Chapter 12
Dual-Modality Preclinical SPECT/CT Instrumentation

Youngho Seo and Carina Mari Aparici

1 Limitations of Standalone Preclinical SPECT

Preclinical imaging using SPECT and small animal models provides a very high spatial resolution using pinhole geometries or other convergent collimator geometries [1, 2], typically in submillimeters [3]. In addition, multiple apertures of pinholes in combination with multiple radionuclide detectors potentially provide a desirable high detection efficiency of radionuclide gamma-ray photons [4, 5]. However, the utility of preclinical SPECT imaging is limited especially when the imaging studies require more than the functional information that SPECT alone can provide [6–8].

1.1 Localizing Tracer Distribution in Small Animal Models

When the physiologic target of a radiotracer used in preclinical SPECT imaging studies is located anywhere within the animal body, correlating tracer uptake seen by SPECT to its anatomy is sometimes challenging. A similar issue occurs with clinical SPECT studies. In the clinical setting, nuclear medicine physicians are trained to distinguish abnormal uptake versus normal physiologic uptake of a known radiotracer; however, in the preclinical setting, it is rare to have a specifically

Y. Seo (✉)
UCSF Physics Research Laboratory, Department of Radiology & Biomedical Imaging, University of California, San Francisco, CA, USA
e-mail: youngho.seo@ucsf.edu

C. Mari Aparici
Department of Radiology & Biomedical Imaging, San Francisco and Nuclear Medicine Service, San Francisco Veterans Affairs Medical Center, University of California, San Francisco, CA, USA
e-mail: carina.mari@radiology.ucsf.edu

H. Zaidi (ed.), *Molecular Imaging of Small Animals: Instrumentation and Applications*,
DOI 10.1007/978-1-4939-0894-3_12,

trained interpreter who understands the small animal anatomy and the radiotracer distribution well. The complication is augmented when a preclinical evaluation of a new radiotracer is the main utilization of the preclinical SPECT.

1.2 Quantification of Radiotracer

As in clinical SPECT studies, preclinical SPECT studies using dedicated small animal SPECT scanners basically result in images of tracer distribution in small animal models in an arbitrary unit (e.g., pixel value, not in Bq/ml). Tracer quantification is only possible if the user of the preclinical SPECT scanner is confident that most physical compensations are implemented in image generation [9, 10]. Additionally, the poor photon statistics in preclinical SPECT scanners without innovative designs like multidetectors [11] and multipinholes limits quantitative accuracies to an unreliable level.

It is known that out of physical perturbations in SPECT imaging, photon attenuation errors contribute the most when the object size is large and the energy of emission photons from a radiotracer is low (e.g., I-125's 20–30 keV photopeaks). In other words, for small body size of rodents, particularly in mice, physical compensations may not be critical in terms of obtaining quantitative accuracies of tracer distribution in reconstructed images. Yet, when the attenuation correction is necessary, the standalone preclinical SPECT scanners should rely on some external transmission scans for attenuation map generation.

1.3 Limitations of Standalone SPECT Scanners Specific to Preclinical Systems

The anatomical localization capability and the tracer quantification aspect have been widely recognized because these issues are also found in clinical SPECT systems. With regards to preclinical SPECT systems more specifically, the limitations are caused by (a) unfamiliarities of animal anatomies that are not comparable to human anatomy, (b) inherent geometrical limitations such as limited field of view (FOV) caused from focusing collimators like pinholes used in small animal SPECT, and (c) lack of robust correction methods for physical perturbations in SPECT imaging such as photon attenuation errors [12].

2 Preclinical SPECT Combined with CT

Fortunately, most of the limitations mentioned earlier can be completely or partially overcome by having a structural imaging combined with SPECT. The combined SPECT/CT systems have become a common form of clinical SPECT scanners, and it is no wonder that preclinical SPECT/CT systems followed the trend [13]. Magnetic resonance imaging (MRI) integration with SPECT is also an interesting area for discussion [14]; but this chapter focuses only on the SPECT/CT in preclinical settings.

An X-ray computed tomography (CT) has been available in small animal imaging applications in parallel with most other noninvasive imaging modalities. A microfocus X-ray tube producing X-ray current on the order of 1 mA at 50 kVp (50 Watt) and an X-ray detector such as a charge-coupled device (CCD) or a complementary metal oxide semiconductor (CMOS) usually comprise a small animal CT scanner. Combined with SPECT, small animal SPECT/CT systems acquire SPECT radionuclide data and CT X-ray data mostly sequentially without moving an animal from the bed, which benefits to in vivo animal studies that often require a gas anesthesia system with often bulky gas delivery plumbing fixtures. For the sequential imaging, the bed movement is minimal or translational only when required. By performing a sequential imaging of SPECT and CT at known positions, coregistration between the two imaging modalities can be achieved by rigid transformation assuming the animal is stationary during both imaging sequences. Besides, image units in CT can be also converted to energy-dependent linear attenuation coefficients useful for attenuation correction in SPECT reconstruction [15, 16]. There is also a potential use of CT information to model scatter components in SPECT reconstruction. Figure 12.1 illustrates the significance of CT-based attenuation correction even for a small size object (approximately one inch across) when a low-energy gamma emitter like iodine-125 is used for SPECT studies.

CT provides details of small animal anatomies with reconstruction resolutions in the range of 10–200 μm, and the details can be enhanced by either conventional clinical iodinated contrast media or animal-specific iodinated contrast materials [17]. With CT providing both the attenuation coefficients and anatomical details, small animal SPECT/CT is more visually pleasing than standalone SPECT systems, and is capable of providing accurate tracer localization and quantification which are desirable characteristics for drug and new tracer evaluation processes using noninvasive preclinical imaging [18]. The resolution requirements from CT vary depending on how much anatomical details are needed in SPECT investigations. For example, if attenuation correction is the only use of CT, the resolution of CT can be as poor as the typical resolution of SPECT, ~1 mm full-width at half-maximum (FWHM). In contrary, when a full anatomic detail is essential in SPECT/CT investigations of small animals, even 10–20 μm spatial resolution with contrast enhancement is marginal.

Although the promises of preclinical SPECT/CT are strong and implementations in system instrumentations seem straightforward assuming both preclinical SPECT and CT are separately mature technologies, there are still inherent issues when combining the two systems together. These issues are not negligible in most applications, and occasionally application and animal specific.

– Coregistration between SPECT and CT: In preclinical SPECT systems, convergent collimation geometries such as pinholes or multipinholes are of a common use. The convergent geometry introduces imaging magnification or minification of the object so that applying reconstruction algorithms needs inputs from collimator geometries. In addition, the projection data for both preclinical SPECT and CT are collected typically in a cone-beam geometry which also introduces other geometry complications that include cone-beam artifacts and image truncation issues. As a result, the geometry defined in preclinical SPECT/CT needs

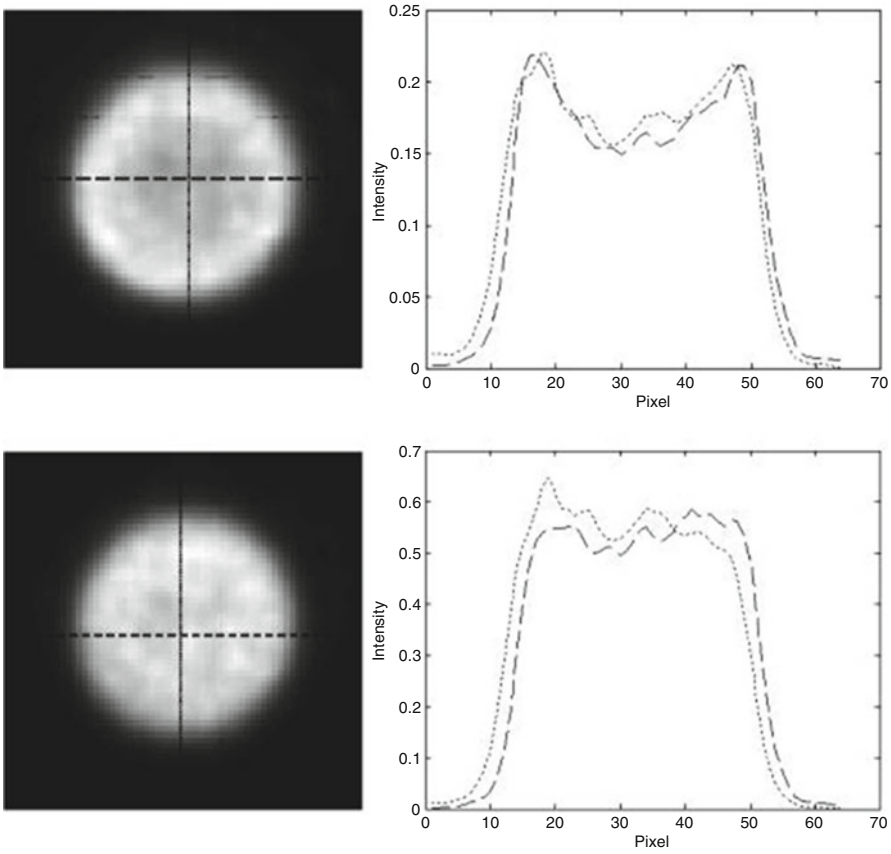

Fig. 12.1 Photon attenuation corrected reconstruction versus uncorrected reconstruction using a uniform cylindrical phantom filled with iodine-125 solution (Reprinted with permission from [6])

a coregistration strategy that includes adjustments for complex geometries from reconstructed SPECT and CT images.

– Temporal resolution difference between SPECT and CT: Surprisingly, currently available preclinical CT scanners on the market do not yet provide a very fast multidetector CT acquisition capability except for very few products or prototypes. What is not surprising is that still the data acquisition of preclinical CT even on the current market, typically in the range of 1–10 min to achieve approximately 150 μm in-plane spatial resolution, is faster than that of preclinical SPECT. This difference in temporal resolutions does not always cause serious problems when CT is only used for anatomic localization of radiotracer or attenuation map generation. A more serious problem is that the preclinical CT using small animal models suffers motion-related spatial resolution degradation, resulting in blurred CT images because the breathing of the animal model induces a non-negligible movement during the CT acquisition. In a volume where SPECT radiotracer localization can potentially benefit greatly from anatomical details

such as brain and thorax, the anatomy provided by CT can be less valuable in determining precise location of radiotracer concentrations.

– Approaches to prospective gating in SPECT and CT: The two common gating strategies to reduce any motion-related image artifacts using electrocardiogram (ECG) or respiratory signals are implemented and can be used in both preclinical SPECT and CT studies [19, 20]. The caveat of performing either ECG-gated or respiratory-gated SPECT/CT studies is the degradation of temporal resolution for both imaging modalities. Without significant innovations for which some of implementable technologies are mentioned in other chapters, the total image acquisition time could be very impractical considering the speed of both SPECT and CT in preclinical settings and the small amount of radiotracer that can be administered without altering the biology of given studies (e.g., radiation-related carcinogenesis) [21].

3 Historical Perspective on Dual-Modality Preclinical SPECT/CT Developments

Similarly to its human scale version, a pioneering work on developing a dual-modality preclinical SPECT/CT system was first conducted at the University of California, San Francisco (UCSF) in early 2000 [22–26]. However, the development of the full scale preclinical SPECT/CT scanner from the UCSF project had been plagued by complications of the system design and novelty of the technology. The system was actually built (shown in Fig. 12.2), and evaluated for small animal SPECT/CT studies. Although the details of technical design considerations will be discussed in the following section for this scanner, notable features include the slip-ring gantry that enables continuous rotations of SPECT and CT and the use of a solid-state detector material (CdZnTe or CZT) for the SPECT module.

During this period of developments, Gamma Medical-Ideas went ahead with commercialization of preclinical SPECT/CT system combining its A-SPECT preclinical scanner with a CMOS-based X-ray CT subsystem in a scanner gantry rotating around a horizontal axis [27]. After the success of this commercial platform, most of other commercial vendors and academic researchers started to offer or build other preclinical SPECT/CT systems.

4 Design Considerations of Dual-Modality Preclinical SPECT/CT

The following list is a list of implemented dual-modality preclinical SPECT/CT systems. Although this list probably does not include all of the systems developed or being developed, key features that are generally applicable to any other developments of the combined SPECT/CT system are mentioned for each development. Also, the status of the development, either research or commercial, is indicated for each system. Some different flavors of SPECT/CT integrations are depicted in Fig. 12.3.

Fig. 12.2 UCSF MoHawk SPECT/CT scanner with two CZT-based pinhole SPECT cameras and X-ray cone-beam CT subsystem placed on a disk-gantry attached to a slip-ring (*left*). This system is designed to mount up to four pinhole/multipinhole CZT-based gamma cameras with a retractable in-plane microfocus CT (*right*) built on the same disk-gantry

4.1 University of California, San Francisco (Research)

The preclinical SPECT/CT scanner built at UCSF is also known as MoHawk ("Mo"use "Hawk"eye) named after the Hawkeye technology from GE Healthcare's clinical SPECT/CT products for which the UCSF group contributed significantly in its original innovation. The key features of the MoHawk SPECT/CT are:

- SPECT/CT integration type: In-plane,
- Helical scan capability: Both imaging modalities (continuous rotation),
- SPECT detector material: CdZnTe,
- CT detector material: GOS (gadolinium oxysulfide)/CCD,
- Collimators: single pinholes down to 0.5 mm diameter,
- Other notable features: Slip-ring platform and a large disk-shape optical table for mounting scalable CT and SPECT components.

4.2 Gamma Medica-Ideas, Inc. (Commercial)

The first preclinical integrated SPECT/CT scanner was from Gamma Medica-Ideas' X-SPECT™ that combined their NaI(Tl)-based LumaGEM® gamma camera with a microfocus conebeam X-ray CT scanner (X-O™). As of June 2009, Gamma Medica-Ideas has a product line FLEX Triumph™ preclinical platform that can consist of a combination of SPECT, CT, and PEt all in one platform.

Fig. 12.3 Different flavors of preclinical SPECT/CT integration. (**a**) Compact box system that includes both small FOV X-ray CT and SPECT components from University of Arizona (Reprinted with permission from [28]). (**b**) An inside view drawing of Gamma Medica-Idea's FLEX Triumph™ gantry that shows the triple-modality (SPECT–CT–PET) configuration. (**c**) Another triple-modality configuration of a large gantry design with sufficient room around the scanner components (Siemens Inveon Multimodality gantry). (**d**) Docked SPECT/CT configuration–U-SPECT/CT from MILabs (figures of (**b**–**d**) are from product brochures)

The key features of Gamma Medica-Ideas' preclinical multimodality imaging systems for SPECT/CT offering are (from http://www.gm-ideas.com/):

- SPECT/CT integration type: In-plane,
- Helical scan capability: Spiral SPECT, but not continuous rotation over one spiral,
- SPECT detector material: NaI(Tl) or CdZnTe,
- CT detector material: GOS/CMOS,

– Collimators: parallel hole, single pinholes, multipinholes with different fields of view (FOVs) for mice and rats separately,
– Other notable features: Offered as the triple modality (SPECT–PET–CT) configuration.

4.3 University of Arizona (Research)

University of Arizona's Center for Gamma-Ray Imaging has had a long history of gamma imaging technology developments. Based on their enormous resources and accumulated expertise, a combined SPECT/CT system for small animal imaging applications was developed with a focus on its compact design [28]. The key features for this compact SPECT/CT system are:

– SPECT/CT integration type: In-plane,
– Helical scan capability: No,
– SPECT detector material: CdZnTe,
– CT detector material: GOS (gadolinium oxysulfide)/CCD,
– Collimators: high resolution parallel-hole with a matching pitch on detector pixels,
– Other notable features: Compact size (79 cm × 48 cm × 46 cm outside box dimension) and rotation stage (vertical animal holder).

4.4 Jefferson Lab and Johns Hopkins University (Research)

There are two generations of the preclinical SPECT/CT development from the group from Jefferson Lab and University of Virginia in collaboration with Johns Hopkins University [29, 30]. Their original system was configured to be a triple-modality that had an option of adding an optical imaging component to SPECT/CT. The current generation of their preclinical SPECT/CT system is based on a modified Siemens MicroCAT II gantry. The key features of the current generation system design are:

– SPECT/CT integration type: In-plane,
– Helical scan capability: No,
– SPECT detector material: NaI(Tl)-PSPMT (position sensitive photomultiplier tube),
– CT detector material: CsI/CCD,
– Collimators: parallel-hole and pinholes,
– Other notable features: Currently configured to image awake mice using infrared tracking system for animal motion.

4.5 Siemens Medical Solutions (Commercial)

Siemens at its Knoxville, Tennessee facility has developed a high-end line of preclinical imaging systems with a universal platform line named as Inveon. The Inveon Multimodality (MM) can be built as a triple-modality (PET–CT–SPECT) configuration on a single gantry [31]. The key features of Siemens preclinical SPECT/CT configured in the Inveon MM gantry are:

- SPECT/CT integration type: In-plane
- Helical scan capability: No
- SPECT detector material: NaI(Tl)-PSPMT (position sensitive photomultiplier tube)
- CT detector material: GOS/CCD
- Collimators: parallel-holes, single pinholes, and multipinholes
- Other notable features: The Inveon MM can be configured as a triple modality system (SPECT and CT in-plane and PET module next to it).

4.6 Bioscan and MILabs (Commercial)

Bioscan's NanoSPECT and MILabs' U-SPECT II are both multipinhole SPECT systems that provide stationary acquisition modes and very high spatial resolution of SPECT imaging. Unlike other preclinical SPECT/CT systems described above, these two SPECT scanners are also offered as SPECT/CT systems (NanoSPECT/CT and U-SPECT/CT) with a docked or serial configuration combining two separate SPECT and CT modules attached together. The docked or serial configuration is different in many ways from the other SPECT/CT systems described above. The most notable difference is that the in-plane SPECT/CT systems (all systems except Bioscan or MILabs systems) have a stationary animal bed during both SPECT and CT acquisitions. The docked or serial configuration by Bioscan or MILabs systems needs an animal bed that translates between two imaging modalities. Besides, the docked configuration applied to U-SPECT/CT (MILabs) has one clear advantage when separate operations of SPECT and CT are fully utilized for independent applications that do not need both imaging capabilities.

5 Applications of Dual-Modality Preclinical SPECT/CT

The specific applications that absolutely need dual-modality preclinical SPECT/CT systems simultaneously are actually rare. However, the addition of CT to SPECT for the benefits described above makes most SPECT studies more quantitative, easier to the eyes, and provides more confidence in their interpretations than when standalone preclinical SPECT systems are utilized.

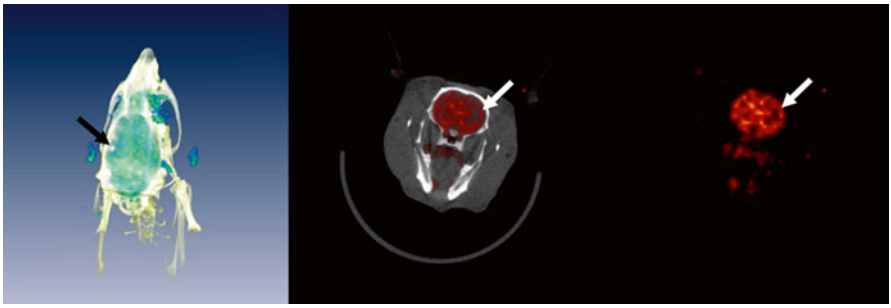

Fig. 12.4 SPECT and CT images obtained from a rat brain imaging study using ^{99m}Tc-exametazime [35]. The rat model of ischemic stroke was imaged by Gamma Medica-Idea's FLEX X-SPECT/X-O system. From *left* to *right*: 3D volume rendered SPECT and CT images fused together, transaxial view of SPECT–CT images, and transaxial SPECT-only image. *Arrows* indicate the hypoperfusive area affected by regional cerebral blood flow

5.1 Drug Discovery and Evaluation

SPECT/CT for drug discovery and evaluation has a significant potential because SPECT/CT is one of few strategies toward quantitative SPECT evaluations of new drug candidates. In this application, tracer quantification is the most essential because in vivo animal imaging with a new drug candidate can be quantified from SPECT reconstructed images without sacrificing animal models at many different time points for biodistribution studies. Technically, when quantitative accuracy of SPECT reconstruction is robust and reliable, a pharmaceutical's concentration (in unit of mg/ml) estimation is feasible, and has a possibility of accelerating the drug evaluation process [18].

5.2 Neurological Applications

Although brain imaging using SPECT in small animals is often conducted [32, 33], there is little use of preclinical CT for neurological applications. In addition, the CT addition to SPECT reconstruction for brain sometimes minimally useful because the brain anatomy is easily identifiable from SPECT-only studies. For example, cerebral blood flow studies using ^{99m}Tc-exametazime SPECT in animal models (as shown in Fig. 12.4). However, neurological applications demand the highest-possible spatial resolution; thus controlling the movement of small animal heads during both SPECT and CT is important to achieve best possible image resolution. One way to maximize spatial resolution in brain imaging using SPECT and CT in small animal models is to use a X-ray-transparent stereotactic device to fix the movement of animal heads during acquisitions [34]. With help of iodinated contrast agent, small animal

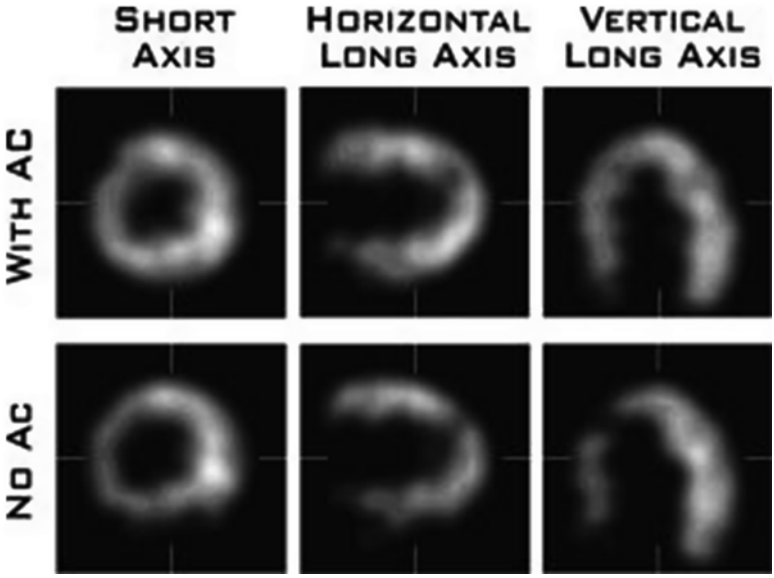

Fig. 12.5 Reconstructed SPECT images with CT-based attenuation correction (*above*) and without AC (*bottom*) visualizing the heart of a normal rat. The imaging agent was iodine-125-labeled iodorotenone, myocardial perfusion imaging agent (Reprinted with permission from [6])

brain CT for cerebrovascular investigation can be combined with brain SPECT applications using a combined preclinical SPECT/CT scanner [35].

5.3 Cardiovascular Applications

Cardiovascular SPECT using small animal models is an emerging and ever-evolving field [36, 37]. Cardiovascular CT using small animal models also witnesses the same enthusiasm from researchers. The motion of the animal's thorax, where the heart sits, is what makes the biggest influence on cardiovascular investigations. Controlling organ motion by ECG or respiratory gating is often another complication of the use of SPECT/CT imaging systems in cardiovascular applications. Prospective ECG/respiratory gating strategies for both systems are desired in quantitative evaluations of cardiovascular disease processes in small animal models.

CT-based attenuation correction (AC) for preclinical SPECT studies also can make a difference in the appearance of SPECT reconstructed images. An example to elucidate the impact of CT-based AC is shown in Fig. 12.5. As in this figure, myocardial perfusion imaging agent radiolabeled with iodine-125 without attenuation correction could lead to false positive reading of perfusion deficit where photon attenuation diminishes image intensity.

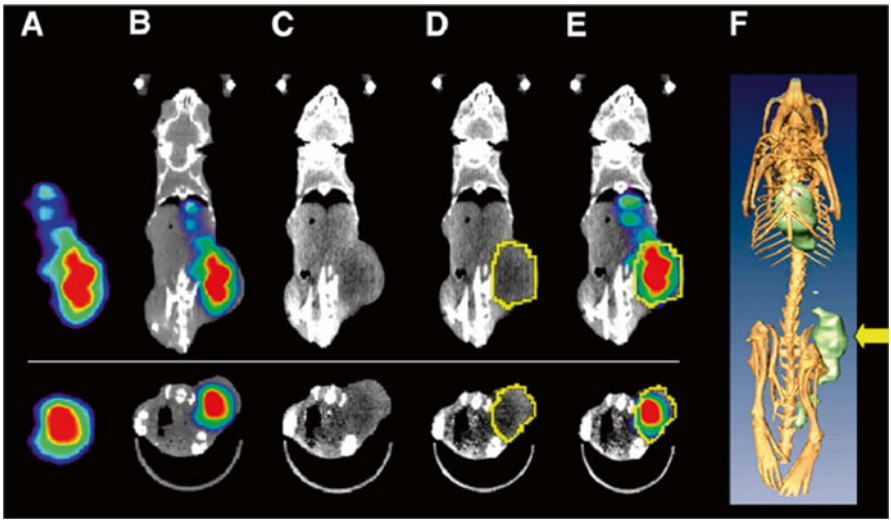

Fig. 12.6 Small animal SPECT/CT in an oncologic preclinical application. Coronal (*top*, **a–e**) and transaxial (*bottom*, **a–e**) are shown. The colored superimposed images are from SPECT, and the *black* and *white* images are from CT. (**f**) depicts 3D rendered volumes simultaneously showing SPECT and CT images (Reprinted with permission from [13])

5.4 Oncologic Applications

In oncologic applications, having SPECT/CT capability in preclinical studies is potentially significant because CT guides exact anatomical localization of uptake of SPECT oncologic agents, and provides a gateway to tracer quantification [24, 38]. Figure 12.6 elucidates this point. The tracer distribution seen by SPECT using prostate specific membrane antigen (PSMA) targeting 7E11 antibody radiolabeled with indium-111, pinpoints tracer accumulation in mouse xenograft model (LNCaP) [39]. CT overlay images provide means to delineate the tumor boundaries for tracer uptake quantification.

6 Perspectives on Future Developments

The progress on advanced SPECT/CT preclinical systems is dependent on technological advances on each modality independently. The integration of SPECT and CT will hardly change because there are benefits for both in-plane or side-by-side configurations, and few other configurations are practical. However, one should note that cost-effective rail- or track- based modular imaging systems for SPECT/CT using existing standalone SPECT and CT scanners can be also realized although this approach should be not confused with integrated SPECT/CT systems.

This approach has been implemented using clinical systems [40] as well as small animal systems [41]. Commercializations of emerging technologies such as use of solid-state detectors like CZT will also depend on the progress of each imaging modality separately. The progress of the field itself is expected to be centered around biological applications of the systems. One example is that MRI integration of SPECT may provide better anatomical reference of SPECT studies because of high soft-tissue contrast provided by MRI over CT. In small animal applications, this combination may prove a wider spectrum of applications than its human version because the FOV from both SPECT and MRI can be implemented sufficiently large to cover the whole animals.

Acknowledgments This work was partially supported by National Cancer Institute Grant #5K25 CA114254 (Y.S.), and by the University of California Industry-University Cooperative Research Program Grant dig 06–10210 (C.M.A.).

References

1. Beekman F, van der Have F (2007) The pinhole: gateway to ultra-high-resolution three-dimensional radionuclide imaging. Eur J Nucl Med Mol Imaging 34:151–161.
2. Zeniya T, Watabe H, Aoi T, Kim KM, Teramoto N, Takeno T, et al. (2006) Use of a compact pixellated gamma camera for small animal pinhole SPECT imaging. Ann Nucl Med 20:409–416.
3. Vastenhouw B, Beekman F (2007) Submillimeter total-body murine imaging with U-SPECT-I. J Nucl Med 48:487–493.
4. van der Have F, Vastenhouw B, Rentmeester M, Beekman FJ (2008) System calibration and statistical image reconstruction for ultra-high resolution stationary pinhole SPECT. IEEE Trans Med Imaging 27:960–971.
5. Nuyts J, Vunckx K, Defrise M, Vanhove C (2009) Small animal imaging with multi-pinhole SPECT. Methods 48:83–91.
6. Hwang AB, Hasegawa BH (2005) Attenuation correction for small animal SPECT imaging using x-ray CT data. Med Phys 32:2799–2804.
7. Panetta D, Belcari N, Baldazzi G, Carpentieri C, Cicalini E, Del Guerra A, et al. (2007) Characterization of a high-resolution CT scanner prototype for small animals. Nuovo Cimento B 739–747.
8. DiFilippo FP (2008) Design and performance of a multi-pinhole collimation device for small animal imaging with clinical SPECT and SPECT-CT scanners. Physics in Medicine and Biology 53:4185–4201.
9. Wieczorek H (2007) SPECT image quality and quantification. 2006 IEEE Nuclear Science Symposium Conference Record (IEEE Cat. No.06CH37832):5–5.
10. Chen CL, Wang Y, Lee JJ, Tsui BM (2009) Toward quantitative small animal pinhole SPECT: assessment of quantitation accuracy prior to image compensations. Mol Imaging Biol 11:195–203.
11. Funk T, Despres P, Barber WC, Shah KS, Hasegawa BH (2005) A high efficiency small animal imaging system based on position sensitive avalanche photodiodes. Proceedings of the SPIE - The International Society for Optical Engineering 5923:1–9.
12. Boutchko R, Balakrishnan K, Reutter BW, Sauve A, Gullberg GT (2007) Small animal imaging with attenuation correction using clinical SPECT/CT scanners. 2007 IEEE Nuclear Science Symposium Conference Record 4294–4295.
13. Franc BL, Acton PD, Mari C, Hasegawa BH (2008) Small-animal SPECT and SPECT/CT: important tools for preclinical investigation. J Nucl Med 49:1651–1663.

14. Goetz C, Breton E, Choquet P, Israel-Jost V, Constantinesco A (2008) SPECT low-field MRI system for small-animal imaging. Journal of Nuclear Medicine 49:88–93.
15. Vanhove C, Defrise M, Bossuyt A, Lahoutte T (2009) Improved quantification in single-pinhole and multiple-pinhole SPECT using micro-CT information. Eur J Nucl Med Mol Imaging 36:1049–1063.
16. Zaidi H, Hasegawa B (2003) Determination of the attenuation map in emission tomography. J Nucl Med 44:291–315.
17. Badea CT, Fubara B, Hedlund LW, Johnson GA (2005) 4-D micro-CT of the mouse heart. Mol Imaging 4:110–116.
18. Seo Y (2008) Quantification of SPECT and PET for drug development. Curr Radiopharm 1:17–21.
19. Vandehei T, Li J, Iwata K, Patt BE, Caravaglia G, Hartsough NE, et al. (2004) Gated cardiac SPECT in rodents using a dedicated SPECT system: X-SPECT. Proceedings of the SPIE 5541:165–170.
20. Tsui BMW, Segars WP, Lalush DS (2000) Effects of upward creep and respiratory motion in myocardial SPECT. IEEE Transactions on Nuclear Science 47:1192–1195.
21. Funk T, Mingshan S, Hasegawa BH (2004) Radiation dose estimate in small animal SPECT and PET. Medical Physics 31:2680–2686.
22. Iwata K, Wu MC, Hasegawa BH (1999) Design of combined x-ray CT and SPECT systems for small animals. 1999 IEEE Nuclear Science Symp/Medical Imaging Conf.,Seattle, WA, vol. 3, pp. 1608–1612.
23. Izaguirre EW, Sun M, Carver J, Thompson S, Hasegawa BH (2005) Dual modality micro-SPECT and micro-CT for small animal imaging: technical advances and challenges. Proceedings of the SPIE 5923:59230C.
24. Izaguirre EW, Mingshan S, Drummond DC, Kirpotin DB, Funk T, Thompson S, et al. (2006) SPECT-CT study of directed drug delivery using sup 111/In-labeled liposomes in a murine mammary carcinoma model. 2005 IEEE Nuclear Science Symposium Conference Record (IEEE Cat. No.05CH37692C):4–4.
25. Sun M, Izaguirre EW, Funk T, Hwang AB, Carver J, Thompson S, et al. (2006) A small animal helical SPECT scanner. 2005 IEEE Nuclear Science Symposium Conference Record (IEEE Cat. No.05CH37692C):2066–2069.
26. Sakdinawat AE, Iwata K, Hwang AB, Tang HR, Wong KH, Hasegawa BH (2003) Development of external fiducial markers for image registration in small animal SPECT/CT. 2002 IEEE Nuclear Science Symposium Conference Record (IEEE Cat. No.02CH37399) 2:842–845.
27. Iwata K, MacDonald LR, Li J, Williams SP, Sakdinawat AE, Hwang AB, et al. (2002) Dual isotope imaging with a dedicated small animal CT-SPECT system. Mol Imaging Biol 4:S21.
28. Kastis GA, Furenlid LR, Wilson DW, Peterson TE, Barber HB, Barrett HH (2004) Compact CT/SPECT small-animal imaging system. IEEE Trans. Nucl. Sci. 51:63–67.
29. Stolin A, Pole D, Majewski S, Kross B, Weisenberger A, Wojcik R, et al. (2005) Design and characteristics of a small animal multi-modality scanner. 2005 IEEE Nuclear Science Symp/Medical Imaging Conference Record 2183–2186.
30. Weisenberger A, Kross B, Majewski S, Popov V, Smith MF, Tran VH, et al. (2006) Instrumentation development of a SPECT-CT system to image awake mice. 2006 IEEE Nuclear Science Symp/Medical Imaging Conf.,San Diego, CA, vol. pp. 3000–3003.
31. Gleason SS, Austin DW, Beach RS, Nutt R, Paulus MJ, Yan S (2006) A new highly versatile multimodaltiy small animal imaging platform. 2006 IEEE Nuclear Science Symp/Medical Imaging Conf.,San Diego, CA, vol. pp. 2447–2449.
32. Bal H, Thomas D, Zixiong C, Ferrari V, Horowitz J, Acton PD (2006) A novel method for the estimation of infarct size in a reperfused rat model for pinhole SPECT. 2005 IEEE Nuclear Science Symposium Conference Record (IEEE Cat. No.05CH37692C) 4–4.
33. Zixiong C, Bal G, Accorsi R, Acton PD (2005) Optimal number of pinholes in multi-pinhole SPECT for mouse brain imaging-a simulation study. Physics in Medicine and Biology 50: 4609–4624.

34. Seo Y, Hashimoto T, Nuki Y, Hasegawa BH (2008) In vivo microCT imaging of rodent cerebral vasculature. Phys Med Biol 53:N99–107.
35. Seo Y, Gao DW, Hasegawa BH, Dae MW, Franc BL (2007) Rodent brain imaging with SPECT/CT. Med Phys 34:1217–1220.
36. Acton PD, Thomas D, Zhou R (2006) Quantitative imaging of myocardial infarct in rats with high resolution pinhole SPECT. International Journal of Cardiovascular Imaging 22:429–434.
37. Zhou R, Thomas DH, Qiao H, Bal HS, Choi SR, Alavi A, et al. (2005) In vivo detection of stem cells grafted in infarcted rat myocardium. Journal of Nuclear Medicine 46:816–822.
38. Muller C, Forrer F, Schibli R, Krenning EP, de Jong M (2008) SPECT study of folate receptor-positive malignant and normal tissues in mice using a novel sup 99m/Tc-radiofolate. Journal of Nuclear Medicine 49:310–317.
39. Pan MH, Gao DW, Feng J, He J, Seo Y, Tedesco J, et al. (2009) Biodistributions of 177Lu- and 111In-labeled 7E11 antibodies to prostate-specific membrane antigen in xenograft model of prostate cancer and potential use of 111In-7E11 as a pre-therapeutic agent for 177Lu-7E11 radioimmunotherapy. Mol Imaging Biol 11:159–166.
40. Bailey DL, Roach PJ, Bailey EA, Hewlett J, Keijzers R (2007) Development of a cost-effective modular SPECT/CT scanner. Eur J Nucl Med Mol Imaging 34:1415–1426.
41. Beekman F, Hutton BF (2007) Multi-modality imaging on track. Eur J Nucl Med Mol Imaging 34:1410–1414.