Imaging Characterization of NCI Patient Derived Model Repository (PDMR) Xenografts

Paula M. Jacobs, James L. Tatum, Joseph D. Kalen, Lilia V. Ileva, Lisa A. Riffle, Keita Saito, Nimit L. Patel, Jessica Phillips, Melinda Hollingshead, Yvonne A. Evrard, Michelle Gottholm-Ahalt, Chelsea Sanders, Amy James, Simone Difilippantonio, Elijah F. Edmondson, James H. Doroshow.

National Cancer Institute, Bethesda, MD, Frederick National Laboratory for Cancer Research, Frederick, MD

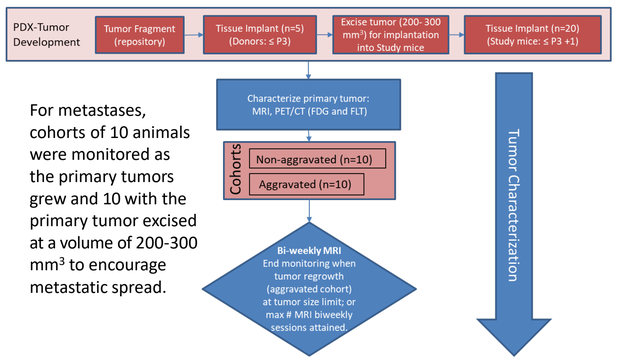
Introduction

The purpose of this work is to provide imaging data on patient derived xenografts models that are available from the National Cancer Institute Patient-Derived Models Repository (https://pdmr.cancer.gov) that may be useful to investigators in deciding which models to use in testing therapeutics or designing co-clinical trials. The PDMR contains PDMs from primary and metastatic tumor tissues and blood specimens supplied by NCI-supported clinical trials and NCI-designated Cancer Centers and is providing these models to the research community. The models include limited patient data including previous clinical therapies, smoking history, and race/ethnicity and whole exome, and RNASeq data. Using imaging to monitor progress of a treatment or evaluate development or prevention of metastases has advantages in minimizing the number of mice required as well as providing more information about metabolic status and tumor heterogeneity.

Methods and Materials

NSG mice were implanted subcutaneously with each model and monitored with non-invasive imaging. The core imaging methodologies were T2W magnetic resonance imaging (MRI), to visualize heterogeneity and determine the usefulness of MRI to detect metastatic disease; 18F fluorodeoxyglucose PET/CT, to evaluate aerobic glycolysis; and 3'-Deoxy-3'-(18)F-fluorothymidine PET/CT, to evaluate proliferation. The MRI and PET Imaging SOPs can be downloaded from the Cancer Imaging Archive. Metastases were confirmed by pathological examination.

Workflow: Characterization of PDX primary tumor



For metastases, cohorts of 10 animals were monitored as the primary tumors grew and 10 with the primary tumor excised at a volume of 200-300 mm³ to encourage metastatic spread.

Results

This work is ongoing and to date we have performed MRI on over 80 models with diverse tumor histology with a subset also undergoing FDG PET (77 models) and FLT PET (36 models). The complete list of models evaluated is shown in Table 1.

Nineteen models have demonstrated metastatic disease that could be detected by non-contrast MRI imaging with pathological confirmation, including ones derived from melanoma, lung, colon, pancreatic, uterine, anal, and head & neck as shown in Tables 2 and 3. Five of these (two colon adenocarcinoma, one melanoma. one pancreatic adenocarcinoma and one bladder) have undergone more extensive characterization evaluating cohorts to determine location, timing of appearance, and penetrance of metastasis and the images from those models are available for download from The Cancer Imaging Archive, https://cancerimagingarchive.net/ .Examples are shown in Figure 1.

The different models demonstrated a variety of textures, from quite homogeneous to very heterogenous. Examples of the varieties of textures is shown in Figure 2.

Results: Models evaluated– Table 1

Model	FDG	FLT	Model	FDG	FLT
Adenocarcinoma - rectum			**Lung Cancer-Squamous Cell Carcinoma**		
779769-127-R			287614-091-R		
Adenocarcinoma-Colon			**Malig. periph. nerve sheath tum.**		
128783-104-T			589616-265-R		
172845-121-B			632484-111-R		
172845-121-T			**Malignant Peripheral Nerve Sheath**		
172845-142-T			719797-321-R		
172845-288-R			**Melanoma**		
435261-313-R			137849-337-R		
625472-104-R			156681-154-R		
762968-020-R			174941-126-T		
782815-120-R			425362-245-T		
997537-175-T			633993-097-R		
CN0375-F725			695669-166-R		
Adenocarcinoma-Pancreas			**Merkel Cell Tumor**		
CN0375-F725-PDC			269878-174-B		
193399-133-R			269878-174-B		
292921-168-R			787269-337-R		
463931-005-R			**Mesothelioma**		
466636-057-R			933738-175-T		
521955-158-R3			**Neuroendocrine cancer, NOS**		
521955-158-R4			144126-210-T		
521955-158-R6			544552-058-R		
833975-119-R			LG0978-F1565		
885724-159-R			**Non Small Cell Lung Cancer**		
K24384-001-R			LG0481-F231		
Alveolar Soft Part Sarcoma			**Non-Rhabdo, soft tissue sarcoma**		
377368-042-T2			158883-120-T		
Carcinosarcoma of the uterus			**Osteosarcoma**		
327498-153-R			594176-295-R		
Female reprod. system cancer, NOS			698357-238-R		
193523-008-R			**Ovarian Cancer**		
Cervical cancer, NOS			575813-281-R1		
116653-108-T			**Ovarian epithelial cancer**		
Adenocarcinoma anal			683768-134-T		
CN0446F447			**Papillary thyroid carcinoma**		
Ewing sarcoma/Peripheral PNET			377391-170-R		
287954-098-R			**Rhabdomyosarcoma**		
994434-217-R			979852-250-R		
Gastrointestinal stromal tumor			**Renal cell carcinoma, NOS**		
636974-082-R			743489-281-T		
949853-013-R			**Salivary gland cancer**		
H & N squamous cell car., NOS			114551-80-T		
295223-140-R			**Small cell lung cancer**		
Hurthle Cell Neoplasm (thyroid)			592484-111-B		
248138-237-R			**Squamous cell carcinoma - anus**		
JAX – Lung Cancer			894883-131-R		
LG1049F1704			**Squamous cell carcinoma - skin**		
JAX - Lung Squamous Cell			415371-026-R		
LG1197F385			**Squamous cell lung carcinoma**		
Laryngeal squamous cell carcinoma			618468-307-R		
246569-268-R			692585-246-R		
784116-028-R			765638-272-R		
Leiomyosarcoma - not uterine			LG0520-F434		
712175-110-R			**Synovial Sarcoma**		
Lip/oral cavity squam. cell car.			119177-322-R1		
184893-071-T			**Transitional cell car. - uroth.**		
Liposarcoma			BL0479-F1894		
286954-287-R			**Urothelial/bladder cancer, NOS**		
845534-334-R			146476-266-R		
Lung adenocarcinoma			512744-197-R		
952719-076-R			558786-286-R		
K22795-001-R			BL0293-F563		
			BL0382-F1232		

Models named with CN and LG are available from Jackson Laboratories. All models had T2 weighted imaging. The color intensity in the table reflects the SUV(max) for the PET imaging.

SUVmax Level: <1.5 | 1.5 - 2.5 | 2.5 - 3.5 | 3.5 - 4.5 | >4.5

Results: Metastatic Models

Table 2: Characterized models

Model #	Diagnosis	# with metastasis in MRI	Days post Implant
292921-168-R	Adenocarcinoma-Pancreas Lung metastases	40%(non-resected)	56
		100% (resected)	38
425362-245-T (*)	Melanoma Lung metastases	40%(non-resected)	87
		100% (resected)	64
997537-175-T	Adenocarcinoma-Colon Lung metastases	6(non-resected)	35
		90%(resected)	27
625472-104-R (†)	Adenocarcinoma-Colon Lung metastases	10%(non-resected)	42
		40%(resected)	35
BL0293-F563	Urothelial/bladder cancer, Liver metastases	70%(non-resected)	52
		100% (resected)	52

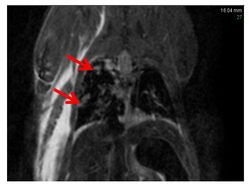
(*): Challenge with model due to rapid growth of xenograft tumor and regrowth
(†): Model has limited potential as metastatic imaging model due to low penetrance and rapid growth of xenograft tumor.

Table 3: Models that show metastases after resection

Model #	Diagnosis	Metastases	%
521955-158-R4	Pancreatic	Lung	55%
327498-153-R	Uterine Sarcoma	Liver, Lung	22%
BL0479-F1894	Bladder	Lung	12%
695669-166-R	Melanoma	Liver; Lung	44%
174941-126-T	Melanoma	Lung	33%
894883-131-R	Anal Cancer	Lung	80%
LG1049F1704	JAX-Lung Cancer	Lung	64%
156681-154-R	Melanoma	Liver, Lung	15%
765638-272-R	NSCLC	Liver	7%
172845-142-T	Adenocarcinoma Colon	Lung	14%

Figure 1: Examples of metastatic models

BL0293-F563
Urothelial Bladder: Liver mets



997537-175-T
Adenocarcinoma Colon: Lung mets

425362-245-T
Melanoma: mets in Lung, Kidney, pancreas, adrenal, liver

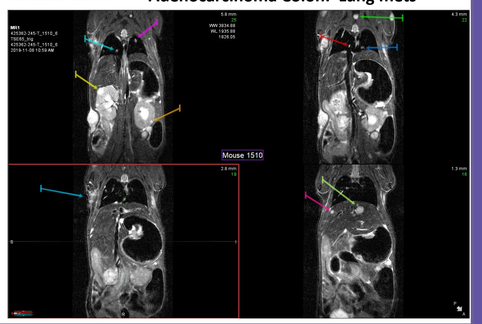
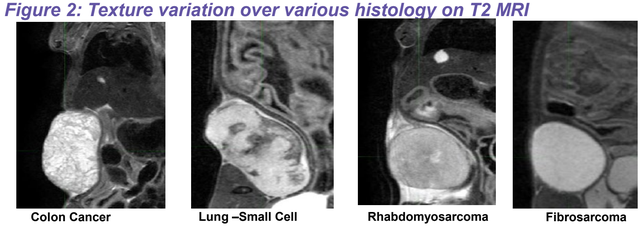
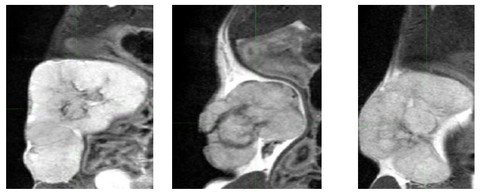


Figure 2: Texture variation over various histology on T2 MRI



Colon Cancer | Lung –Small Cell | Rhabdomyosarcoma | Fibrosarcoma

Texture reveals habitats on T2 MRI



Ovarian | Osteosarcoma | Hurtle Cell

Discussion

Success of precision oncology depends on understanding the complexities of tumor biology, requiring new techniques and resources. One needed resource is animal models that recapitulate the inherent heterogeneity in the tumor and its environment, providing a platform for probing the biology and predicting response to intervention on a whole tumor level. While multiple pre-clinical and co-clinical models exist, few duplicate the macro-environment of a tumor or demonstrate metastatic potential.

Under the Precision Oncology Initiative, the NCI has developed the PDMR and currently has over 450 tissue models available to investigators, as well as more than 500 related *in vitro* cultures. Among the tissue models we have so far identified 19 models with metastatic potential and fully characterized five. Additionally, we have confirmed the anticipated heterogeneity of most PDX models derived from tumor fragments; using T2 MRI we been able to visualize tumor habitats as shown in the figure. Using PET/MRI these habitats may be interrogated as to differential radio-genomics and differential therapeutic response.

Conclusion

The goal of this poster is to make investigators aware of the availability of this complementary imaging data as they consider research on models accessible from the NCI PDMR.
Links to imaging SOPs and complete listings of the models that have been tested are available. Please email Paula.Jacobs@nih.gov

References

National Cancer Institute Patient-Derived Models Repository (https://pdmr.cancer.gov)
The Cancer Imaging Archive: https://cancerimagingarchive.net Browse for PDMR
SOPs for using the PDMs: https://pdmr.cancer.gov/sops/default.htm
MRI & PET Imaging SOPs: https://doi.org/10.7937/TCIA.0ECK-C338
J Transl Med 17, 425 (2019). https://doi.org/10.1186/s12967-019-02177-y

This project has been funded in whole or in part with federal funds from the National Cancer Institute, National Institutes of Health, under contract HHSN261200800001E. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

All animals used in this research project were cared for and used humanely according to the following policies: the *U.S. Public Health Service Policy on Humane Care and Use of Animals* (2000); the *Guide for the Care and Use of Laboratory Animals* (1996); and the *U.S. Government Principles for Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training* (1985). All Frederick National Laboratory animal facilities and the animal program are accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International.

Contract HHSN261200800001E – Funded by the National Cancer Institute