Expert Review of Medical Devices

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierd20

# Progress in large field-of-view interventional planar scintigraphy and SPECT imaging

**Martijn M.A. Dietze & Hugo W.A.M de Jong**

**To cite this article:** Martijn M.A. Dietze & Hugo W.A.M de Jong (2022) Progress in large field-of-view interventional planar scintigraphy and SPECT imaging, Expert Review of Medical Devices, 19:5, 393-403, DOI: 10.1080/17434440.2022.2088355

**To link to this article:** https://doi.org/10.1080/17434440.2022.2088355

EXPERT REVIEW OF MEDICAL DEVICES
2022, VOL. 19, NO. 5, 393–403
https://doi.org/10.1080/17434440.2022.2088355

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS Check for updates

# Progress in large field-of-view interventional planar scintigraphy and SPECT imaging

Martijn M.A. Dietze and Hugo W.A.M de Jong

Radiology and Nuclear Medicine, Utrecht University and University Medical Center, Utrecht, Netherlands

**ABSTRACT**

**Introduction:** Handheld gamma cameras and gamma probes have been successfully implemented for enabling nuclear image or radio-guidance in minimally-invasive procedures. There is an opportunity for large field-of-view interventional planar scintigraphy and SPECT imaging to complement these small field-of-view devices for two reasons. First, a large field-of-view camera enables imaging of relatively larger organs and activity accumulations that are not close to the patient's skin. And second, more precise corrections can be implemented in the SPECT reconstruction algorithm, improving its quality.
**Areas covered:** This review article discusses the progress that has been made in the field of large field-of-view interventional planar scintigraphy and SPECT imaging. First, an overview of planar scintigraphy and SPECT is provided. Second, an exploration is given of the potential applications where large field-of-view interventional planar scintigraphy and SPECT imaging may be employed. And third, the requirements for scanner hardware are discussed and an overview of the possible system configurations is provided.
**Expert opinion:** We believe that there is an opportunity for large field-of-view interventional planar scintigraphy and SPECT imaging to assist clinical workflows. A major effort is now required to evaluate the prototype systems in clinical studies so that valuable practical experience can be obtained.

**ARTICLE HISTORY**
Received 7 January 2022
Accepted 7 June 2022

**KEYWORDS**
Nuclear imaging; planar scintigraphy; SPECT; image-guided procedures; dosimetry

## 1. Introduction

Handheld gamma cameras and gamma probes have been successfully implemented for enabling nuclear image or radio-guidance in minimally-invasive procedures [1]. Such procedural guidance is achieved by administrating radiopharmaceuticals to the patient and using the gamma detector to localize depositions of activity. This added nuclear image guidance has proven to be very useful in parathyroidectomies and sentinel node procedures for ensuring that the correct tissues are resected.

The nuclear image guidance devices that have been used clinically up to now have a small field-of-view. There is an opportunity for large field-of-view interventional planar scintigraphy and single-photon emission computed tomography (SPECT) imaging to complement handheld gamma cameras and gamma probes because of two reasons:

(1) A large field-of-view camera enables planar scintigraphy and SPECT imaging of relatively larger organs and activity accumulations that are not close to the patient's skin than is achieved with a small field-of-view camera. This provides the opportunity to perform nuclear image guidance in procedures that were previously considered unfeasible. This includes the guidance of cardiac and liver interventions and interventions on lesions and lymph nodes that may be hard to locate with small field-of-views.
(2) With a large field-of-view, 3D volumes can be reconstructed with fewer truncation artifacts and with more corrections applied in the reconstruction algorithm when compared with a small field-of-view. For example, a large field-of-view camera allows for scatter correction to be more precisely performed by incorporating scattered photons originating from surrounding tissue. Likewise, the point spread function of the collimator can be better included. These advantages improve the SPECT image quality and make it feasible to obtain quantitative images. Such quantitative imaging may allow for image guidance of therapeutic radionuclide procedures.

It is expected that large field-of-view interventional imaging will primarily be beneficial in niche applications and will not gain a widespread use. Nevertheless, we envision that in these niche applications such devices may realize a substantial benefit to the patient's care. For this reason, we believe that it is interesting to investigate these specialized devices.

This article will review the current status of large field-of-view interventional planar scintigraphy and SPECT imaging. The review is split into three parts. First, we will discuss the two imaging modes that may be performed with large field-of-view interventional imaging. Second, we will give an exploration of the applications where large field-of-view interventional imaging may be of benefit. And third, we will discuss

**CONTACT** Martijn M.A. Dietze m.m.a.dietze@umcutrecht.nl Radiology and Nuclear Medicine, Utrecht University and University Medical Center Utrecht 85500, 3508 GA, Netherlands

**Article highlights**

- A list of potential applications of large field-of-view interventional planar scintigraphy and SPECT imaging is given
- The requirements for scanner hardware are discussed
- An overview of the currently available scanner configurations is provided

the requirements for interventional scanner hardware and provide an overview of the possible system configurations.

## 2. Imaging modes

Large field-of-view interventional imaging may be realized through two different imaging modes: planar scintigraphy (2D) and SPECT (3D). We expect that the applications for large field-of-view interventional imaging (as discussed in the next section) will each require a different form of imaging for their optimal procedural guidance.

### 2.1. Planar scintigraphy

The first imaging mode concerns planar scintigraphy. This imaging mode is the same as is most often performed with handheld gamma cameras. Compared with handheld devices, large field-of-view gamma cameras would enable imaging of relatively larger organs and activity accumulations that are not close to the patient's skin. The advantage of planar scintigraphy over SPECT is that immediate or even real-time feedback on the activity distribution is obtained. This allows for the imaging of dynamic events (e.g. the injection of activity in the body). However, the downside of this imaging mode is that image interpretation can be challenging. For example, gamma photons originating from overlapping tissues will be detected at the same location, gamma photons may be differently attenuated in different parts of the body (e.g. when passing lung tissue), collimator resolution will make the image blurrier, and substantial noise will be present at low count rates. These image-deteriorating effects will be more severe for activity accumulations that are relatively far away from the patient's skin because the gamma photons traverse more attenuating material and because the source to collimator distance is larger. These effects make large field-of-view planar scintigraphy primarily interesting for cases in which either the image volume is large (e.g. the liver) or the activity is located in a dense hotspot (e.g. in biopsies).

### 2.2. SPECT

The second imaging mode concerns SPECT imaging. In SPECT imaging, the gamma camera needs to be rotated around the patient in some way (e.g. by using a gantry or by manually moving the camera) so that projections of the activity distribution are acquired under multiple angles. These projections are hence reconstructed into a 3D volume. The current state-of-the-art reconstruction software packages allow for scatter correction via energy window-approaches and resolution recovery through the modeling of the point spread functions. When an attenuation map of the patient is available, the reconstructions can furthermore be corrected for photon attenuation. The advantage of SPECT over planar scintigraphy is that improved image quality is obtained, the images can be quantitative, and the distribution can be assessed in 3D. When the activity distribution is registered to tissue delineations, the dose that is administered to tissues can furthermore be quantified, which is important for dosimetric purposes in therapeutic applications. SPECT has been shown to outperform planar scintigraphy for the detection of low-activity or small activity depositions and hence may be preferred to planar scintigraphy for nuclear image guidance. There are, however, a few disadvantages to SPECT imaging: it usually requires a complicated gantry capable of acquiring different project angles, imaging takes relatively more time, and only a single snapshot of the activity distribution in time is generally made (limiting the options for dynamic imaging).

## 3. Potential applications

Large field-of-view interventional imaging may be beneficial for a range of procedures involving radionuclides. Below, we have compiled a list of applications where we believe that the greatest benefit may be achieved. The list can be considered as an initial exploration. As the use of radionuclides for diagnostic and therapeutic purposes is still expanding, we expect that more applications will arise over time.

### 3.1. Radio-guided surgery

Small field-of-view gamma cameras and gamma probes have been successfully used in several forms of radio-guided surgery. The two most common procedures in which radio-guidance is employed are parathyroidectomies and sentinel node procedures. In these procedures, image guidance is used to respectively localize the adenoma and the sentinel node for their surgical removal. A major advantage of small field-of-view gamma cameras and gamma probes is that they are flexible and hence can be positioned very close to the patient skin. This ensures that the spread of activity in the planar images (due to the collimator resolution and scattered photons) is kept as low as possible, increasing the interpretability of the images.

Nevertheless, large field-of-view gamma cameras may provide a benefit over small field-of-view gamma cameras by being able to better perform quantitative SPECT. By having images that are corrected for collimator resolution, photon attenuation, and photon scatter, the interpretability of these images will be greater than with regularly acquired planar scintigraphy/SPECT images. Previously, it has been demonstrated that SPECT imaging outperforms planar scintigraphy for the detection of small or low activity depositions in both thyroid [2,3] and sentinel node [4,5] imaging when using a conventional SPECT/CT system. Such improvements may also be realized in an interventional setting.

### 3.2. Biopsies

Biopsies are performed to determine the pathology of targeted tissue and are often done under CT or ultrasound guidance to guide the needle placement. There are, however, various occurrences where these conventional imaging modalities can poorly visualize the tissue that should be targeted. For such cases, it has been proposed to complement the anatomical images with functional information so that the most metabolically active area can be targeted. This form of image guidance has been successfully demonstrated in a procedure involving interventional PET imaging [6,7].

We envision that a similar functional image guidance approach for biopsies may also be performed with large field-of-view interventional planar scintigraphy and SPECT imaging. Procedural guidance may be realized by adding radioactive material to the biopsy needle tip [8] and using this signal to position the needle in the tissue of interest. A potential advantage of interventional SPECT over interventional PET is that SPECT realizes better cost-effectiveness, for both hardware and the use of more practical long-living isotopes [9], and allows for multi-isotope imaging. Cost-effectiveness may be especially important in an interventional setting in which the devices are likely infrequently employed. A disadvantage of interventional SPECT is the acquired images will be of lower quality than those acquired from interventional PET.

### 3.3. Radioembolization

Radioembolization is a treatment for liver cancer that is performed under fluoroscopic guidance in the intervention room [10,11]. In radioembolization, small radioactive spheres (microspheres) are injected into the liver bloodstream where the spheres lodge in the tumor vessels and deliver damaging radiation to the surrounding tissue. The microspheres must accumulate at the correct locations to realize the best treatment outcome. To this end, the radioembolization treatment is mimicked in a pre-treatment procedure in which $^{99m}$Tc-MAA particles (which have similar kinetic behavior to the microspheres but are less ionizing) are injected instead.

Large field-of-view interventional imaging could aid radioembolization in two ways. First, the injection of MAA particles and microspheres can be done under dynamic planar scintigraphy. This provides the physician with direct feedback on the acquired distribution. Should an incorrect distribution be observed, then the injection can be immediately altered: the injection location or the injection pressure can for instance be changed. And second, when a SPECT scan of the MAA distribution can be made inside the intervention room, it becomes possible to merge the pre-treatment procedure with the treatment into a single session [12,13]. Within such a single-session procedure, a personalized dosimetry plan for the patient can be designed (because the predictive power of the pre-treatment procedure is expected to improve) and immediately executed [14,15]. Furthermore, the costs for the hospital are reduced and the burden for the patient is decreased.

### 3.4. Intra-arterial radionuclide therapy

Peptide Receptor Radionuclide Therapy (PRRT) [16,17] and radioimmunotherapy (RIT) [18,19] are forms of radionuclide therapy that target tumor cells by binding radioisotopes with tumor receptors and antigens, respectively. This specific binding to the tumor cells (instead of normal cells) accomplishes a relatively local deposition of radiation. PRRT and RIT are normally performed by an intravenous administration. It has, however, for these procedures been proposed to instead inject the radiopharmaceuticals intra-arterially in a procedure done in the operation room [20–22]. The hypothesis is that the deposition of radiopharmaceuticals close to the tumors increases their relative uptake (the 'first-pass effect'), which in turn increases the dose to the tumors and decreases the dose to healthy tissue.

Large field-of-view interventional imaging could aid such intra-arterial radionuclide therapy procedures in two ways. First, similar to radioembolization, direct feedback on the radiopharmaceutical injection is obtained using dynamic planar scintigraphy. This allows the physician to change the injection position should an incorrect distribution be observed. Ideally, planar scintigraphic imaging would simultaneously be coupled to anatomical images, such as the x-ray images acquired from a CBCT scanner. And second, nuclear image guidance can be performed for dosimetric purposes. With planar scintigraphy and SPECT, it can be studied at which point the uptake of radiopharmaceutical in a tumor saturates. Such image guidance hence allows to maximize the dose or ensure a minimal effective dose that is being administered to the tumor. With quantitative SPECT imaging, the absolute doses to the tissues can furthermore be calculated and monitored during the procedure.

### 3.5. Cardiac interventions

Nuclear imaging has historically been used for a long time for the assessment of cardiac tissue functioning. In myocardial perfusion imaging (MPI), a radiopharmaceutical that accumulates in functioning heart muscle (often, $^{99m}$Tc-sestamibi) is administered to the patient [23]. The acquired SPECT images reveal which cardiac tissues have correct perfusion and which tissues possess a defect. Based on the images, a treatment plan for the patient is made. Often, the patient will undergo a procedure in the intervention room to improve the defective tissues (e.g. by performing a percutaneous coronary intervention (PCI)).

With large field-of-view interventional imaging, it becomes possible to combine these two concepts: an MPI SPECT scan can be made during or after the cardiac procedure in the intervention room. We envision that such a workflow enables two options for procedural guidance. First, one can perform a SPECT scan after the intervention is finished and compare the acquired images with a previously acquired MPI SPECT scan. By visualizing the difference between the two images, it can be determined whether the intervention was a success in terms of functional outcome. If this proves not to be the case, the interventional workflow may be altered and repeated. And second, one can delineate a cardiac defect on a live-acquired SPECT MPI scan and use maximum intensity projections to guide the interventional procedure (e.g. to position the stent to inject close to the tissue defect). This form of image guidance requires that good integration with anatomical images is available. We envision that this last form of nuclear image guidance may improve the success rate of the cardiac intervention.

Another application of large field-of-view interventional imaging for cardiac purposes may lie in the delivery of therapeutics to the heart [24]. There are several molecular targeted treatments for cardiac dysfunction (e.g. cell therapy) which have shown promising results in animal studies but have resulted a limited efficacy in clinical trials thus far [25]. It has been suggested that the success rate of these therapies may be improved by putting more emphasis on the tissue targeting so that e.g. off-target events are reduced [26]. Interventional nuclear imaging in combination with molecular targeted radiotracers may be used to place the catheter in the optimal delivery location.

## 4. Scanner configurations

The use of imaging devices in the operation room comes with specific requirements. The same as with diagnostic devices, the large field-of-view interventional scanners should ideally be able to provide both planar scintigraphy and SPECT scanning. While the interventional nature of the devices may allow for slightly worse image quality compared with diagnostic devices, ideally a similar sensitivity and resolution should be achieved. We believe that there are furthermore two requirements that are specific to interventional imaging:

1. The scanner design must be optimized for the intervention room. For example, the footprint of the scanner should ideally be small to ensure that few modifications to the room are required. The scanner should preferably be compact so there is sufficient space for the physicians to operate in. The scanner should be sufficiently flexible to easily move toward and from the patient when nuclear image guidance is required. And it is desirable to have a mobile system so that the scanner can be employed on multiple sites.
2. Good integration with live anatomical imaging should be available. In an interventional setting, live anatomical imaging (e.g. fluoroscopy) is frequently employed to guide procedures by visualizing the catheter position. Hence, it should be possible to quickly switch between live anatomical imaging and planar scintigraphy/SPECT (or even acquire both at the same time). Similar to diagnostic imaging, anatomical imaging is also important for planar scintigraphy/SPECT because i) nuclear images can be difficult to interpret without an anatomical reference, ii) attenuation correction is required for achieving quantitative SPECT images, and iii) tissue delineations are necessary when the doses to tissues need to be calculated.

The above requirements can be met in multiple ways. Below, we have compiled a list of scanner configurations that could enable large field-of-view interventional imaging: this list is a mixture of commercially available products that can be adapted for interventional purposes, scanner designs that have been evaluated through simulations, and prototype scanners that have been experimentally tested. There is currently no commercially available system that meets all of the discussed requirements.

### 4.1. Sliding SPECT/CT

The most obvious choice for achieving large field-of-view interventional imaging would be to place a conventional SPECT/CT scanner in the operation room. These scanners are, however, currently not optimized on their flexibility. With an unmodified system, the patient would need to be transported from the operation table to the scanner bed when interventional imaging is desired. This is highly impractical and not acceptable for clinical use. Furthermore, the majority of commercially available scanners are relatively bulky. This is great for increasing the system stability (e.g. it allows for heavy collimators to be mounted) and improving the usability (e.g. by storing collimators beneath the table and providing built-in quality assurance tools) but these added functions are not necessarily required in an interventional environment.

A possible modification to the current SPECT/CT scanner design would be to couple the operating table bed to the scanner bed and to slide either the bed or the scanner to cover the patient when interventional imaging is desired. Such a modification has already been successfully introduced for CT [27,28], MRI [29,30], and PET [31,32] scanners (see Figure 1a) and should be relatively straightforward to implement for SPECT/CT scanners similarly. Ideally, the scanner should also be made somewhat more compact by optimizing the design for interventional use.

The major benefit of the above modification is that interventional imaging would be performed with the same image quality as in diagnostic imaging, which allows for an unbiased comparison between pre- and post-procedural images. With an integrated CT detector ring, the SPECT images furthermore

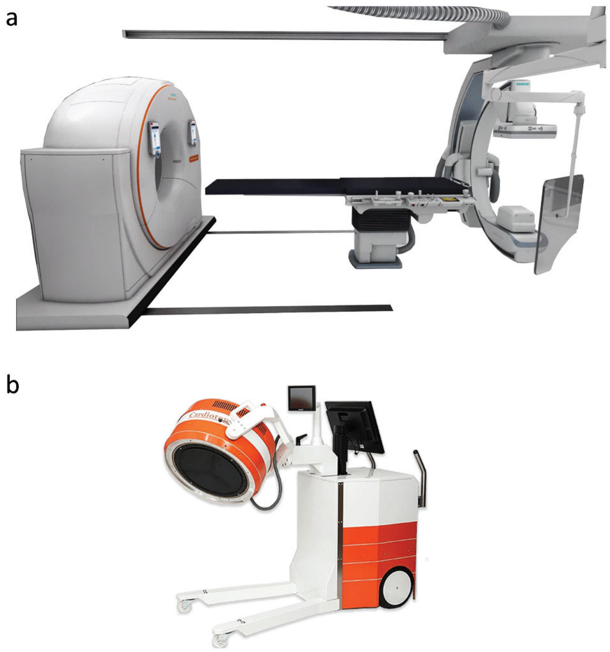

Figure 1. Commercially available systems that may be altered to achieve interventional nuclear image guidance. (a) A configuration with a sliding scanner has been developed for CT imaging in the intervention room. image courtesy of siemens Healthineers [33]. we believe that such a sliding scanner design may similarly function for a SPECT/CT scanner. (b) the Cardiotom system realizes a form of 3D imaging with a static detector and rotating segmented collimator. image courtesy of Adolesco [37].

can be made quantitative, and registered tissue delineations become available [34]. Disadvantages of this design are that the operation room needs to be substantially altered and that the design would make interventional imaging only available in one dedicated operating room. A sliding SPECT/CT scanner in the intervention room will hence likely not be a cost-effective solution for most hospitals.

### 4.2. Mobile cameras

Several companies have introduced mobile gamma cameras to translate large field-of-view imaging to the operation room. Three examples, that are based on a conventional NaI(Tl) scintillation crystal that is coupled with photomultiplier-tubes, are the Nucline TH by Mediso Medical Imaging Systems [35], the SoloMobile by DDD Diagnostic [36], and the Cardiotom by Adolesco AB (see Figure 1b) [37–39]. These devices have the benefit that they are based on the conventional gamma camera design for which a lot of experience is already available. A disadvantage is that this conventional gamma camera is relatively bulky: this makes it somewhat less appropriate for use in the dynamic environment of the intervention room (because there is a bigger chance for collisions) and this places more demands on the supporting gantry.

A more recently developed mobile gamma camera is the Ergo by Digirad [40,41]. This system uses a CsI(Tl) scintillation crystal that is coupled with silicon photodiodes, which results in a lighter and more compact detector when compared with the above discussed conventional gamma cameras. The Digirad Ergo system is hence also considerably more flexible than the above systems, which should result in an easier integration in the intervention room. This system demonstrates that solid-state technology can be of great assistance for realizing compact and lightweight detectors.

The four discussed mobile gamma cameras share the disadvantage of being unable to provide an anatomical reference to the nuclear images. Furthermore, three systems (Nucline TH, SoloMobile, and Ergo) can only perform planar scintigraphy. The Cardiotom performs a technique named ‘ectomography’ that uses a rotating collimator to retrieve three-dimensional information. Although this methodology works to some extent, current state-of-the-art reconstruction software requires projections over more angles to ensure an optimal reconstruction quality. Hence, none of the discussed devices can currently be considered to provide SPECT reconstructions with a quality that is currently widely available.

It seems that the supporting gantries of the mobile scanners could be relatively easily adapted to perform interventional SPECT by making the gantry automatically rotate the camera around the patient. An anatomical reference may be retrieved from the CBCT scanner that is available in the intervention room. With a method to calibrate the reference frames of both systems (e.g. by positioning radioactive sources that can be detected on both SPECT and CBCT), sufficiently accurate registration between both frames should be achievable. We recommend medical device manufacturers to further explore this option.

### 4.3. IXSI

The next system concerns the smart integration of two existing imaging modalities: planar scintigraphy and fluoroscopy. This combined imaging modality is named ‘Interventional X-ray and Scintigraphy Imaging’ (IXSI) (see Figure 2a) [42–46]. The scanner consists of an x-ray flat panel detector that is positioned in front of a gamma camera that is mounted with a cone-beam collimator. The detector stack is placed together with an x-ray tube on a custom-made gantry. The focal length of the cone-beam collimator is approximately the same as is

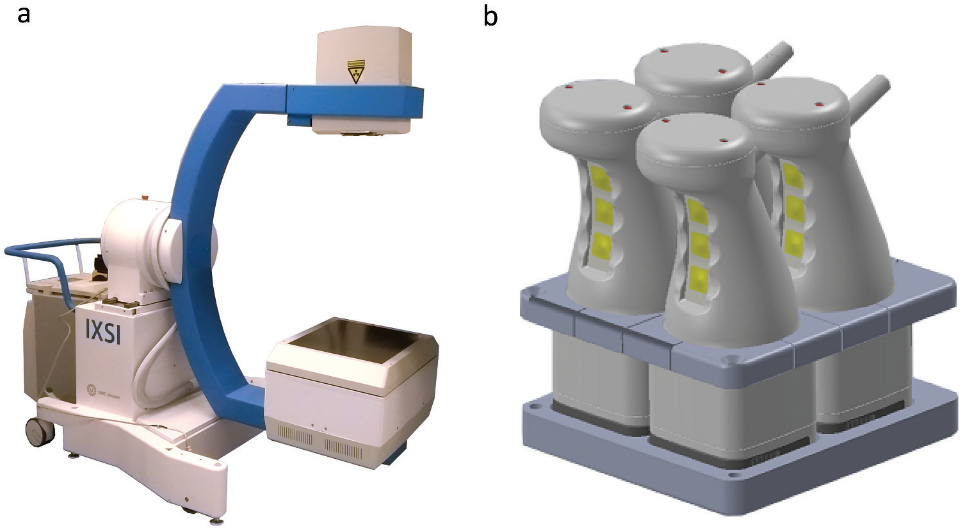

Figure 2. Prototype systems that may be used to achieve interventional nuclear image guidance. (a) IXSI, which realizes simultaneous acquisition of fluoroscopic (CBCT) and nuclear (SPECT) images. (b) Quadcam, which couples four CrystalCam’s in a 2 × 2 configuration to achieve a larger field-of-view that is compatible with freehand SPECT. Image courtesy of SurgicEye [50].

the distance of the x-ray tube to the flat panel detector so that x-ray and nuclear projections are intrinsically registered. By rotating the detector around the patient (using parameterized non-circular orbits), SPECT and CBCT reconstructions can furthermore be acquired. The CBCT reconstruction can be used for attenuation correction so that the SPECT reconstruction becomes quantitative.

This design likely meets the requirements for use in the intervention room as it resembles the well-known (mobile) C-arm. The system can perform quantitative SPECT and the ability to simultaneously acquire x-ray images with the nuclear images provides an anatomical reference for planar scintigraphy. Although the gamma camera is still bulky, the supporting gantry is mobile and relatively compact. A disadvantage of the design is that the positioning of the flat panel detector in front of the gamma camera decreases the gamma sensitivity and increases the source-to-detector distance, which respectively increases the noise and worsens the spatial resolution. Nevertheless, it seems that this scanner system may relatively easily be implemented in clinical workflows, which can provide valuable practical experience concerning large field-of-view interventional imaging.

### 4.4. *Freehand SPECT*

An interesting prototype design has been proposed by SurgicEye GmbH, which is the manufacturer of the declipseSPECT Imaging Probe [47]. The declipseSPECT consists of a small field-of-view gamma camera (the CrystalCam [48] that is based on CZT technology) that is coupled with an optical tracking system. The user can manually rotate the gamma camera around the patient so that a reconstruction is made, which is named freehand SPECT [49]. In their proposed design for large field-of-view imaging, four small field-of-view cameras are combined in a 2 × 2 configuration (named the QuadCam, see Figure 2b) [50]. Based on the existing CrystalCam parameters, this design should result in a detector with a 16 × 16 $\text{cm}^2$ field-of-view with a weight of approximately 3.2 kg. An advantage of CZT is that this material can cope with high radiation fluxes that are present in therapeutic interventions [51,52]. The Quadcam has been proposed to be used during radioembolization [53].

The QuadCam system has many advantages: it is truly mobile and flexible, a SPECT scan can be made relatively easy, and the system builds upon the success achieved by the small field-of-view gamma camera. There are two major disadvantages: i) although new applications can certainly be studied, the newly achieved field-of-view of 16 × 16 $\text{cm}^2$ will not be sufficient for the imaging of all organs (e.g. the liver will generally be too large), and ii) the weight of the collimator will limit freehand SPECT to the imaging of low-energy radionuclides. The proposed QuadCam design does, to our knowledge, not yet come with a live anatomical reference image. SurgicEye GmbH has, however, previously demonstrated successful integration of ultrasound into their systems [54–56]. This integration may be beneficial for the QuadCam system as well. The translation from ultrasound to a 3D map to be used in the SPECT reconstruction will, however, certainly not be trivial.

### 4.5. *Robotic arms*

Several research groups have suggested the use of robotic arms for enabling large field-of-view interventional imaging since the robotic arm can closely follow the contour of the patient to acquire SPECT images. A group from the Université Catholique de Louvain demonstrated the design with an animation (see Figure 3a) and evaluated a prototype configuration with a pinhole collimator for the interventional imaging of therapeutic isotopes used in radioembolization [57,58]. A group from the Technische Universität München placed a handheld gamma camera on the robotic arm [59]. Although this prototype had a small field-of-view, it can likely fairly easily be extended to larger field-of-views. And finally, a group from Duke University Medical Center constructed a much larger robotic arm (of which it is debatable whether it can still be considered sufficiently flexible, see Figure 3b) and tested this system with parallel-hole and pinhole collimators [60,61].

An interesting alternative design to the above systems that rely on a single robotic arm fixed to the floor, is the SKYLight

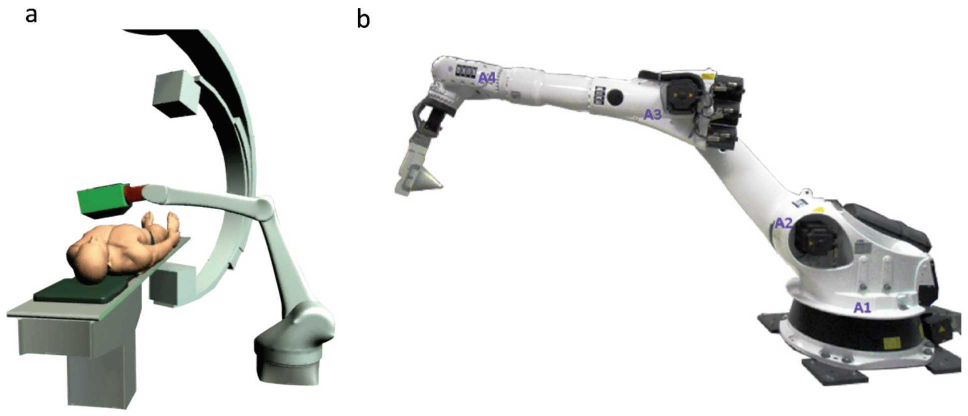

Figure 3. Robotic arms that may be used to achieve interventional nuclear image guidance. (a) A design in which a robotic arm is coupled to a gamma camera and is placed in an intervention room that has CBCT scanner functionality. Image adapted from [57]. (b) A prototype robotic arm configuration developed by Duke University. Image adapted from [61].

design produced by Philips Healthcare. This design is different from the above systems by having two arms with detectors that are mounted to the ceiling. The design was at the time of manufacturing proposed as a method to remove the limitations in the size and positioning of the patient. We, however, believe that the design may also function for usage in an interventional setting, although this specific construction may interfere. An advantage over the above discussed robotic arms is that with two robotic arms, the sensitivity is doubled.

Robotic arms require a fixed mounting point in the operation room to achieve sufficient stability. This may be a substantial hurdle for its implementation in the clinic. The robotic arm systems furthermore share the disadvantage of being only able to image in a single dedicated operation room instead of being a transportable device. And finally, the robotic arm configuration cannot gather anatomical images. Several authors have, however, suggested using their device in the intervention room where the CBCT scanner is already available. If a precise alignment between these two imaging modalities is achieved, the CBCT reconstructions may be used to complement the SPECT reconstruction with tissue delineations and an attenuation map. Anatomical guidance of planar scintigraphy would however still not be possible.

### 4.6. Hybrid detector

Many operation rooms are configured with a CBCT scanner for fluoroscopic procedural guidance. An innovative solution has been proposed for achieving large field-of-view interventional planar scintigraphy/SPECT imaging by using the CBCT flat panel detector [62] additionally for SPECT imaging (see

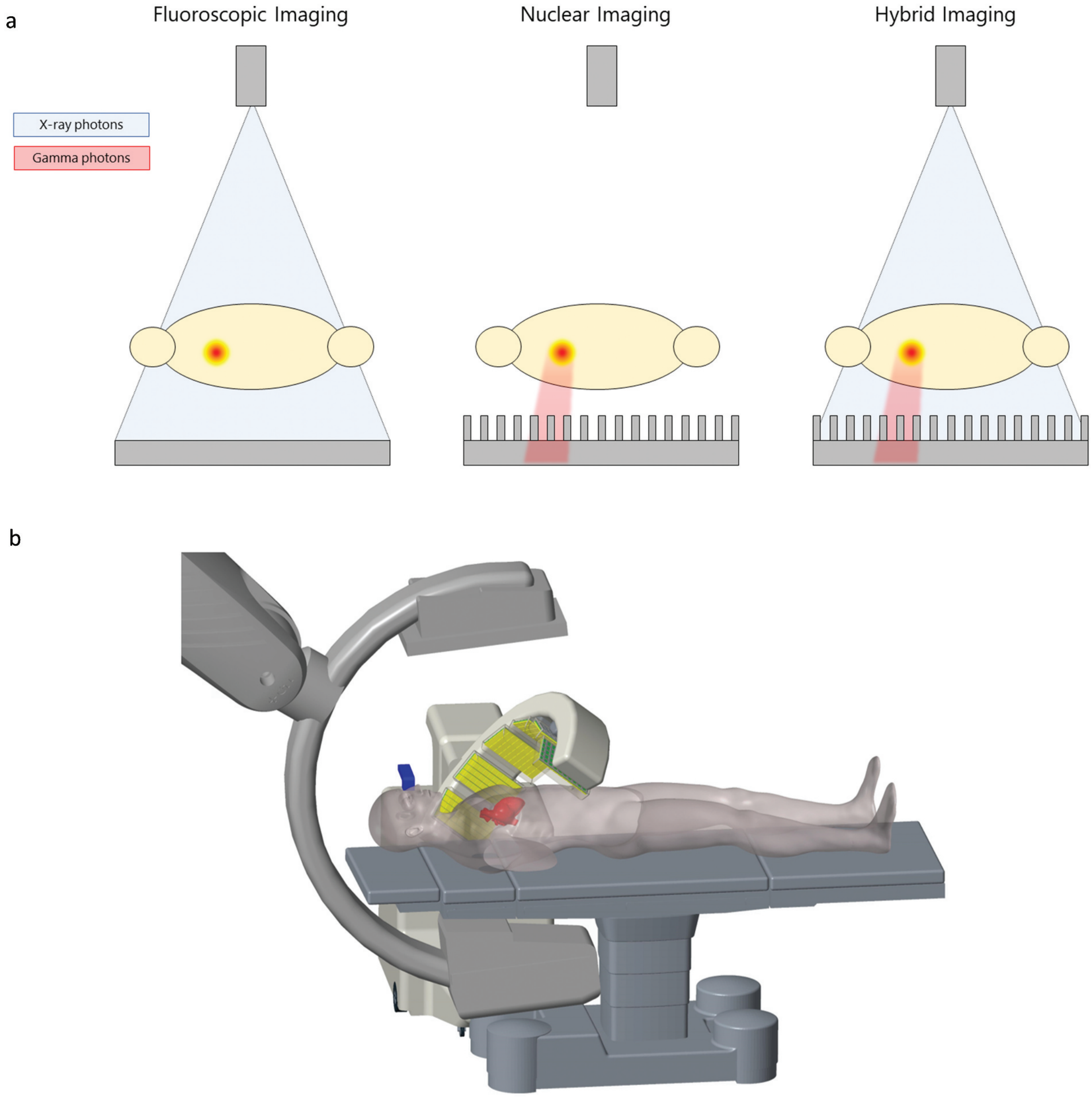

Figure 4. Simulated designs that may be used to achieve interventional nuclear image guidance. (a) A configuration that accomplishes fluoroscopic, nuclear, and hybrid imaging by using a hybrid detector together with a removable collimator. (b) A design where many small CZT cameras (focused on the target volume) are placed on a compact and mobile c-arm gantry. Image courtesy of University of Illinois [66,67].

Figure 4a). This is possible since x-rays and gamma photons rely (apart from the collimator that needs to be positioned in front of the detector) on similar detection mechanisms. The collimator may be loaded onto CBCT gantry as soon as interventional planar scintigraphy/SPECT imaging is required. It was demonstrated that this approach is feasible in a proof-of-concept experiment [63] and a group from the University of Nevada evaluated the concept through simulations [64,65].

The shared detector design has a major advantage over the other discussed designs by adapting an existing gantry rather than introducing a new one. This saves costs, space, and builds upon the success of the already available CBCT scanner. However, at least three adjustments to the CBCT scanner would need to be performed. First, a collimator should be (automatically) loaded onto the flat panel detector. Second, the CBCT scanner movements should be adjusted to also include an option for performing non-circular orbits. And third, the system must be made sufficiently rigid to support the additional weight of the collimator. We believe these adjustments should be possible to implement seeing these characteristics are also achieved in commercially available SPECT scanners.

There are two disadvantages to the hybrid detector configuration. First, the detection sensitivity for higher energy photons (e.g. those used in therapeutic applications) will be low since the flat panel detector is optimized for x-rays with a mean energy < 100 keV. This challenge may be mitigated to some extent by increasing the thickness of the scintillator material. And second, a normal flat panel detector system will generally not be able to perform photon energy measurements. The lack of energy selection and subsequent inclusion of all scattered photons in the data places additional requirements on the SPECT reconstruction. It may be taken into account in the reconstruction (e.g. by detailed model-based scatter correction) so that quantitative images are still achieved.

With a combined SPECT and CBCT scanner, it may additionally become feasible to perform hybrid imaging (i.e. simultaneous nuclear and fluoroscopic imaging). This form of imaging is similar to the imaging performed in the IXSI design but instead uses a single detector instead of two separate detectors. In this hybrid imaging configuration, a shadow of the collimator septa will be cast on the fluoroscopic images. This decreases the fluoroscopic image quality. However, with the use of gap-filling techniques, these images may still be of sufficient quality for image guidance of certain procedures.

### 4.7. C-arm SPECT

The final discussed design is somewhat different from the other discussed systems since it is a more stationary system instead of a rotation one (see Figure 4b) [66,67]. The authors propose to couple small CZT modules to pinhole collimators and place these along a compact and mobile gantry that is placed over the patient. The open area in the middle of the patient is used for fluoroscopic imaging with the CBCT scanner in the intervention room. The CZT detector modules all point toward the target volume in the middle of the patient (in a 'compound eye' configuration). With this configuration, data for a SPECT reconstruction of the target volume can be continuously acquired.

This c-arm design is interesting since it will have a high sensitivity in the target volume and could enable dynamic SPECT acquisitions [68]. Dynamic SPECT imaging is largely unfeasible with the previously discussed rotating detector systems because they acquire different projection angles over time. Dynamic SPECT imaging may allow a radioactive marker to be tracked in 3D (provided that the reconstruction and acquisition are sufficiently fast), which provides an interesting approach to achieve procedural guidance. There are two disadvantages to the c-arm SPECT design: i) the many required detectors (with proposed state-of-the-art technology) may make the scanner configuration relatively costly and ii) it may be more difficult to closely follow the patient contour because of the fixed c-arm, which potentially causes some reconstruction resolution degradation.

## 5. Conclusion

This article has provided an overview of the current status of large field-of-view interventional nuclear imaging. We discussed the possibility for different forms of imaging, introduced potential applications, and evaluated possible interventional scanner configurations.

## 6. Expert opinion

This review discussed five potential applications for interventional imaging. For radioembolization, we believe that there is strong evidence that large field-of-view interventional imaging will provide a benefit to the clinical workflow. For cardiac interventions and intra-arterial radionuclide therapy, we found several leads that make a further exploration of these applications worthwhile. For radio-guided surgery and biopsies, we believe that there may be a benefit in using large field-of-view interventional imaging but we expect lower potential gains than in the previous three applications. More applications of interventional nuclear imaging are expected to arise over time seeing that the use of radionuclides in the intervention room is still expanding.

Out of the five discussed potential applications, only in radioembolization and intra-arterial radionuclide therapy there is strong evidence that real-time acquisitions will be beneficial for the clinical workflow. For cardiac interventions, interventional nuclear imaging will be used to verify the acquired distribution and make adjustments to the workflow if necessary. And for radio-guided surgery and biopsies, interventional nuclear imaging will be used for image guidance.

In the case of radio-guided surgery and biopsies, it may also be possible to acquire a SPECT/CT image before the intervention and register this image to e.g. the CBCT images acquired during the intervention to enable image guidance. The advantage of this approach is that it may be easier and faster realized than using a dedicated scanner as proposed in this review. There are two disadvantages: i) there may be registration errors and ii) the anatomy of the patient may change in the sometimes weeks between the scan to register and the intervention. We believe that both methods should be explored in parallel, after which the optimal strategy can be determined.

Regarding the discussed scanner designs, we demonstrated that several prototype scanners can be expected to meet the requirements for use in the intervention room. However, it is currently not clear which scanner option would be best suited for this purpose since the discussed devices have different strengths and weaknesses. Most of the time, the trade-offs in the scanner design were between the achieved image quality and the practical use of the scanner (e.g. having sufficient flexibility). For now, it seems that a slightly worse image quality than in diagnostic imaging may be acceptable seeing that no interventional devices are currently commercially available.

A major hurdle of the implementation of large field-of-view interventional nuclear scanners lies in the weight of the scanner components: the scintillator, collimator, and lead shielding demand a strong support that impedes the flexibility of the devices. As previously mentioned, the use of CZT (instead of the regular NaI scintillator and photomultiplier-tube combination) reduces the weight of the system. For reducing the weight of the collimator, designs based on a pinhole structure (instead of the regular parallel-hole collimator) may prove useful. The lead shielding can likely not be easily removed. Nevertheless, for applications involving low-energy isotopes (e.g. the frequently-used $Tc^{99m}$), a low-weight shielding of a few millimeters lead may already be sufficient.

The majority of the devices discussed in this work only comprise a SPECT scanner, while for modern SPECT imaging also a CT component is available. The CT component is important in SPECT imaging because it: i) provides a reference of the anatomy of the patient in relation to the activity distribution and ii) because the CT image can be used to include attenuation correction in the SPECT reconstruction so that the optimal image quality is obtained. Ideally, one would have a mobile SPECT/CT scanner, but given the requirements of the intervention room such a system would be difficult to achieve. Instead, we have for some of the devices discussed in this article proposed to realize a smooth integration with the CBCT scanner that is often already available in the intervention room. With this scanner, there is a reference for the anatomy of the patient and attenuation can be included in the SPECT reconstruction by registration with a previously-acquired CT. We believe that with such a CBCT scanner integration it will not necessary to have a dedicated CT component, at least for the discussed applications.

Apart from the scanner hardware, interventional nuclear imaging gives specific requirements for the acquisition and analysis protocols. A regular SPECT measurement is normally in the order of ~20 minutes in duration. This scan duration should ideally be shortened to not waste valuable time in the intervention room. The analysis of the acquired data (e.g. the SPECT reconstruction) should furthermore be available as quickly as possible, which requires fast and robust software. Luckily, the shortening of the scan duration and the fast analysis of data are also challenges in regular SPECT imaging and hence a lot of work has already been performed in this area.

There are several methods in which the acquisition duration may be reduced. The most evident option would be to simply reduce the scan time and accept a slightly lower quality than is clinically achieved because of the unique nature of the interventional workflow. One option is to work toward a goal-focused scan duration, i.e. to dynamically evaluate a certain metric (e.g. can a tumor be distinguished from the background) and terminate the scan when the objective has been achieved. Other options include a smart acquisition of data, i.e. to focus the measurement on the locations where most information can be gathered. This can be achieved by using e.g. focusing collimators, sparse-angle acquisitions, or non-uniform projection durations. We believe that it should generally be possible to keep the total extra required time for interventional nuclear imaging within 15 minutes.

There are also several methods in which the analysis may be accelerated. Normally, the SPECT reconstruction takes up the most time in the analysis workflow. The most evident option to speed up the reconstruction would be to simplify the problem, e.g. by reconstructing with a simple form of scatter correction (e.g. dual-energy window) or reconstructing on a smaller grid. While these options may result in a slightly worse reconstruction quality, it may be clinically acceptable because of the unique nature of the interventional workflow. More sophisticated methods to speed up the reconstruction include the use of graphical processing units (GPUs) for fast parallel calculations or employing deep learning to replace (parts of) the reconstruction pipeline. We believe that it should generally be possible retrieve satisfactory reconstruction results within one minute after the acquisition.

Apart from the scanner hardware, the devices used during interventions should also be optimized for interventional nuclear imaging. For example, in applications where a therapeutic dose is administered to the patient and interventional nuclear imaging is used for guidance, the dose to inject needs to be precisely controlled. This requires administration devices that monitor the dose and can terminate the injection when the dose threshold is achieved. Other interesting developments are in catheters that are radiation sensitive [69]. In combination with large field-of-view interventional nuclear imaging, such catheters may be used to guide the delivery of therapeutics to the optimal tissue locations.

Concluding, we believe that there is a major opportunity for interventional imaging to assist clinical workflows. We hope that the research groups that are developing products in the field of large field-of-view interventional imaging will test their developed devices in a clinical setting so that valuable practical experience with these devices is obtained. We believe that in five years, the advantage of large field-of-view interventional nuclear imaging will have been demonstrated in multiple clinical applications using prototype scanners. With these results, scanner device manufacturers may be interested in developing commercial systems so that more widespread use of the devices can be achieved.

## Funding

This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreements No 646734 and No 963934.

## Declaration of Interest

MMA Dietze is involved in the development of the IXSI scanner and has evaluated the performance of a hybrid detector for x-ray and gamma imaging. HWAM De Jong is involved in the development of the IXSI scanner and the performance of a hybrid detector for x-ray and gamma imaging, and has received funding from the European Union's Horizon 2020 under grant agreements No 646,734 and 963,934. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

## Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

## ORCID

Martijn M.A. Dietze http://orcid.org/0000-0003-1159-3510

## References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Mariani G, Olmos RAV, Vidal-Sicart S, et al. Radioguided surgery (Letter to the Editor). J Nucl Med. 2021;62(4):591.2–592.
2. Spanu A, Solinas ME, Chessa F, et al. 131 I SPECT/CT in the follow-up of differentiated Thyroid Carcinoma: incremental value versus planar imaging. J Nucl Med. 2009;50(2):184–190.
3. Barwick T, Murray I, Megadmi H, et al. Single photon emission computed tomography (SPECT)/computed tomography using Iodine-123 in patients with differentiated thyroid cancer: additional value over whole body planar imaging and SPECT. Eur J Endocrinol. 2010;162(6):1131–1139.
4. Lerman H, Lievshitz G, Zak O, et al. Improved sentinel node identification by SPECT/CT in overweight patients with Breast Cancer. J Nucl Med. 2007;48(2):201–206.
5. Vermeeren L, Olmos RAV, Meinhardt W, et al. Value of SPECT/CT for detection and anatomic localization of sentinel lymph nodes before Laparoscopic sentinel node lymphadenectomy in prostate Carcinoma. J Nucl Med. 2009;50(6):865–870.
6. Cornelis F, Silk M, Schoder H, et al. Performance of intra-procedural 18-fluorodeoxyglucose PET/CT-guided biopsies for lesions suspected of malignancy but poorly visualized with other modalities. Eur J Nucl Med Mol Imaging. 2014;41(12):2265–2272.
7. Solomon SB, Cornelis F. Interventional molecular imaging. J Nucl Med. 2016;57(4):493–496.
8. Wagner RH, Karesh SM (1999) Radioactive needle for biopsy localization and a method for making the radioactive needle
9. van der Wall EE. Cost analysis favours SPECT over PET and CTA for evaluation of coronary artery disease: the SPARC study. Neth Heart J. 2014;22(6):257–258.
10. Braat AJAT, Smits MLJ, Braat MNGJA, et al. 90 Y hepatic radioembolization: an update on current practice and recent developments. J Nucl Med. 2015;56(7):1079–1087.
11. Sangro B, Iñarrairaegui M, Bilbao JI. Radioembolization for hepatocellular carcinoma. J Hepatol. 2012;56(2):464–473.
12. Gabr A, Kallini JR, Gates VL, et al. Same-day 90Y radioembolization: implementing a new treatment paradigm. Eur J Nucl Med Mol Imaging. 2016;43(13):2353–2359.
13. Li MD, Chu KF, DePietro A, et al. Same-Day Yttrium-90 radioembolization: feasibility with resin microspheres. J Vasc Interv Radiol. 2019;30(3):314–319.
14. Bastiaannet R, Kappadath SC, Kunnen B, et al. The physics of radioembolization. EJNMMI Phys. 2018;5(1):22.
15. Garin E, Rolland Y, Edeline J, et al. Personalized dosimetry with intensification using 90 Y-loaded glass microsphere radioembolization induces prolonged overall survival in hepatocellular Carcinoma Patients with Portal Vein Thrombosis. J Nucl Med. 2015;56(3):339–346.
16. van Essen M, Krenning EP, Kam BLR, et al. Peptide-receptor radionuclide therapy for endocrine tumors. Nat Rev Endocrinol. 2009;5 (7):382–393.
17. Pavel M, O'Toole D, Costa F, et al. ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, Bronchial neuroendocrine neoplasms (Nen) and nen of unknown primary site. Neuroendocrinology. 2016;103 (2):172–185.
18. Sharkey RM, Goldenberg DM. Cancer radioimmunotherapy. Immunotherapy. 2011;3(3):349–370.
19. Larson SM, Carrasquillo JA, Cheung N-KV. Radioimmunotherapy of human tumours. Nat Rev Cancer. 2015;15(6):347–360.
20. Ebbers SC, Barentsz MW, Braat AJAT, et al. Intra-arterial peptide receptor radionuclide therapy for Neuroendocrine Tumor Liver Metastases. Digestive Disease Interventions. 2019;03 (1):81–90.
21. Kratochwil C, López-Benítez R, Mier W, et al. Hepatic arterial infusion enhances DOTATOC radiopeptide therapy in patients with neuroendocrine liver metastases. Endocr Relat Cancer. 2011;18(5):595–602.
22. Sultana A, Shore S, Raraty MG, et al. Randomised Phase I/II trial assessing the safety and efficacy of radiolabelled anti-carcinoembryonic antigen I(131) KAb201 antibodies given intra-arterially or intravenously in patients with unresectable pancreatic adenocarcinoma. BMC Cancer. 2009;9(1):66.
23. Dorbala S, Ananthasubramaniam K, Armstrong IS, et al. Single photon emission computed Tomography (SPECT) Myocardial perfusion imaging guidelines: instrumentation, Acquisition, Processing, and Interpretation. J Nucl Cardiol. 2018;25(5):1784–1846.
24. Pickell Z, Sinusas AJ. Nuclear Cardiac imaging in the interventional suite. Curr Cardiol Rep. 2022;24(3):261–269.
   - **Review article discussing interventional nuclear imaging in the context of cardiac imaging.**
25. Menasché P. Cell therapy trials for heart regeneration — lessons learned and future directions. Nat Rev Cardiol. 2018;15(11):659–671.
26. Li J, Hu S, Zhu D, et al. All roads lead to Rome (the Heart): cell retention and outcomes from various delivery routes of cell therapy products to the Heart. J Am Heart Assoc. 2021;10(8):e020402.
27. Lunsford LD, Parrish R, Albright L. Intraoperative imaging with a therapeutic computed tomographic scanner. Neurosurgery. 1984;15(4):559–561.
28. Uhl E, Zausinger S, Morhard D, et al. Intraoperative computed tomography with integrated navigation system in a multidisciplinary operating suite. Neurosurgery. 2009;64(5 Suppl 2):231–239. discussion 239-240.
29. White MJ, Thornton JS, Hawkes DJ, et al. Design, operation, and safety of single-room interventional MRI suites: practical experience from two centers. J Magn Reson Imaging. 2015;41(1):34–43.
30. Azmi H, Gibbons M, DeVito MC, et al. The interventional magnetic resonance imaging suite: experience in the design, development, and implementation in a pre-existing radiology space and review of concepts. Surg Neurol Int. 2019;10:101.
31. Tempany CMC, Jayender J, Kapur T, et al. Multimodal imaging for improved diagnosis and treatment of cancers. Cancer. 2015;121 (6):817–827.
32. Shyn PB. Interventional positron emission tomography/computed tomography: state-of-the-art. Tech Vasc Interv Radiol. 2013;16 (3):182–190.

33. Nexaris A-CT. https://www.siemens-healthineers.com/nl/angio/nexaris-therapy-suites/nexaris-angio-ct. cited 2021 Mar 25
34. Schillaci O. Hybrid SPECT/CT. a new era for SPECT imaging? Eur J Nucl Med Mol Imaging. 2005;32(5):521–524.
35. Mediso Medical Imaging Systems. http://www.mediso.com/products.php?fid=1,5&pid=61. cited 2020 Oct 7
36. SoloMobile. In: DDD Diagnostic. http://ddd-diagnostic.dk/solomobile/. cited 2021 Mar 17
37. About cardiotom. In: Adolesco. https://www.adolesco.se/index.php/about-cardiotom. cited 2020 Oct 7
38. Persson M (2001) Development of a mobile tomographic gamma camera based on ectomography - Cardiotom
39. Dale S, Holmberg M, Larsson M, et al. A mobile tomographic gamma camera system for acute studies. IEEE Trans Nucl Sci. 1997;44(2):199–203.
40. Siman W, Kappadath SC. Performance characteristics of a new pixelated portable gamma camera. Medi.Physics. 2012;39 (6Part1):3435–3444.
    - **Performance evaluation of a compact portable gamma camera.**
41. Ergo. In: digirad. https://www.digirad.com/cameras/ergo/. cited 2020 Oct 6
42. Dietze MMA, Kunnen B, van der Velden S, et al. Performance of a dual-layer scanner for hybrid SPECT/CBCT. Phys Med Biol. 2019;64 (10):105020.
43. van der Velden S, Kunnen B, Koppert WJC, et al. A dual-layer detector for simultaneous fluoroscopic and nuclear imaging. Radiology. 2019;290(3):833–838.
44. Beijst C, Elschot M, Viergever MA, et al. Toward simultaneous real-time fluoroscopic and nuclear imaging in the intervention room. Radiology. 2016;278(1):232–238.
45. Dietze MMA, Kunnen B, Lam MGEH. Jong HWAM de (2021) Interventional respiratory motion compensation by simultaneous fluoroscopic and nuclear imaging: a phantom study. Phys Med Biol. 2021;66(6):065001.
46. Dietze MMA, Kunnen B, Brontsema F, et al. A compact and mobile hybrid C-arm scanner for simultaneous nuclear and fluoroscopic image guidance. Eur Radiol. 2021;32(1):517–523.
    - •• **Interventional nuclear imaging scanner that is ready for clinical evaluation.**
47. declipse®SPECT Imaging Probe. In: SurgicEye GmbH. https://www.surgiceye.com/for-healthcare-professionals/declipsespect-imaging-probe/. Accessed 2020 Oct 7
48. Crystal Photonics GmbH | Crystal Optical Systems. https://crystal-photonics.com/enu/products/cam-crystalcam–enu.htm. Accessed 2020 Oct 7
49. Bluemel C, Matthies P, Herrmann K, et al. 3D scintigraphic imaging and navigation in radioguided surgery: freehand SPECT technology and its clinical applications. Expert Rev Med Devices. 2016;13(4):339–351.
    - **Review article discussing the potential of freehand SPECT imaging.**
50. Real-time dosimetry for SIRT based on image fusion. In: SurgicEye GmbH. https://www.surgiceye.com/realtime-sirt-dosimetry/. Accessed 2020 Oct 6
51. Koppert WJC, van der Velden S, Steenbergen JHL, et al. Impact of intense x-ray pulses on a NaI(Tl)-based gamma camera. Phys Med Biol. 2018;63(6):065006.
52. Koppert WJC, Dietze MMA, van der Velden S, et al. A comparative study of NaI(Tl), CeBr 3, and CZT for use in a real-time simultaneous nuclear and fluoroscopic dual-layer detector. Phys Med Biol. 2019;64(13):135012.
53. Wuestemann J, Pinto F, Mesri M, et al. (2018) Interventional real-time quantification of $^{90}$y-microspheres distribution in selective internal radiotherapy. In: EANM 18 PosterNG. https://posterng.netkey.at/eanm/viewing/index.php?module=viewing_poster&task=&pi=3637. cited 2021 Apr 13
54. Freesmeyer M, Opfermann T, Winkens T. Hybrid integration of real-time US and freehand SPECT: proof of concept in patients with thyroid diseases. Radiology. 2014;271(3):856–861.
55. Bluemel C, Kirchner P, Kajdi GW, et al. Localization of parathyroid adenoma with real-time ultrasound: freehand SPECT fusion. Clin Nucl Med. 2016;41(3):e141–142.
56. Bluemel C, Safak G, Cramer A, et al. Fusion of freehand SPECT and ultrasound: first experience in preoperative localization of sentinel lymph nodes. Eur J Nucl Med Mol Imaging. 2016;43 (13):2304–2312.
57. Walrand S, Hesse M, Demonceau G, et al. Yttrium-90-labeled microsphere tracking during liver selective internal radiotherapy by bremsstrahlung pinhole SPECT: feasibility study and evaluation in an abdominal phantom. EJNMMI Res. 2011;1(32):32.
    - **Introduction of robotic arm for interventional nuclear imaging.**
58. Walrand S, Hesse M, Wojcik R, et al. Optimal design of Anger camera for bremsstrahlung imaging: monte Carlo evaluation. Front Oncol 4:. 2014;4. 10.3389/fonc.2014.00149.
59. Gardiazabal J, Esposito M, Matthies P, et al. Towards personalized interventional SPECT-CT imaging. Medical image computing and computer-assisted intervention: MICCAI. International Conference on Medical Image Computing and Computer-Assisted Intervention. 2014; 17: 504–511.
60. Bowsher J, Yan S, Roper J, et al. Onboard functional and molecular imaging: a design investigation for robotic multipinhole SPECT. Med Phys. 2014;41(1):010701.
61. Yan S, Bowsher J, Tough M, et al. A hardware investigation of robotic SPECT for functional and molecular imaging onboard radiation therapy systems. Med Phys. 2014;41(11):112504.
62. Jaffray DA, Siewerdsen JH, Wong JW, et al. Flat-panel cone-beam computed tomography for image-guided radiation therapy. Int J Radiat Oncol Biol Phys. 2002;53(5):1337–1349.
63. Dietze MMA, Koppert WJC, Rooij R. Rooij R van, Jong HWAM de (2020) Technical Note: nuclear imaging with an x-ray flat panel detector: a proof-of-concept study. Med Phys. 2020;47 (8):3363–3368.
64. Wang H, Nie K, Kuang Y. An On-Board Spectral-CT/CBCT/SPECT imaging configuration for small-animal radiation therapy platform: a monte carlo study. IEEE Trans Med Imaging. 2020;39 (3):588–600.
65. Wang H, Nie K, Chang J, et al. A monte carlo study to investigate the feasibility of an on-board SPECT/spectral-CT/CBCT imager for medical linear accelerator. Med Phys. 2020;47 (10):5112–5122.
66. Zannoni EM, Meng L-J. Intraoperative C-arm SPECT for hybrid operating room: a design study. J Nucl Med. 2019;60:316.
    - **C-arm SPECT design for interventional nuclear imaging.**
67. Yang C, Zannoni EM, Meng L-J (2020) Design study of the i-spect system: an intraoperative SPECT system using a deformable dense camera array (DCA) and High-resolution Imaging Spectrometers. https://www.eventclass.org/contxt_ieee2020/online-program/session?s=M-03#e2292. cited 2021 Mar 25
68. Gullberg GT, Reutter BW, Sitek A, et al. Dynamic single photon emission computed tomography—basic principles and cardiac applications. Phys Med Biol. 2010;55(20):R111–R191.
69. Stendahl JC, Liu Z, Boutagy NE, et al. Prototype device for endoventricular beta-emitting radiotracer detection and molecularly-guided intervention. J Nucl Cardiol. 2022;29(2):663–676.