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INTRODUCTION

With researchers' growing understanding of the complexity of cancer biology, the need to image cancer in a multiparametric way with quantitative capability has almost become a necessity instead of an additional feature in the world of preclinical cancer research.

Magnetic Resonance Imaging (MRI), with its naturally superior soft-tissue contrast and a rich collection of pulse sequences, has enabled researchers to visualize tumor morphology, vascularity, oxygenation and even some growth-signaling pathways.

Positron Emission Tomography (PET), on the other hand, provides incomparable sensitivity, quantitative accuracy and a paramount variety of tracers that can specifically mark oncological biomarkers hence illuminating metabolic and other functional features of cancer progression.

While designing a whole new PET/MR instrument has become a focus for technologists in order to combine two outstanding modalities, there is a highly effective way to add PET to research protocols right now.

Employing state-of-the-art Silicon Photomultiplier (SiPM) technology, Cubresa has designed a high-performance, compact and portable PET scanner 'insert' that is compatible with a variety of existing preclinical MRI platforms for *simultaneous* image acquisition. Here we demonstrate a simultaneous PET/MRI study on ovarian tumor progression at BIOTIC in Halifax, NS in Canada with a NuPET™ MR-compatible PET scanner in the bore of an Agilent 3T MRI.

OBJECTIVE

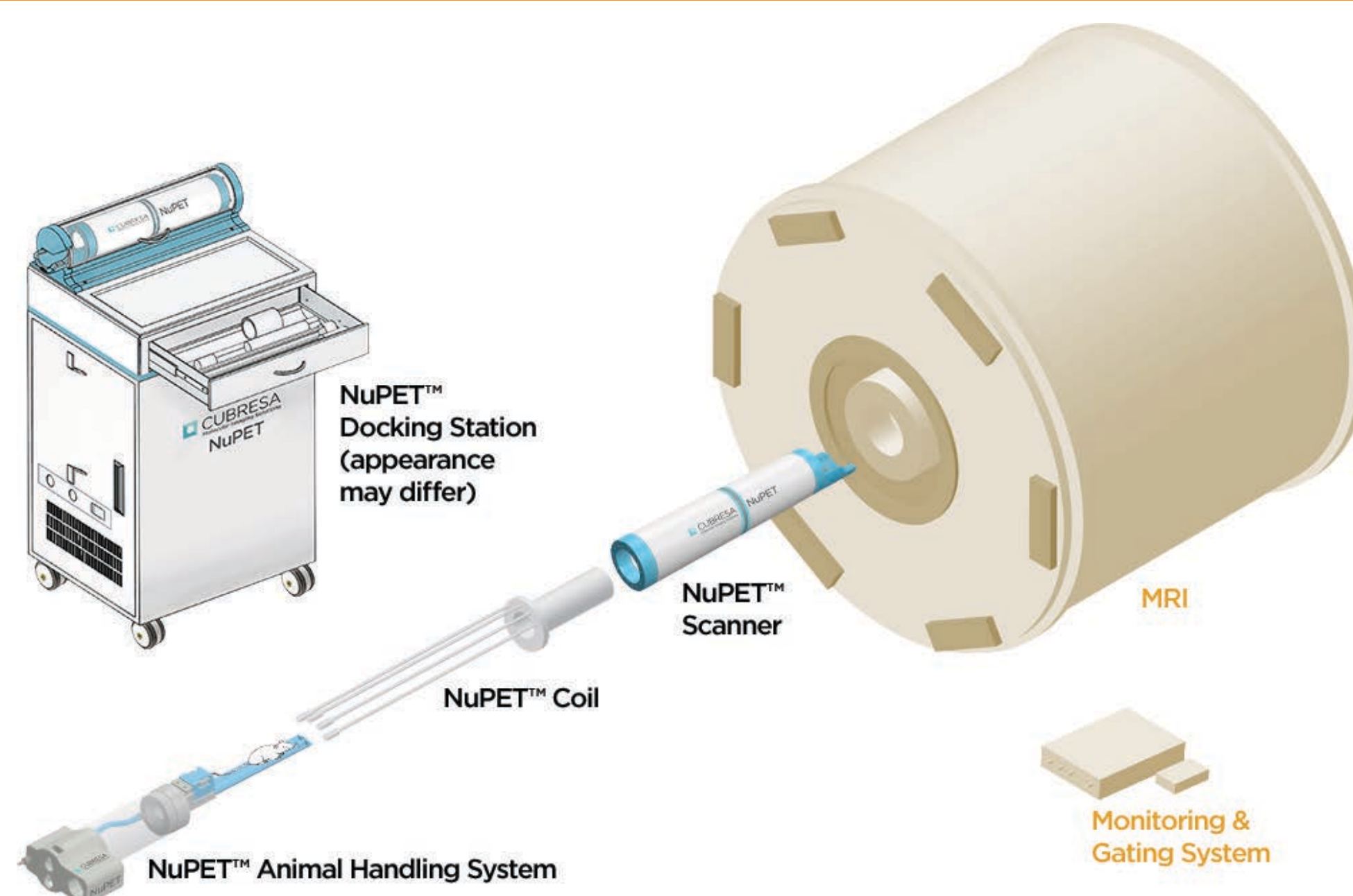
- To evaluate the efficiency of integration from workflow to image quality as well as the accuracy of a hybrid PET/MRI instrument created using an existing MRI and an in-bore MR-compatible PET scanner
- To help establish a PET/MRI study protocol for orthotopic ovarian cancer animal model imaging with the focus on:
 - Detectability of progression and metastasis
 - Establishing the connection between progression and metabolism.

METHOD – MRI & PET INSTRUMENTATION

Cubresa's NuPET scanner utilizes ultra-low profile SiPM detectors blocks arranged in 2 rings, resulting in a 75mm / 112mm (inner / outer) diameter insert compatible with small-animal MRI gradients in a wide variety of systems.

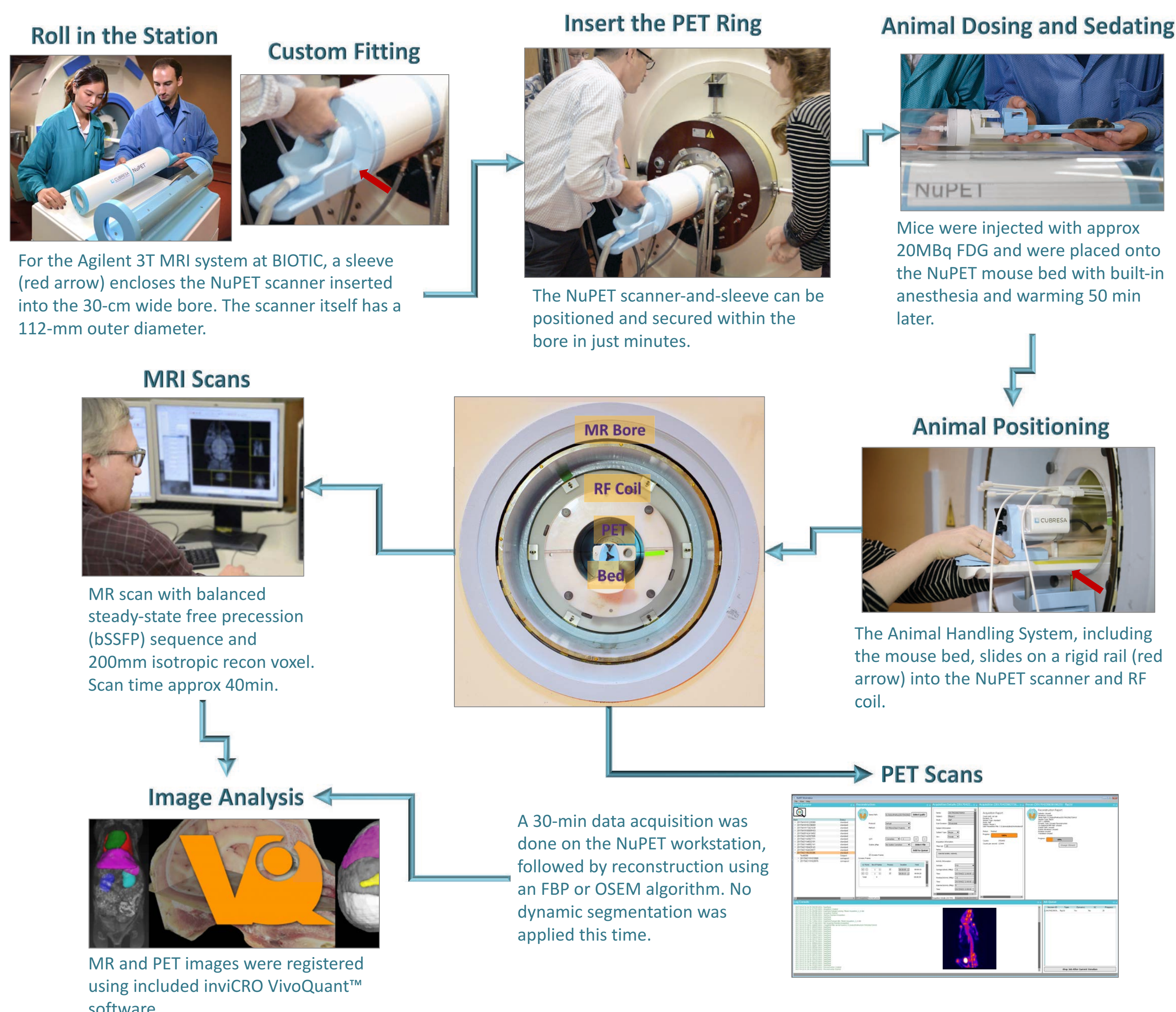
The scanner provides a 58mm (radial) x 66mm (axial) field of view, and features a unique, dual-layer offset scintillator design which improves spatial resolution and uniformity across the entire FOV.

The NuPET scanner supports a variety of methods to reconstruct listmode PET data, including an MLEM implementation which models the scanner's unique geometry. The scanner has been shown to have less than a 5% impact to B0/B1 uniformity and SNR for most sequences.

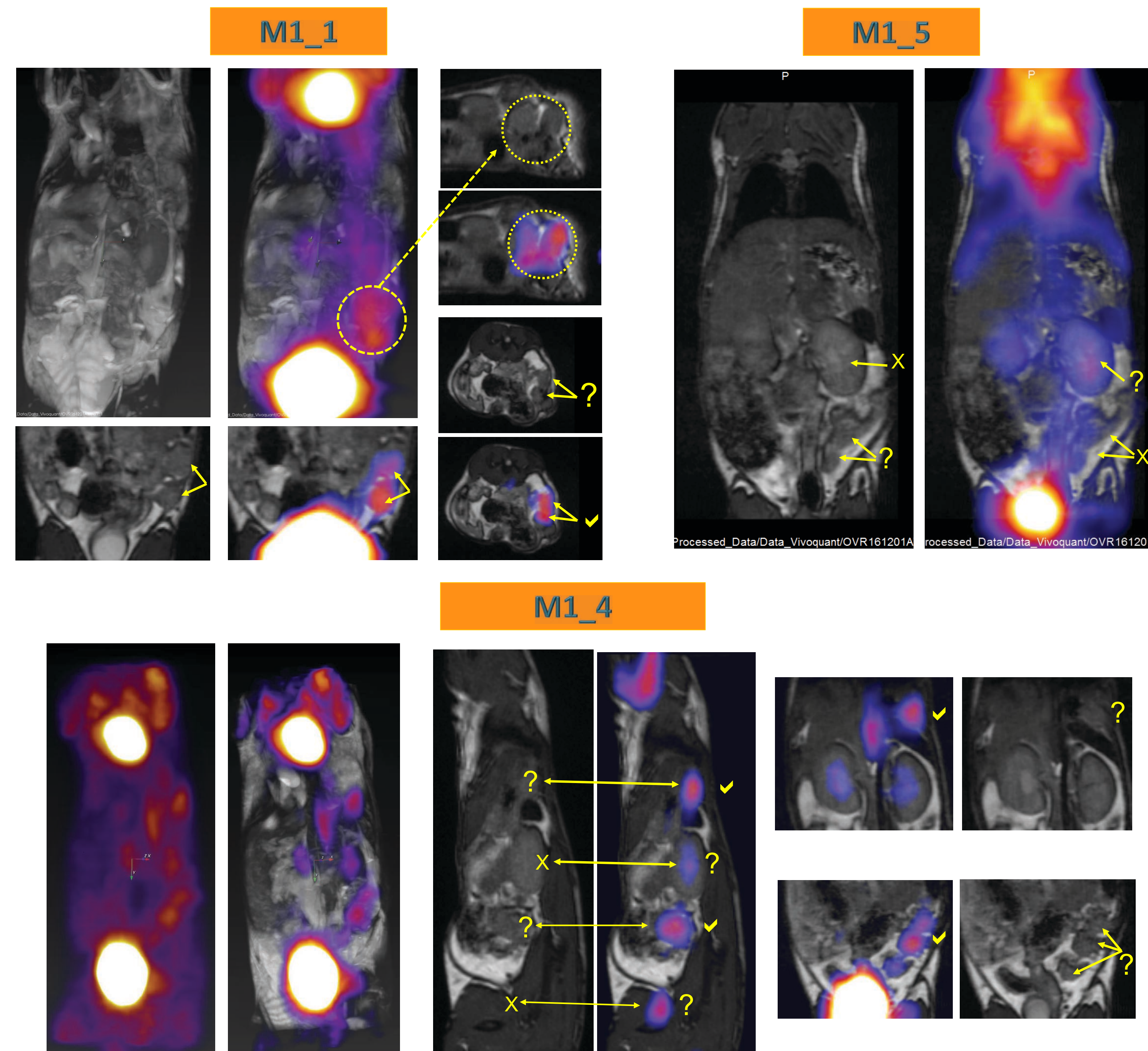


The Cubresa NuPET system is a simple yet powerful addition to an existing MRI system (highlighted in orange). Not pictured for reasons of clarity are the cable between the NuPET scanner and the docking station and the MRI and NuPET workstations in the control room.

METHOD - WORKFLOW



RESULTS



An ovarian cancer mouse model was established through single intra-bursal injection of 50,000 cancer cells. On the 42nd day after tumor implantation, the mice were subjected to a simultaneous PET/MRI scan. Data from three mice are shown above.

On average it took slightly over an hour to complete one set of dual-modality scans, which included 10-min animal preparation, a 40-min MR and a 30-min PET scan. The animals maintained steady vital signs throughout the scanning process. Co-registration was done with a rigid (6-coord) parameter metric fairly consistently from scan to scan.

Tumor lesions detected (yellow arrows/circles) or suspected (question marks) by MR were effectively confirmed or negated (crosses) by PET scans in M1_1 or M1_4 mice, and one incidence (M1_5) where a suspicious observation in MR had no PET confirmation at all was proven to be swelling uterine horn in necropsy analysis later (data not shown). What can also be confirmed was that the sizes of the lesions were not proportional to PET intensity.

DISCUSSION

Ovarian cancer is known for its symptomless onset as well as metastasis, which makes it one of the hardest cancers to detect and monitor. Xenograft models, while effective in many pathological studies, often fail to capture this significant trait.

Spontaneous or orthotopically introduced tumors, on the other hand, aim to address this feature. Yet the intraperitoneal location which is filled with various soft tissue makes it a nightmare for morphological imaging modalities such as CT to detect, especially during early stage.

PET tracers can detect the onset and progression through metabolic activities which often proceed tumor growth, yet the inherent background uptake in the IP area often introduce high noise hence doubts. MRI, with the right sequence, can bring clear delineation of sub-tissue types based on its microenvironment, giving PET a trusted boundary. PET, in turn, can provide confidence on cancerous nature of the tissue based on metabolic activity.

Simultaneous PET/MRI addresses the third hurdle of live imaging: breathing- and motion-induced position shift, which can be phenomenal when the targets are 1-2mm lesions. Therefore, this orthotopic ovarian cancer model with simultaneous PET/MRI provides an ideal example for the use of this particular instrument on this particular type of cancer research.

The preliminary establishment, both of the instrumentation and in the result, proved just that. In the guts of a group of free-breathing animals, we manage to confidently identify a variety of spontaneous lesions with one animal-positioning. The discordance between the sizes of some lesions and the PET intensity may also indicate the possibility that, with multiple sequences and different PET tracers, we might be able to follow the sub-steps of cancer progression in a temporal fashion, such as metabolic increase, angiogenesis, glycolysis rerouting, hypoxia finally apoptosis or migration.

Currently we have proved the concept that we were able to conduct simultaneous dual-modality imaging. The quantitative nature of PET as well as the multiparametric nature of MR are yet to be more effectively employed. The sampling of the animals was still limited. Future work is paramount for us to reach our final goal.

FUTURE

- Standard testing shall be conducted to systematically assess the interference of PET and MRI.
- PET image quality shall be further improved by:
 - High-performance iteration reconstruction algorithms
 - Scatter corrections and attenuation corrections
- Further quantitative calibration shall be conducted on the PET system to enable absolute quantitation of the PET signals, hence enabling cross-sample statistics.
- Full-scale time-course study with controlled, tumor animals as well as tumor animals treated with cancer therapeutic reagents shall be planned to monitor tumor progression starting with early time points to establish dynamic profiles of growth and metabolism.

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