



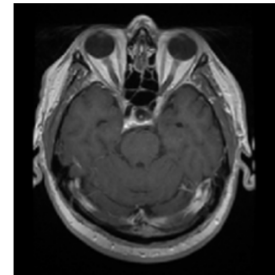
CASE STUDY

Calyx CNS / Neuro-Oncology Experience

OVERVIEW

Calyx Medical Imaging is a leading imaging core lab with the experience and ability to provide a wide range of services involving neuroimaging in clinical trials. Calyx Imaging's CNS group understands the unique and custom requirements of neuro-oncology trials and has the flexibility, creativity, bandwidth, and understanding in place to effectively manage and support these clinical trials.

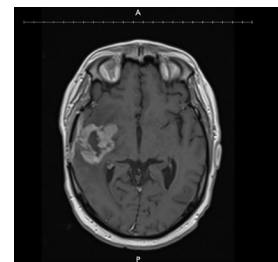
In addition to standard MRI acquisitions, the use of advanced imaging techniques in neuro-oncology has been steadily increasing. Dynamic Contrast-Enhanced MRI (DCE-MRI) is being used to evaluate the microvasculature of glioblastomas to determine the effects of treatments on vascular permeability. Diffusion Tensor Imaging (DTI) allows for the mapping of the orientation of white matter tracts. Both DCR-MRI and DTI, may be able to distinguish between different types of brain tumors, as well as other brain abnormalities. This can be helpful in assuring that the appropriate patients are enrolled in trials. Various Positron Emission Tomography (PET) techniques can also be used to target and evaluate the biological activity of the tumors.



UNIQUE FEATURES OF GLIOBLASTOMA

Because of the biologic complexity of primary CNS tumors, there are many ways to use imaging to assess the magnitude of disease. Despite glioblastomas being solitary tumors, they often have different morphologies and may contain multiple regions in different stages of malignant degeneration. T2-weighted MRI can approximate the entirety of the tumor, whereas gadolinium-enhanced T1-weighted MRI can sensitively detect the regions of highest-grade malignancy.

The RANO criteria and iRANO for immunotherapies can be used to determine response to treatment for primary brain tumors and brain metastases but require significant clarifications to accomplish standardized approaches to central independent neuroradiology and neuro-oncology review and harmonization for investigators in multi-site studies.



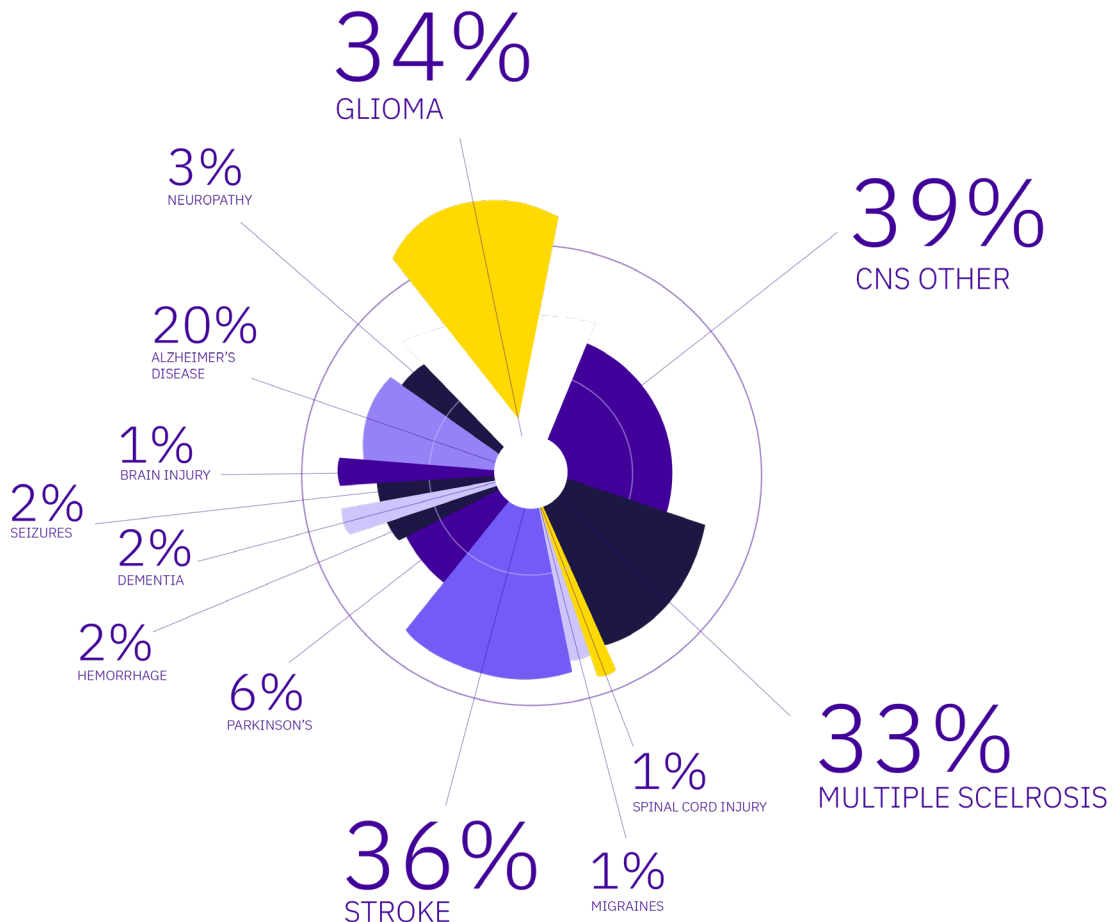
CASE STUDY

Neuro-oncology trials often require non-standard and custom procedures. In a recent glioblastoma multiforme trial that required a sponsor-initiated collaboration with an academic lab for DCE-MRI and DTI analysis, Calyx created an efficient workflow that fulfilled both the academic lab's and the sponsor's needs. Trained Calyx team members expertly processed both the DCE-MRIs and the DTI in a timely fashion and to the lab's expectations. The sponsor utilized the data to accomplish some of the exploratory endpoints of the protocol. This workflow, coupled with the primary image processing and review handled by Calyx, contributed to the trial's success.

CALYX EXPERIENCE

Calyx Medical Imaging's overall experience is drawn from managing over 2600 trials to date which include more than 4.5 million images from roughly 145,000 sites globally. Included in this experience is the management of nearly 180 neurology and 100 neuro-oncology studies in various indications and trial phases. And, Calyx has supported numerous large immuno-oncological trials applying IO image assessment criteria such as iRANO.

In the neurology studies we are currently supporting, MRI, CT, and PET are used to determine safety and efficacy endpoints. In addition to our in-house staff of more than 80 scientific experts, Calyx has access to neuroradiology and neuro-oncology key opinion leaders for consulting or reading services, depending on each trial's specific needs.



CALYX EXPERIENCE IN BRAIN METASTASES STUDIES

INDICATION	# OF TRIALS	# SITES	# SUBJECTS	#TOTAL TIMEPOINTS
Melanoma	1	28	135	2900
Lung Cancer	28	2500	6780	73000
Breast Cancer	3	414	1491	1850
Solid tumor	9	362	1263	15375
PCNSL (Lymphoma)	1	30	100	700

CALYX EXPERIENCE IN NEUROFIBROMATOSIS STUDIES

PHASE	# OF TRIALS	INDICATION	REVIEW CRITERIA	MODALITIES	# SITES	# SUBJECTS	#TOTAL TIME-POINTS
I	2	Neurofibromatosis	REINS	MRI, Photography	6	44	527
I/II	1	Neurofibromatosis	REINS	MRI	18	38	228
IIa	1	Neurofibromatosis	REINS	MRI	30	160	1280
III	2	Neurofibromatosis	REINS	MRI	71	254	1994

CALYX EXPERIENCE IN PRIMARY BRAIN TUMOR STUDIES

PHASE	INDICATION	REVIEW CRITERIA	MODALITIES	# SITES	# SUBJECTS	#TOTAL TIMEPOINTS
	Glioma, Glioblastoma (Brain Cancer)		MRI	30	630	763
II	Glioma, Glioblastoma (Brain Cancer)	RECIST 1.0, Volumetric Brain, PET	CT, MRI, X-ray, Bone Scan, PET, ECHO	95	220	660
I/II	Glioma, Glioblastoma (Brain Cancer)	McDonald Criteria, volumetric measurements	CT	16	105	210
II	Glioma, Glioblastoma (Brain Cancer)		MRI	148	665	1995
III	Glioma, Glioblastoma (Brain Cancer)	efficacy and overall response	CT, Brain MRI, DWI/PWI	40	300	1569
II	Glioma, Glioblastoma (Brain Cancer)	RECIST 1.0, Volumetric Brain	CT, MRI, bone scan, x-ray	45	110	660
I	Glioma, Glioblastoma (Brain Cancer)	RECIST 1.0, McDonald Criteria, volumetric measurements safety hemorrhage assessment including volume of hemorrhage	DWI/PWI	5	20	80
II	Glioma, Glioblastoma (Brain Cancer) (pediatric)	Rate of tumor response and overall survival; McDonald Criteria Modified	MRI	120	3200	3358
III	Glioma, Glioblastoma, astrocytoma (Brain Cancer)	McDonald Criteria (modified), volumetric measurements; safety	Brain MRI	115	27	150
III	Glioma, Glioblastoma (Brain Cancer)	RECIST 1.0, volumetric measurements, McDonald Criteria, McDonald	Brain MRI	70	500	2000
III	Glioma, Glioblastoma (Brain Cancer)	efficacy and overall response, McDonald Criteria, volumetric; separate T2/ FLAIR assessment	Brain MRI	82	300	1500
II	Glioma, Glioblastoma (Brain Cancer)	McDonald Criteria, volumetric measurements	Brain MRI	12	70	250
III	Acromegaly, Pituitary Adenoma	3D volume measurement, size (include volume) of pituitary	Brain MRI	123	360	2050
II	Glioma, Glioblastoma (Brain Cancer)	volumetric, qualitative, quantitative	Brain MRI	20	64	240
II	Glioma, Glioblastoma (Brain Cancer)	McDonald, volumetric measurements		19	69	188
III	Glioma, Glioblastoma (Brain Cancer)	McDonald Criteria	Brain MRI	20	64	247
III	Glioma, Glioblastoma (Brain Cancer)	McDonald Criteria, volumetric measurements				
II	Glioma, Glioblastoma (Brain Cancer)	Custom Brain Mets Evaluation	CT, Brain MRI	100	650	1950
I	Glioma, Glioblastoma (Brain Cancer)	Qualitative, safety	Brain MRI	2	40	120
I	Glioma, Glioblastoma (Brain Cancer) (pediatric)	n/a	CT, MRI, Pet Scan, Spect; X-ray	12	57	228
I	Solid Tumors	RECIST 1.1, RANO, PCWG2	CT, MRI, Bone Scan	27	500	2710

I	Glioma, Glioblastoma (Brain Cancer)	RANO, consulting				
II	Glioma, Glioblastoma (Brain Cancer)	Qualitative	MRI	4	120	240
I	refractory neuroectodermal tumors and rhabdomyosarcoma (pediatric)	RANO, Modified WHO	CT/MRI	30	83	360
II	Solid Tumors	RECIST 1.1	CT, MRI	83	972	7082
IIa	Glioma, Glioblastoma (Brain Cancer) (pediatric)	RANO	MRI	102	240	1200
III	Glioma, Glioblastoma (Brain Cancer)	RANO	MRI	200	500	8000
Ib/II	Solid Tumors & Primary CNS Disease	RECIST 1.1, RANO	CT, MRI	81	183	2106
III/IIII	Mutated Rare Cancers	RECIST 1.1, RANO	CT, MRI, Brain	23	87	2684
Ib	Glioma, Glioblastoma (Brain Cancer)	RANO	MRI	30	72	504
III	Non-Small Cell Lung Cancer (NSCLC)	RECIST 1.1	CT, MRI	20	226	1130
II	Pancreatic Cancer	RECIST 1.1, irRECIST	CT, MRI	20	100	440
	Glioma, Glioblastoma (Brain Cancer)	None	PET, PET/CT, PET/MRI	25	250	
	Glioma, Glioblastoma (Brain Cancer)	RANO	MRI	10	60	180
II	Prostate cancer	None	CT/ MRI/ bone scan	12	60	450
III	Glioma, Glioblastoma (Brain Cancer)		MRI Brain	1	120	360
II	Advanced Solid Tumors	RECIST 1.1, RANO,	CT/MRI, X-ray, DXA	180	280	1400
	Solid Tumors	RANO, RECIST 1.1,		30	35	300
I	Breast, Ovarian, Pancreatic and Prostate Cancer	RECIST 1.1, PCWG3, , RANO-LGG, RANO-HGG	CT, Brain MRI, Bone Scan	40	135	1535

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