Cross-Platform MRI/PET or MRI/SPECT Imaging, and Co-Registration

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Application Overview

Individual in vivo imaging modalities have relative strengths (i.e. sensitivity, resolution, quantitative accuracy, throughput capabilities) for molecular, anatomical and physiological detections in preclinical and clinical oncology (Keunen et al., 2014, James & Gambhir, 2012). Fluorescence (FLI) and bioluminescence imaging (BLI), Positron Emission Tomography (PET), and Single-Photon Emission Computed Tomography (SPECT) provide functional information while X-ray Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and UltraSound (US) provide mostly anatomical information. BLI offers high throughput and highly sensitive detections (Müller et al., 2013). PET and SPECT are quantitative and can allow for dynamic imaging. Imaging techniques can be combined to leverage the strengths of multiple modalities. Most frequently, a functional imaging modality is performed in sequence with an anatomical modality to obtain an anatomical reference. Combined and system-integrated SPECT/CT and PET/CT is now common in the preclinical imaging field. There is currently a growing interest in combining functional imaging with MRI (Sauter et al., 2010). This is driven in part by a desire to avoid the specimen dose associated with CT imaging. Additionally, MRI provides superior soft tissue contrast and the ability to perform advanced MRI techniques such as diffusion weighted imaging (DWI) that can be leveraged in oncology studies (Preuss et al., 2014). Multiple functional imaging modalities may also be performed on the same sample. For example, BLI is highly sensitive and may be employed to monitor tumor development from the early stages of development. This may be combined with highly quantitative PET imaging in studies of therapeutic response. A full discussion of the merits of the various imaging modalities is available in the recent reviews by de Jong et al. (2014), Albanese et al. (2013), and James & Gambhir (2012).

Recently, there has been some movement toward the development of more integrated imaging systems (Lu et al., 2014). There are now commercially available systems that integrate optical, PET, SPECT, CT, and/or MRI imaging in various combinations, but these systems are typically only bi- or tri-modal. Integrated imaging systems do offer potential value in space savings and some enhanced application potential. However, there are benefits to employing individual modality imaging systems and cross-platform transport beds for multimodal imaging as well. Individual modality systems may provide superior performance versus integrated imaging systems where performance compromises may have been made in the integration process. More importantly, a cross-platform approach maximizes end-user access to imaging equipment. Firstly, individual modalities may be used simultaneously on different projects when required, or in sequence for cross-platform imaging when appropriate. Secondly, single modality systems typically will have less down time for maintenance

compared to multimodal systems. This can be invaluable at facilities where equipment is utilized at maximum capacity. Thirdly, most imaging facilities started with one or two imaging technology platforms and grow their performance over time by adding new modalities, thus finally providing a mixture of different technological platforms. Probably most importantly, given that fully integrated all-modality imaging systems are not and probably will not be available, more combinations of multimodal imaging is feasible utilizing at least some cross-platform imaging, even if it is between partially multimodal integrated systems.

To achieve cross-platform imaging researchers frequently employ makeshift sample animal transports. While this approach is generally useful, there are typically limitations with animal care, anesthesia, stable positioning and image registration between scans. Nelson et al. (2011) reported on an immobilization bed for cross-platform (PET/CT) imaging in a tumor xenograft model. Interestingly, when the immobilization bed (with fiducial markers) was used inter-user variability for SUV analysis fell from 9.4% to 0.7%, illustrating the importance of stable animal positioning and registration using fiducial markers.

Here we describe a technique employing the Bruker Multimodal Animal Bed (MMAB) for cross-platform preclinical imaging of PET or SPECT with MRI. The Bruker MMABs are equipped with manifolds and connectors aligned with Bruker´s preclinical imaging systems' MMAB docking arms. Animal care docking station ports provide stable animal care and monitoring. The bed is designed with a snug immobilization shell that maintains the specimen animal positioning. Additionally, our lab produced a unique fiducial markers lid (FML) to facilitate image fusion. This method could provide multimodal imaging across optical (In-Vivo Xtreme II), PET/SPECT/CT (Albira Si system), PET/MR 3T, MRI (ICON and BioSpec systems), Magnetic Particle Imaging (MPI), and dedicated µCT (SkyScan 1176, 1178 and 1278 systems) platforms. Image fusion is made using tools available in the PMOD software (PMOD, Switzerland). Cross-platform multimodal imaging with registration is particularly useful for applications where multiple molecular detections are required, and/or where anatomical registration for MR or CT is beneficial. This method should facilitate flexible cross-platform imaging for a range of modalities, but PET/MR and SPECT/MR was demonstrated as proof-of-principle.

Methods

Animals

For SPECT imaging, Foxn1^{nu} mice (Jackson Laboratories; Bar Harbor, ME) were grafted subcutaneous with 700,000 HCT 116-hNIS-NEO (Imanis Life Science; Rochester, MN) tumor cells expressing the human sodium iodide symporter. Imaging was performed at 2-3 weeks post implantation when tumors reached approximately 1-3 mm diameter. Foxn1^{nu} mice receiving no cell grafts or treatments were used for this initial validation of cross-platform ^{18}FDG-PET/MR imaging.

Imaging

PET and SPECT acqusitions were collected using the Bruker Albira PET/SPECT/CT imaging system. For PET and SPECT imaging mice received between 100 and 200 µCi ^{18}F-FDG and 500 µCi and 1 mCi ^{99m}Tc respectively, one hour prior to imaging. MR imaging was performed using the Bruker ICON 1T MR system using a 3D MR T2-weighted RARE sequence.

Multimodal Animal Bed and Fiducial Marker Lid

The Bruker Multimodal Animal Bed (MMAB) was used for transferring animals between the Bruker Albira PET/SPECT/CT imaging system and the Bruker ICON 1T MR imaging system. The fiducial markers lid (FML) was designed with a 1 mL circuitous fill line. The line extends the length of the bed. This design provides multiple reference points for fiducial matching. The fill line was fit with threaded inlet ports to facilitate filling. The FML was printed using the Projet printer using Somos WaterClear Ultra 10122.

Image Registration

Image registration was performed using PMOD Technologies (Zurich, Switzerland) Fuse It module, provided standard with the Albira PET/SPECT/CT imaging systems. This module allows for dual image plane adjustments including rotations, X, Y, Z movements, and image re-scaling. We used manual registration of the FML line between cross-platform images.

Results/Discussion

During initial cross-platform studies made in the absence of fiducial marker solutions we found post imaging registration to be subjective, relying largely on anatomical/physiological landmarks. Fiducial capillary tubes filled with mixed contrast agents are frequently used to facilitate cross-platform imaging and we later employed capillary tubes filled with contrast agents. Filling and placement of such tubes and secure placement within the confines of an immobilization bed add additional complications to the study preparation process. To facilitate more streamlined fiducial matching we designed a FML (Figure 1) that is compatible with the Bruker MMABs. The FML line can be filled easily using a fill syringe and Luer adapter.

Additionally, the FML lid conforms to the general mold of the Bruker MMAB factory lid and connects similarly to the MMAB bed base (Figure 2). The FML line extends the length of the bed so it can be utilized for any anatomical region.

Figure 1

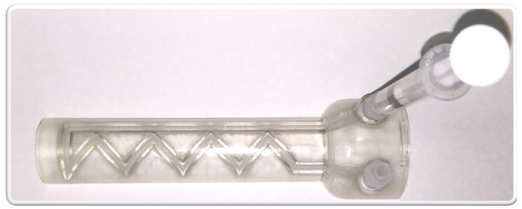

Figure 1: FML with fill syringe installed. The FML inlets are fit with threaded Luers for ease of filling. The line may be filled with mixed contrast agents for MR (water), PET/SPECT (diluted radionuclide), and CT (radiopaque solution).

Figure 2

Figure 2: FML lid installed on MMAB base and mounted to Albira MMAB docking arm.

We initially tested the FML solution with a Foxn1^{nu} mouse without tumor grafting or other experimental treatments (Figure 3). The circuitous FML fill line served as an ideal point of reference to register images. The numerous X, Y, and Z coordinates of the line allowed for simple image registration using the PMOD Fuse It module. Mouse ^{18}FDG-PET/MR tumor studies employing this protocol are currently ongoing.

Figure 3

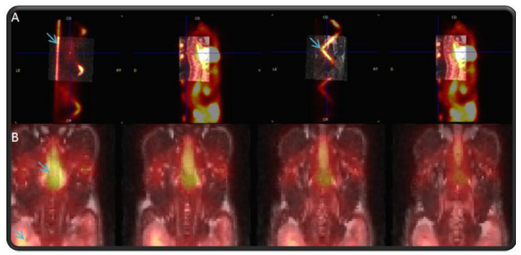

Figure 3: Cross-platform PET/MR image registration of healthy mouse imaged in MMAB with the FML. (A) Image registration between ^{18}FDG-PET (fire) and MR (gray) was made using the Bruker MMABs equipped with the FML and filled with ^{18}FDG in solution. The image panel to the left shows a coronal view plane with the straight region (arrow) of the FML fill line used to register images. The image panel to the right shows a coronal view plane with the circuitous region (arrow) of the FML fill line used to register images. (B) Four slice sequence of PET/MR coronal view of hind region of mouse with kidney (lower arrow left) and spine (upper arrow left) ^{18}FDG signal apparent.

We next evaluated the protocol for cross-platform ^{99m}Tc-SPECT/MR imaging in a HCT 116-hNIS-NEO tumor model. This imaging protocol and registration method resulted in excellent SPECT and MR tumor signal/contrast registration (Figure 4).

Figure 4

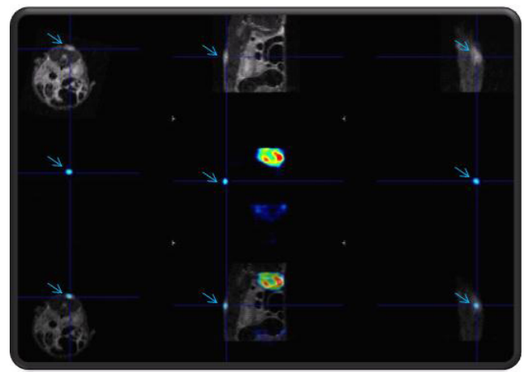

Figure 4: Cross-platform ^{99m}Tc-SPECT (rainbow) and MR (gray) imaging of HCT 116-hNIS-NEO tumor mouse with image registration facilitated by the MMAB with the FML. Top row is MR only in transverse, sagittal and coronal views. Middle row is SPECT only in transverse, sagittal and coronal views. Bottom row is registered MR/SPECT in transverse, sagittal and coronal views.

Frequently, preclinical researchers are required to generate VOIs for tumor analysis based only on the functional PET/SPECT images, either because the integrated CT imaging does not provide sufficient tumor contrast and/or because cross-platform CT/MR image registration is not suitably accurate. However, functional modalities will not always accurately show the true tumor margin, and ideally users would have an option to generate VOIs based on an anatomical visualization of the tumor margin. Our results provide for excellent tumor margin contrast with MRI and reliable cross-platform PET or SPECT registration. This protocol should allow for accurate production of VOIs based on tumor margins identified in MR images and application to functional PET or SPECT images.

Conclusion

Individual functional and structural imaging modalities can be combined for enhanced analytical value. There is a growing trend of combining PET and MR imaging. To fully leverage the potential of cross-platform PET/MR imaging, methods to ensure animal stability and image registration should be considered. Here we describe a method using a commercial Bruker Multimodal Animal Bed with a custom Fiducial Marker Lid for performing cross-platform PET or SPECT with MR that will allow for reliable transport and image registration. The FML fill line is suitable for PET, SPECT, CT, and MR contrast agents and requires minimal preparation, relative to alternative solutions that use makeshift beds and/or capillary tubes, to be used in imaging studies.

References

[1] Keunen, O., Taxt, T., Grüner, R., Lund-Johansen, M., Tonn, J.C., Pavlin, T., Bjerkvig, R., Niclou, S.P., Thorsen, F. (2014) Multimodal imaging of gliomas in the context of evolving cellular and molecular therapies. Adv. Drug Deliv. Rev. 76C, 98-115.

[2] James, M.L., Gambhir, S.S. (2012) A molecular imaging primer: modalities, imaging agents, and applications. Physiol. Rev. 92(2), 897-965.

[3] Müller, J., Wunder, A., Licha, K. (2013) Optical imaging. Recent Results Cancer Res. 187, 221-246.

[4] Sauter, A.W., Wehrl, H.F., Kolb, A., Judenhoger, M.S., Puchler, B.J. (2010) Combined PET/MRI: one step further in multimodality imaging. Trends Mol. Med. 16(11), 508-515.

[5] Preuss, M., Werner, P., Barthel, H., Nestler, U., Christiansen, H., Hirsch, F.W., Fritzch, D., Hoffmann, K.T., Bernhard, M.K., Sabri, O. (2014) Integrated PET/MRI for planning navigated biopsies in pediatric brain tumors. Childs Nerv. Syst. 30(8), 1399-1403.

[6] de Jong, M., Essers, J., van Weerden, W.M. (2014) Imaging preclinical tumor models: improving translational power. Nat. Rev. Cancer. 14(7), 481-493.

[7] Albanese, C., Rodriguez, O.C., VanMeter, J., Fricke, S.T., Rood, B.R., Lee, Y., Wang, S.S., Madhavan, S., Gusev, Y., Petricoin, E.F. 3rd, Wang, Y. (2013) Preclinical magnetic resonance imaging and systems biology in cancer research: current applications and challenges. Am. J. Pathol. 182(2), 312-318.

[8] Lu, Y., Yang, K., Zhou, K., Pang, B., Wang, G., Ding, Y., Zhang, Q., Han, H., Tian, J., Li, C. Ren Q. (2014) An integrated quad-modality molecular imaging system for small animals. J. Nucl. Med. 55(8), 1375-1379.

[9] Nelson, G.S., Perez, J., Colomer, M.V., Ali, R., Graves, E. (2011) Facilitating multimodal preclinical imaging studies in mice using an immobilization bed. Comp. Med. 61(6), 499-504.

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