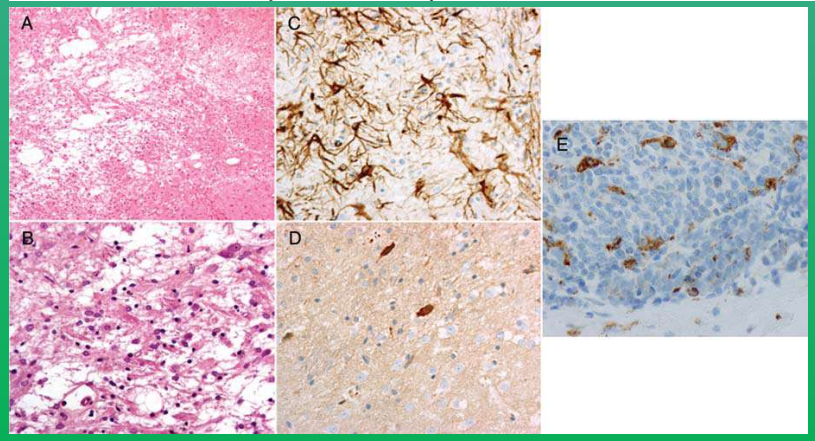












Treated Control

Phillips WT, et al. *Neuro-Oncol* 14:416-425, 2012

Clinical trial
- treatment of recurrent GBM using ^{186}RNL

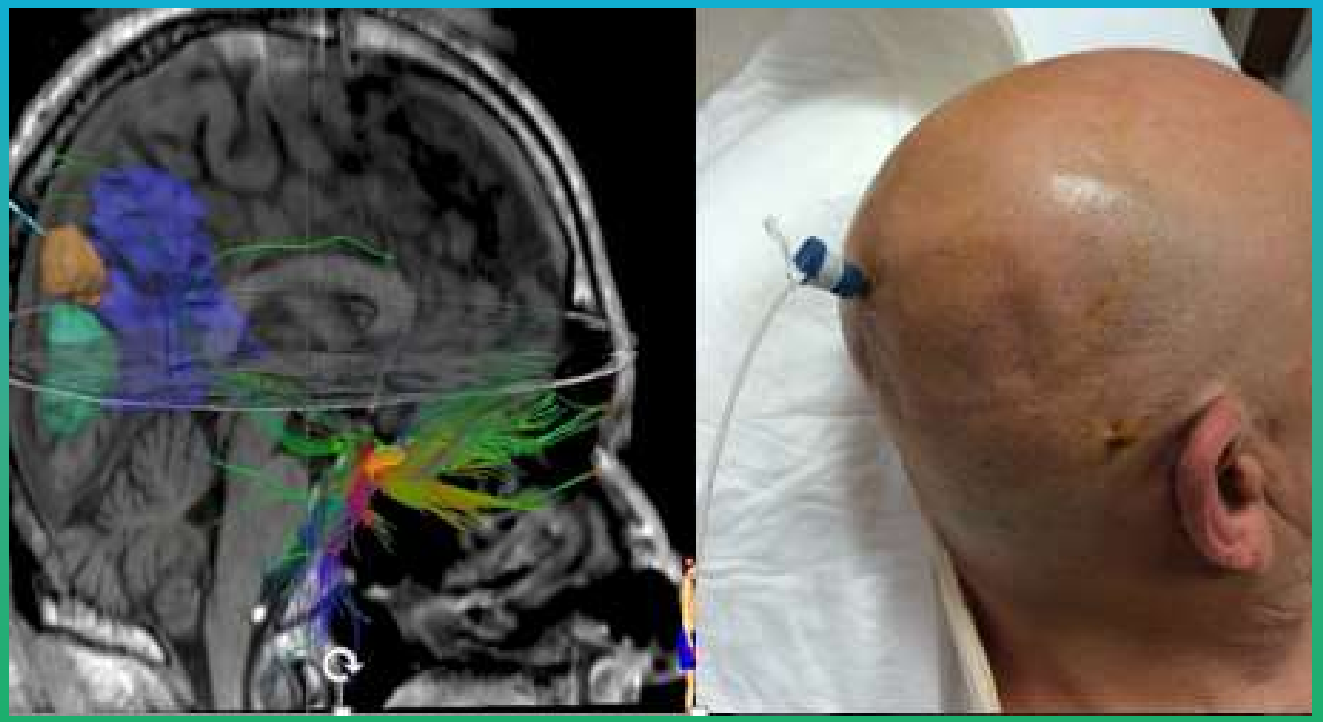
- Phase I/II Clinical Trial
- Dose escalation study

Cohort	Infused Volume (ml)	Total 186RNL Injected (mCi)	Concentration (mCi/ml)	Number of Patients Treated
1	0.66	1.0	1.5	3
2	1.32	2.0	1.5	3
3	2.64	4.0	1.5	3
4	5.28	8.0	1.5	3
5	5.28	13.4	2.5	3
6	8.80	22.3	2.5	6
7	12.30	31.2	2.5	2

*. 23 Patients in total has been studied so far

Planning and therapy

Planning - Mapping of neural pathways to avoid critical structures in the brain

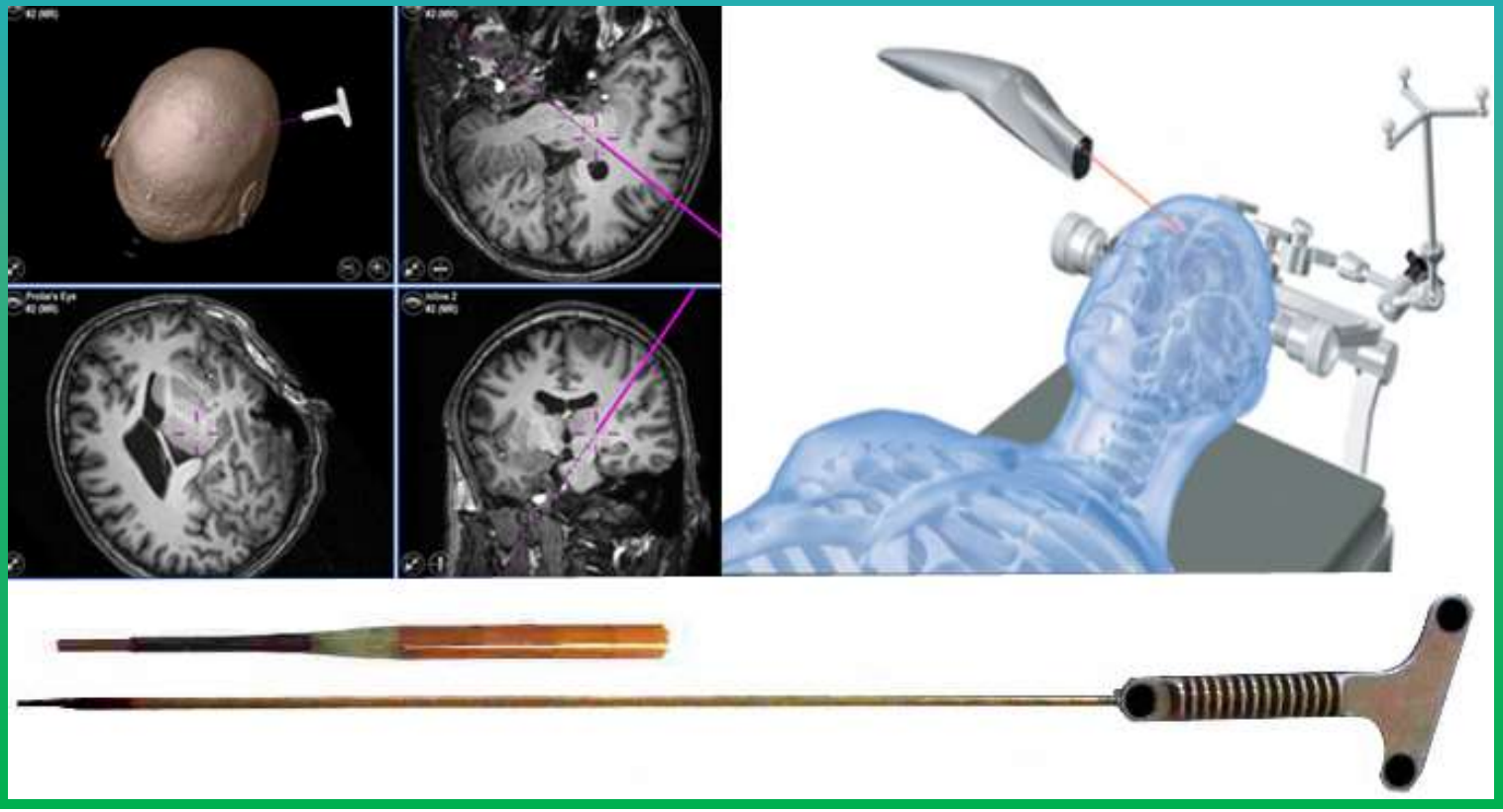


Patient during infusion

- BrainLab iPlan Flow software has been used for planning and stereotactic catheter placement
- 1 – 4 catheters have been used per tumor volume and shape

BrainLab SmartFlow Flex Catheter

- CT and MRI-based image-guidance



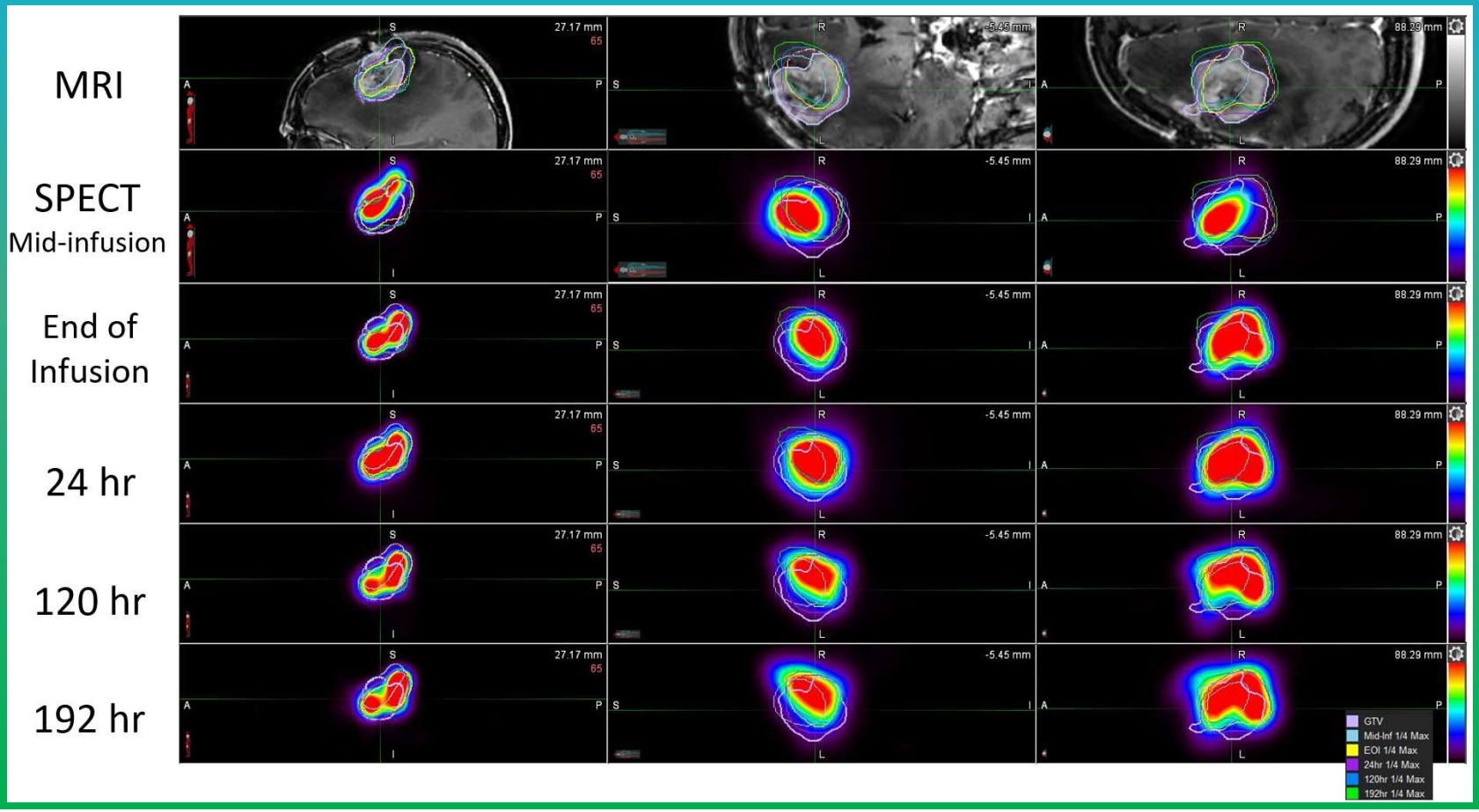
Therapy and Imaging monitoring

- ^{186}RNL distribution and retention following times
  - Whole body planar AP/PA gamma camera imaging
  - Head SPECT/CT imaging
- Follow-up MR images were acquired to monitoring therapy response
- Co-registration (Fusion) of SPECT/CT and follow-up MR images has been used to evaluate tumor coverage by ^{186}RNL, and to study the correlation between % tumor volume covered by ^{186}RNL and tumor therapy effect
- Whole body planar images have been used to analyze and calculate normal organ doses, as well as the reference for 3D dose in the brain.

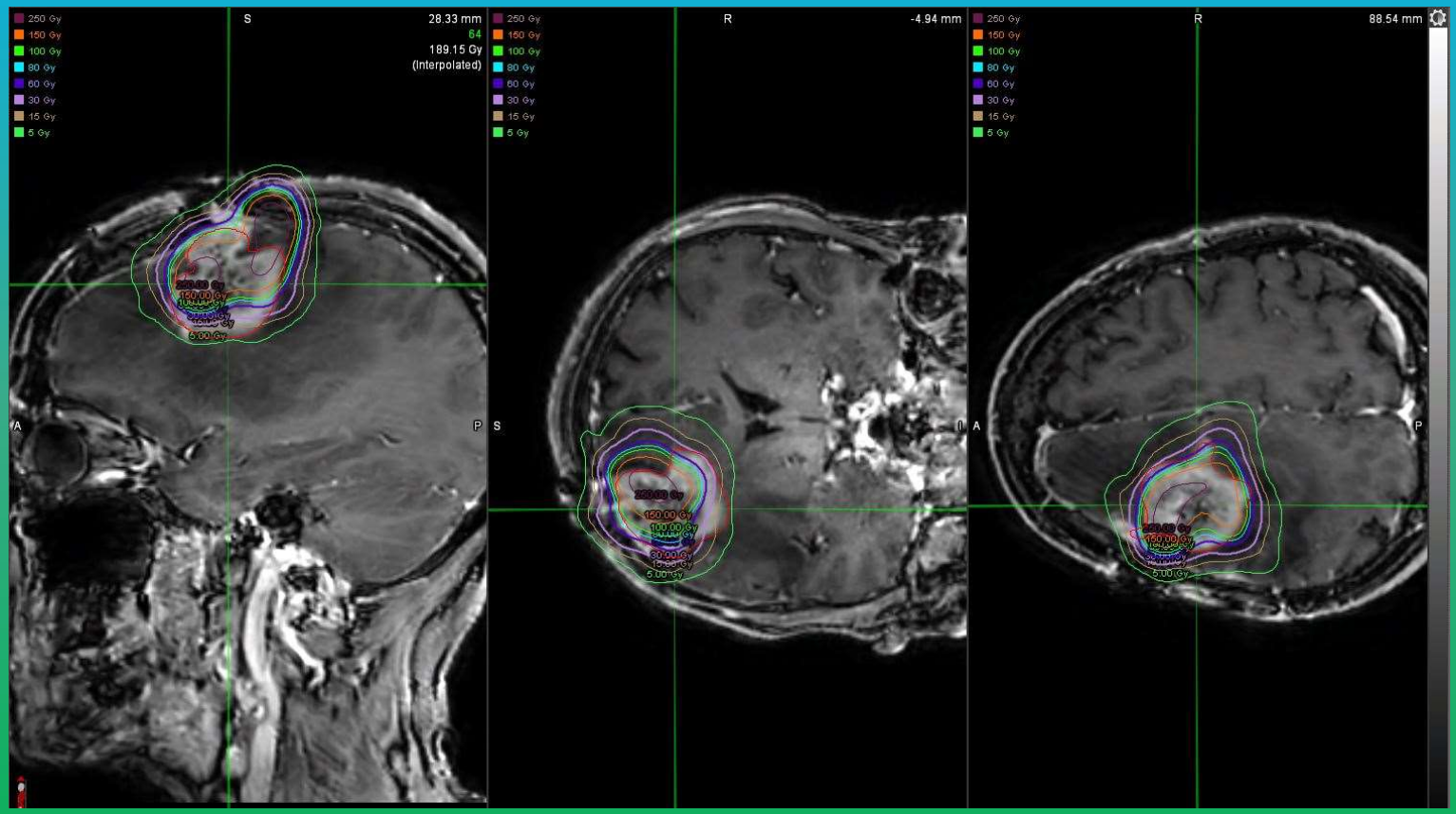
Radiation absorbed dose in tumor

- Radiation absorbed doses in tumor has been quantified with the combination use of planar and SPECT images.
- Partial volume effect with SPECT images has also been considered.

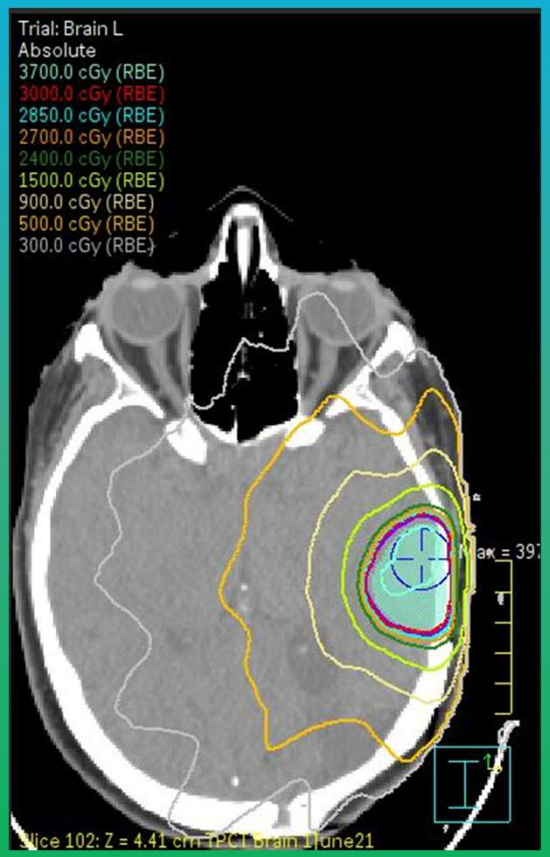
^{186}RNL has sustained distribution and retention in tumor for GBM Therapy



High radiation absorbed dose is highly focused in the local volume

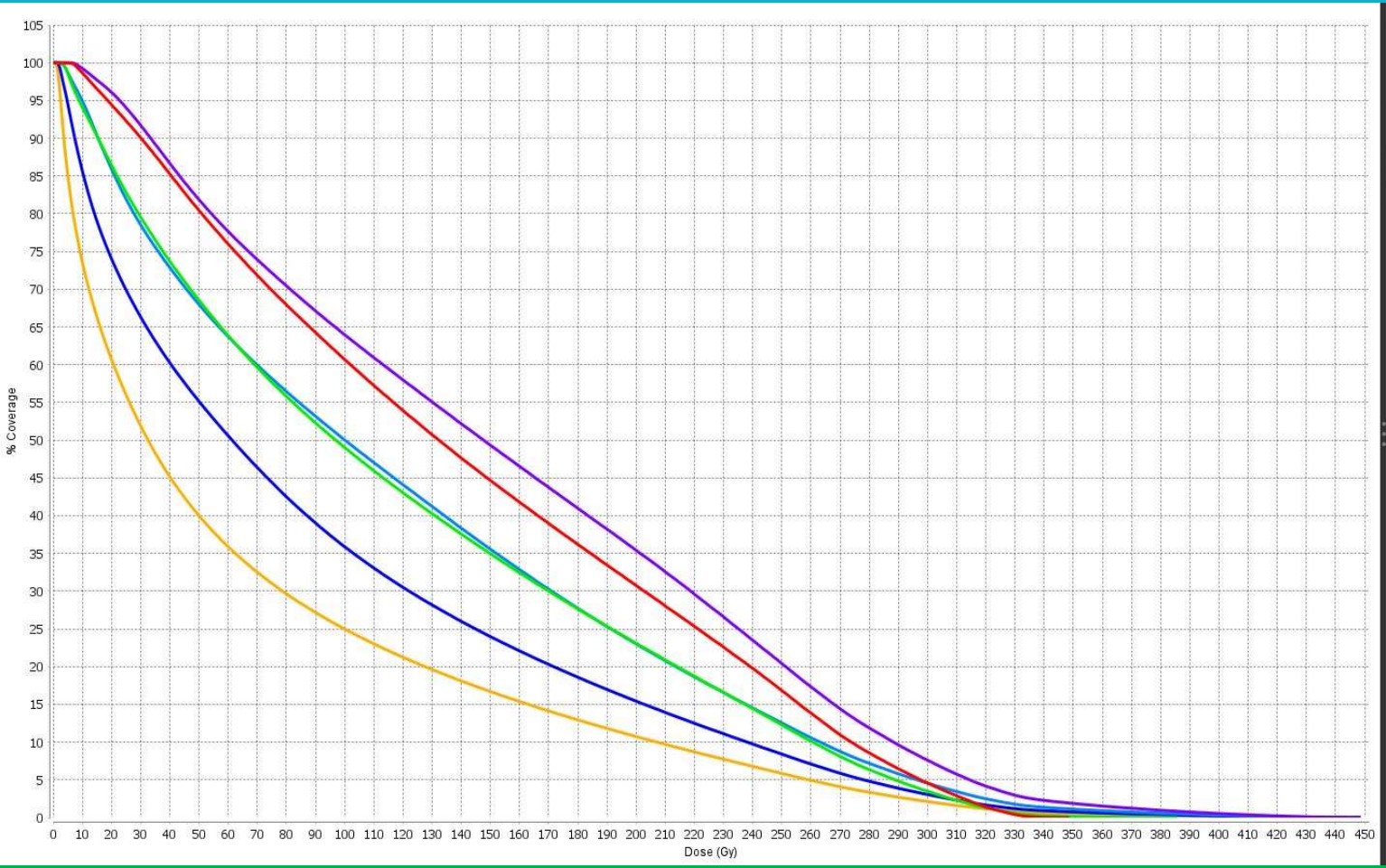


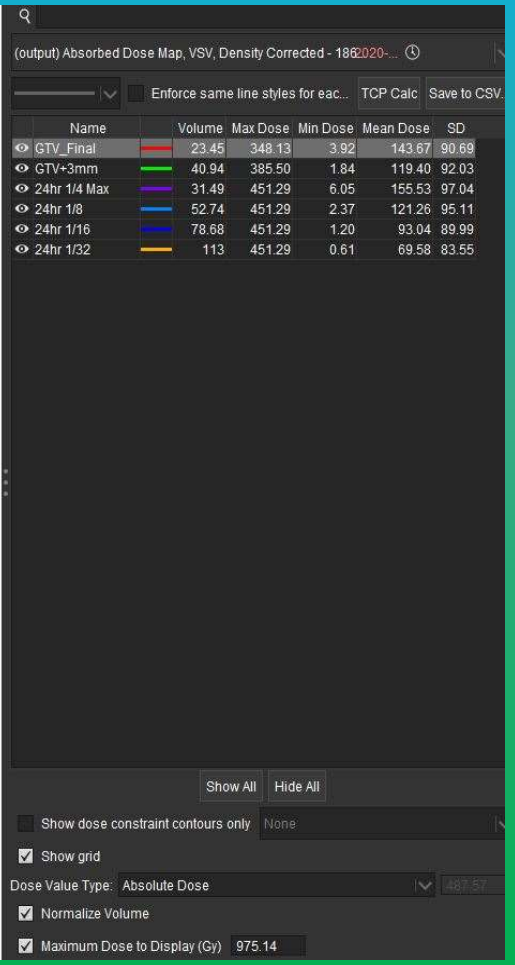
^{186}RNL 3D Dose Distribution



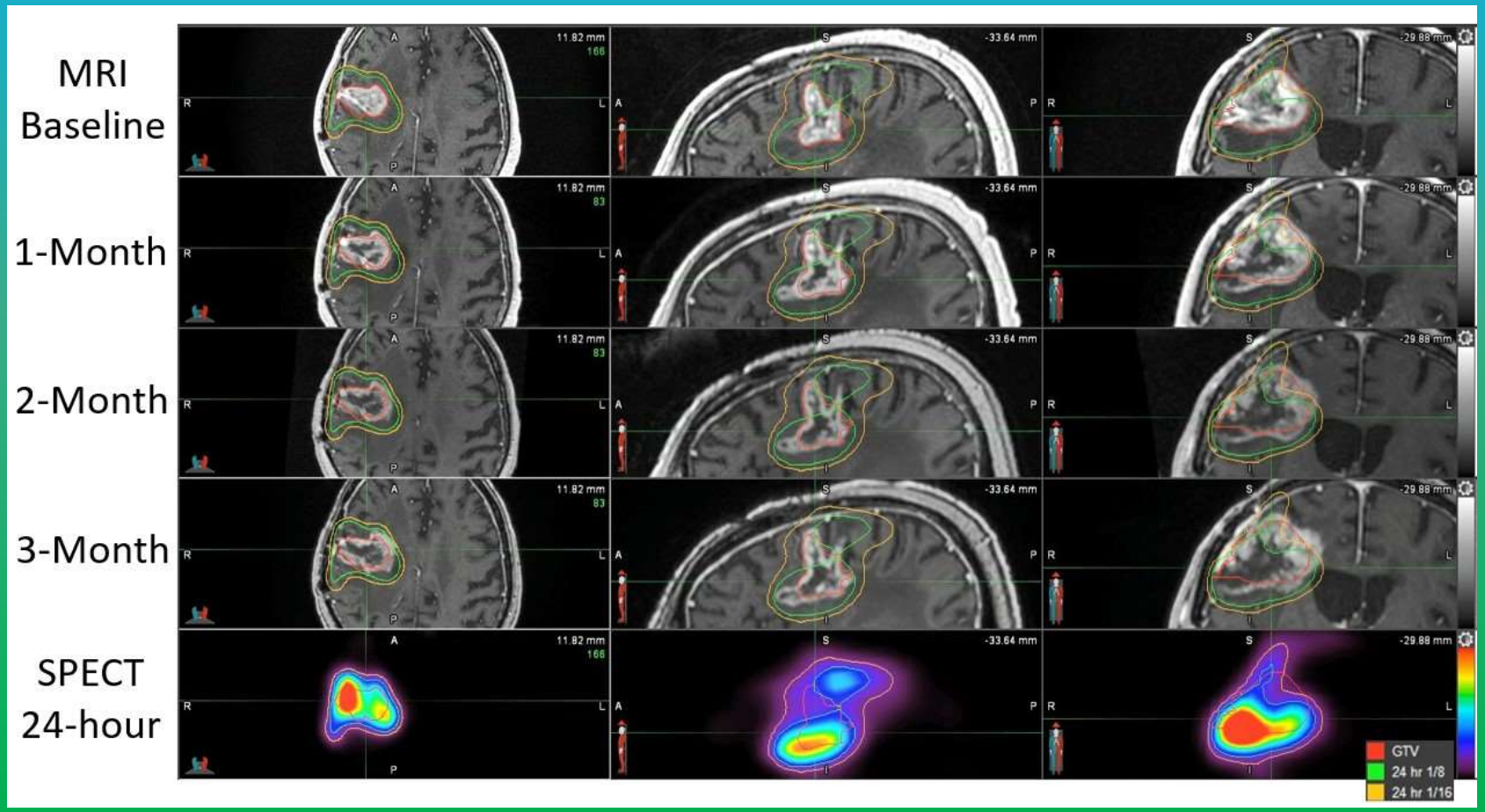
SBRT

High radiation absorbed dose is highly focused in the local volume

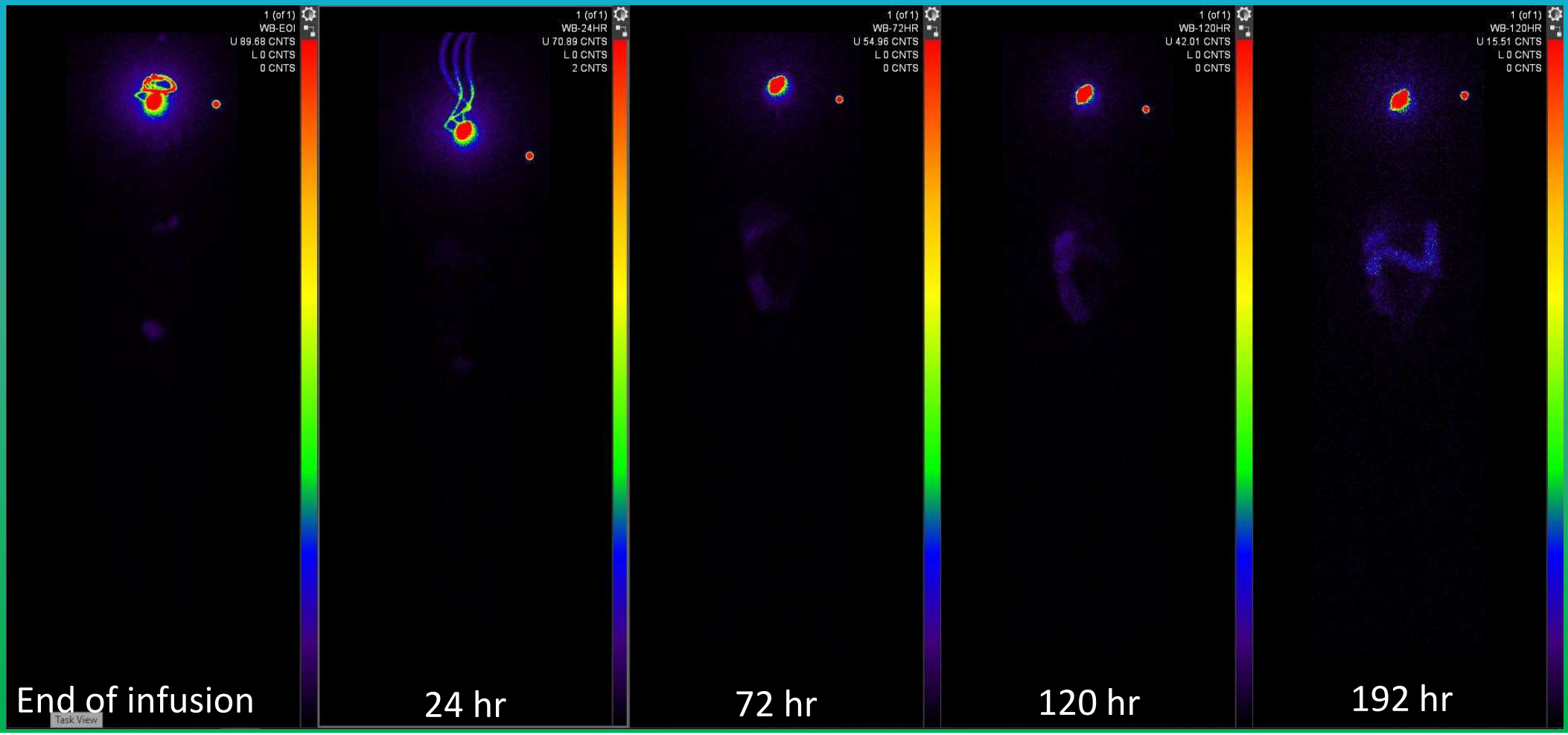




Tumor coverage predicts therapy response in the locoregional tumor volume



^{186}RNL Whole Body Distribution
- Normal organ dose outside brain is low

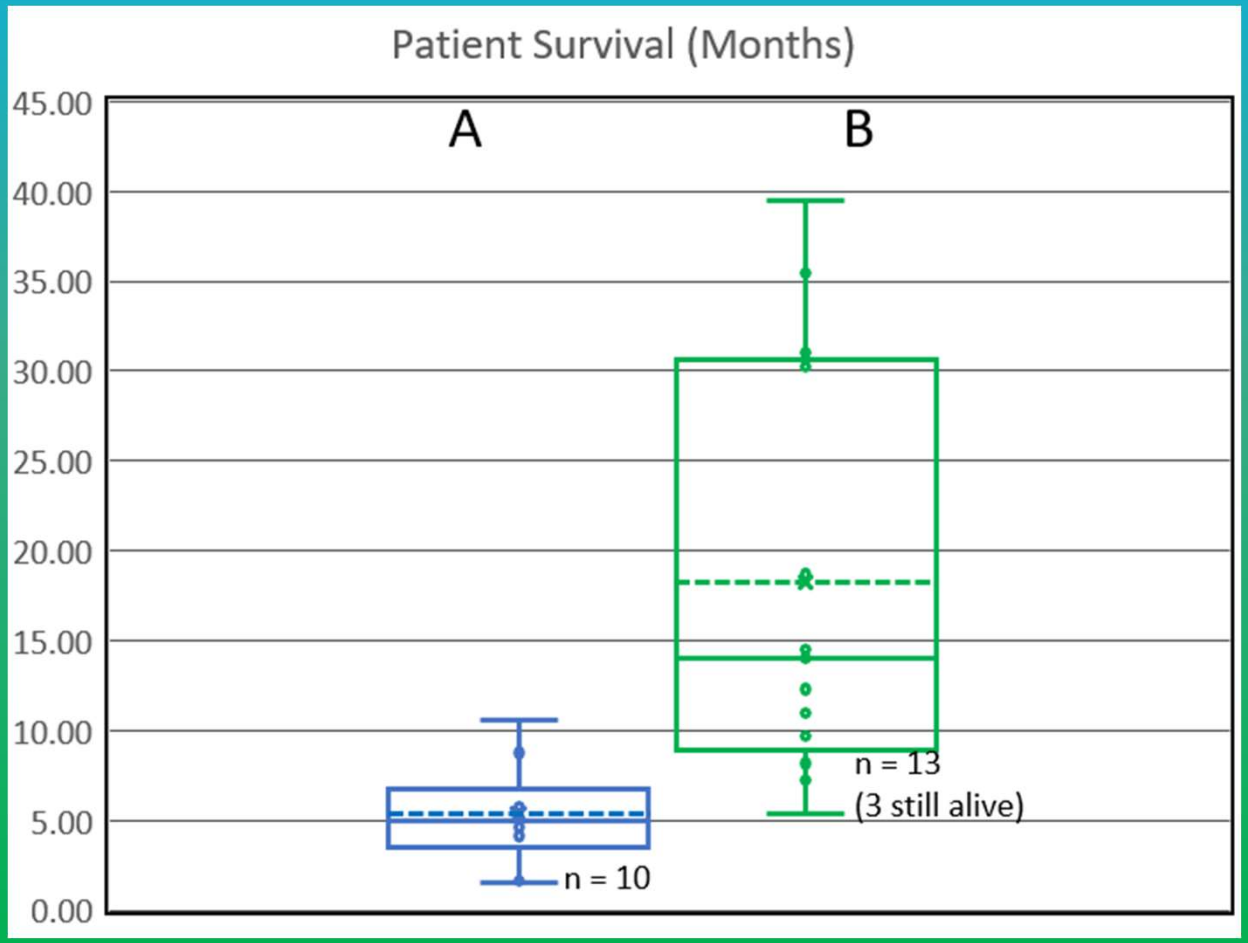


Patient survival has significant correlation with tumor dose and coverage

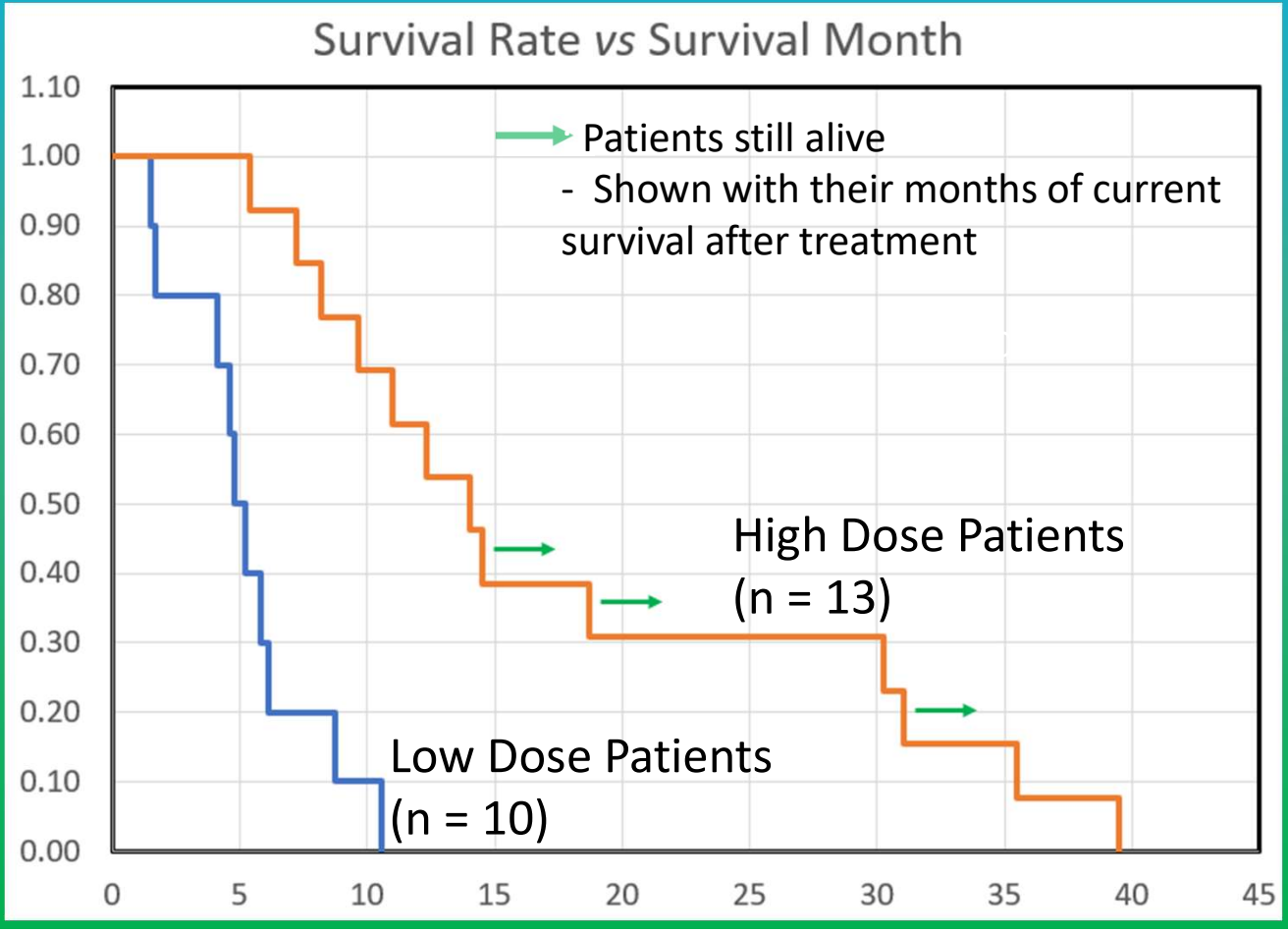
- The patients with < 70% tumor coverage by ^{186}RNL distribution or with < 100 Gy average tumor dose (49.3 ± 25.8 Gy) had a mean survival of 5.3 ± 2.8 months (n = 10), which is similar to previously reported data.
- The patients with > 70% tumor coverage by ^{186}RNL distribution and with > 100 Gy average tumor dose (408.9 ± 154.6 Gy) had a mean survival of 18.4 ± 11.7 months (n = 13) so far, while 3 of them are still alive.

	Low Dose Patients	High Dose Patients
Current Mean Survival (Months)	5.3 ± 2.8 (n = 10)	18.4 ± 11.7 (n = 13)
	P < 0.005	
3 Patients are still alive in High Dose Group		
8 of 10 Low Dose Patients were from earlier cohorts (≤ 8.0 mCi injected activity)		

Patient survival has significant correlation with tumor dose and coverage



Patients with higher tumor dose and coverage has significantly improved patient survival



Focused Therapy of recurrent GBM using ^{186}RNL – summary

- Focused radiation therapy (focused brachytherapy) of recurrent GBM using ^{186}RNL has shown the optimism with significantly improved patient survival.
- The patient survival has significant correlation with tumor coverage and radiation absorbed doses.
- It has been shown the importance of treatment planning, image-guided delivery, imaging distribution, and radiation dosimetry.
- Additional treatment to suboptimal covered tumor volume has been proposed to further improve therapy effect and patient survival.
- Phase 2/3 clinical trials have been requested for FDA approval.

RELEASE OF PATIENTS ADMINISTERED RADIOACTIVE MATERIAL

- NRC Regulatory Guide 8.39
- The regulatory guideline applies to all NRC medical use licensees subject to Title 10 of the *Code of Federal Regulations* (10 CFR) Part 35, "Medical Use of Byproduct Material," Section 35.75, "Release of Individuals Containing Unsealed Byproduct Material or Implants Containing Byproduct Material".
- The NRC determined that while doses should be maintained ALARA, a dose limit of 5 mSv (0.5 rem) provides adequate protection. The Patient Release Rule allows a licensee to authorize the release of a patient from its control if the total effective dose equivalent (TEDE) to any other individual, from exposure to the released patient, is not likely to exceed 5 mSv (0.5 rem). In addition, 10 CFR 35.75 requires that a licensee provide the released individual, or the patient's family or other caregivers, with appropriate instructions, including written instructions, on recommended actions to maintain doses to other individuals ALARA if the TEDE to any other individual is likely to exceed 1 mSv (0.1 rem).

RELEASE OF PATIENTS ADMINISTERED RADIOACTIVE MATERIAL

- NRC Regulatory Guide 8.39
- Table 1. Activities and Dose Rates for Authorizing Patient Release

	COLUMN 1 ACTIVITY AT OR BELOW WHICH PATIENTS MAY BE RELEASED		COLUMN 2 DOSE RATE AT 1 METER, AT OR BELOW WHICH PATIENTS MAY BE RELEASED[b]	
RADIONUCLIDE	**(GBq)**	**(mCi)**	**(mSv/h)**	**(mrem/h)**
Ag-111	19	520	0.08	8
Au-198	3.5	93	0.21	21
Cr-51	4.8	130	0.02	2
Cu-64	8.4	230	0.27	27
Cu-67	14	390	0.22	22
Ga-67	8.7	240	0.18	18
I-123	6.0	160	0.26	26
I-125	0.25	7	0.01	1
I-125 implant	0.33	9	0.01	1
I-131	1.2	33	0.07	7
In-111	2.4	64	0.2	20
Ir-192 implant	0.074	2	0.008	0.8
P-32[c]	c	c	c	c
Pd-103 implant	1.5	40	0.03	3
Re-186	28	770	0.15	15
Re-188	29	790	0.20	20
Sc-47	11	310	0.17	17
Se-75	0.089	2	0.005	0.5
Sm-153	26	700	0.3	30
Sn-117m	1.1	29	0.04	4
Sr-89[c]	c	c	c	c
Tc-99m	28	760	0.58	58
Tl-201	16	430	0.19	19
Yb-169	0.37	10	0.02	2

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- My colleagues and collaborators

- In memory of Dr. Beth Goins, one of my great mentors, friends, and colleagues. In memory of her over 30 years of devotion on research and education; her large contributions on drug delivery, cancer therapy and imaging, and on this project.