Integrating new imaging modalities in breast cancer management
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The current status of augmented reality in nuclear medicine and molecular imaging: a literature overview

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Submitted
Abstract

Introduction
Augmented reality (AR) is used for various purposes and different applications have been shown in navigation, mobile phones, aviation, simulation, military applications, educational purposes, and medicine. In nuclear medicine and molecular imaging, AR is currently applied for a small number of interventional procedures with the aim to visualize certain structures in patients by nuclear imaging and then navigate the physician towards these structures. The purpose of the present study is to provide an overview of mobile AR applications for nuclear medicine and molecular imaging.

Methods
We conducted searches in the databases Pubmed and Medline for relevant literature about AR in medicine focused on nuclear applications using mobile devices. Different AR applications were categorized and tabulated. An overview of each method is provided and the general results and limitations per technique are given.

Results
For AR in nuclear medicine different applications have been identified. Freehand-SPECT can obtain real-time SPECT images of small volumes to facilitate interventional visualisation and navigation. Current implementations of freehand-SPECT use an AR display (SPECT overlaid on optical) to enable instrument navigation. Freehand-SPECT can also be overlaid on real-time ultrasound. AR in neuronavigation or cancer surgery is facilitated by registration of preoperative nuclear scans onto the patient during the surgical procedure.

Conclusion
Mobile techniques using AR are adapted and developed for nuclear medicine in various feasibility studies. Combining different imaging modalities together with an AR display demonstrates useful applications for clinical applications in both interventions and surgery.
Introduction
Augmented reality (AR) is increasingly used in daily and clinical practice and it is defined as “the physical real-world as we can optically perceive with additional virtual information augmented to it or projected over it”. Three aspects characterize AR: (1) a combination of reality with virtuality, (2) registration of the real-world in 3D, and (3) possibility of real-time interactions. [1, 2] In the reality-virtuality continuum described by Milgram and Kishino the whole range from virtuality (completely synthetic-world) to reality (real-world) is described in an orderly form. According to their taxonomy, AR is a form of mixed reality located near the reality end of the reality-virtuality continuum. For example, virtual reality gaming displays are usually at the most virtual site of the virtuality continuum; it generates a complete synthetic-world for the user. AR on the other hand, combines and interacts with reality, while the physical real-world is more dominant.

A literature review of advanced medical displays based on AR was published in 2008 by Sielhorst et al. and provides an overview from the first AR description in 1938 to the developments of many different applications in the last decades. [3] Sielhorst’s study describes the main motivation for the need of visualizing medical data and the patient within the same physical space, in other words, the need for AR. In practice, there are four methods to display AR: external screens, see-through windows, external projections, and head mounted displays, which are all described into more detail in the review from Sielhorst et al. [3, 4] AR is currently used for different applications, for example in navigation, mobile phones, aviation, simulation, military applications, educational purposes, and in medicine. [5-7] Novel medical AR functionalities are rapidly presented, which generally appeal to the general public due to their futuristic applications and visualisations. [8-10]

In nuclear medicine and molecular imaging, AR is currently applied for a small number of procedures. Innovative AR-based applications for the visualisation of nuclear imaging in an interventional setting are under investigation by various pilot and feasibility studies. It is still unknown what we can expect from these applications and how they will benefit healthcare. However, there are already two very different approaches to the AR in nuclear medicine; at the one end there are small, relatively cheap mobile devices and on the other end there are large expensive imaging devices fully integrated into the operating theatre. This review will focus on AR for nuclear medicine and molecular imaging using small mobile devices, as we believe that those systems can be
implemented in the standard clinical workflow within most mid-sized clinical institutions. An overview will be provided covering the technical details, clinical usability and future expectations of these systems.

**Methods**
To provide a complete overview of the literature about AR in nuclear applications involving mobile imaging systems, a search was performed in Pubmed and Medline databases for original research up to March 2015. The initial search terms were: "nuclear" AND ("augmented reality" OR "radioguided surgery" OR "intraoperative imaging"). Based on the results for this query (n = 110) relevant manuscripts and reviews were selected, and reference lists were crosschecked to identify additional publications. For additional citations within the inclusion criteria a Google Scholar search was performed. Only full papers and case reports in English or with an English abstract were included. Additionally, a broad Internet search was conducted to identify future developments in AR-based prototypes and ideas of leading institutes that have not yet been published in scientific journals.

All clinical AR applications were categorized and tabulated based on technique and indication. An overview of each method and the general results and advantages per technique are provided. The technical working mechanism is clarified and the opportunities and limitations of the techniques are discussed.

**Results**
Our search resulted in the selection of 30 relevant publications where AR is described in the field of nuclear medicine and molecular imaging using mobile devices. A table with an overview of all publications and techniques is provided. (Table 1) In the following sections these techniques and their clinical applications will be described in greater detail.

*AR techniques for visualisation and navigation*
Three commercial devices or techniques were found that facilitate mobile visualisation and navigation by means of AR in nuclear medicine, which are 1) declipseSPECT, 2) BrainLAB’s neuronavigation solutions and, 3) Medtronic’s StealthStation TREON plus. All three system use stereo infrared cameras to detect reflective passive markers (fiducials) in the real-world. Two or more reflective markers form one cluster, which in this article is referred to as a target. Within the surgical field there is just one reference
target that acts as the centre of a coordinate system to which the movements of all other targets are related.

The declipseSPECT (SurgicEye GmbH, Munich, Germany) is a system that has been specifically developed for radioguided surgery. Based on an intraoperative SPECT image method, known as freehand-SPECT, it allows real-time SPECT imaging of small volumes. Further it enables the use of preoperative images for navigation as well. Optical tracking of instruments is possible by attaching reflective targets and simultaneous tracking the passive reference target at the patient, thus enabling navigation of the specific instrument (mostly a gamma probe) towards the area of interest. The real-time position of the instrument is visualized in an AR display where the preoperative images or the intraoperative acquired SPECT images are superimposed onto the (optical) image of the patient (either the image of a camera fixed over the operating sites or the video of a laparoscope). Registration is not needed if images are acquired intraoperative (freehand-SPECT). In case of preoperative images registration succeeds automatically as the same reference that is attached to the patient during preoperative image acquisition is used in the OR and can be tracked by optical tracking; markings on the skin of the patient are used to enable repositioning of the reference.

Freehand-SPECT image acquisition during an intervention is an innovative approach that is based on the combination of detected gamma counts using a conventional gamma probe (or portable gamma camera) together with the real-time information on the location and orientation of the gamma detector. Through a calibration procedure, the relation between the gamma detector and the reference target rigidly attached to it can be determined. To acquire an accurate 3D volume reconstruction from the count data, a surface scan is made by hovering the detector over the area of interest ideally in three different orientations (e.g. x, y, and z planes). This takes approximately 2 minutes for most anatomic regions, while the current reconstruction is updated every 5 seconds to guide further data acquisition. During and after the imaging process, the acquired SPECT images are overlaid over the optical images. The window and level of the overlaid SPECT images can be adjusted by using a touch screen to set a visualisation threshold similar to the ones used in conventional nuclear medicine until a proper image is acquired. (Figure 1) This technique is recently also applied with a different approach, where the freehand-SPECT image is not overlaid on an optical image, but onto a real-time ultrasound image. Optical tracking of an ultrasound probe and patient
results in a correct overlay of both different images derived from ultrasound and freehand-SPECT. (Figure 2)

![Figure 1: (a) Freehand-SPECT image with the radioactive targets (here radioactive seeds) superimposed onto the optical image of the patient. (b) 3D visualisation mode (virtual reality) where the view is from the gamma probe tip and allows navigation towards the targets. The distance from the probe tip position towards the target is indicated in the upper right side on the screen.](image)

The second commercial technique found within this review is implemented in the neuronavigation tools by BrainLAB (Munich, Germany). Preoperatively, anatomical images are acquired with passive reference targets attached to the patient (e.g. the fiducials are glued to the skin of the patient). Intraoperative registration of these images onto the real-time optical image of the patient takes place again using the passive reference targets. Alternatively the registration can succeed using the surface of the patient and a laser scanner as implemented in BrainLAB’s Z-Touch or Softouch. Positron Emission Tomography (PET) images or SPECT images can be used intraoperative (after image fusion to align nuclear and anatomical images) to obtain information of the imaged structures in the head area relative to surgical instruments or anatomical structures. The overlay of nuclear medicine images on the anatomical ones given the registration with the patient can be considered an AR representation. [11]

The third system found, the StealthStation TREON plus (Medtronic, Louisville, USA), uses the same principle as the BrainLAB navigation tools where the preoperative images are co-registered to the patient during the surgical procedure. By instrument tracking with infrared cameras it is possible to assess where the tumour margins are. Patients had to wear a removable dental plastic splint provided with fiducials for intraoperative recording during the examinations in order to enable successful registration. [12]
Figure 2: The freehand-SPECT – Ultrasound set-up, declipseSPECT (D), which enables freehand-SPECT imaging by means of a gamma probe or portable gamma camera (P) and an optical tracking system. By means of tracking an ultrasonographer (U), an ultrasound image with the superimposed radioactivity distribution is created (I) and indicates the SN.

Clinical applications

In the next paragraph, an overview is given on different applications of AR by means of the three previously described approaches and the results reported in literature are summarized. A large amount of the studies included sentinel node (SN) procedures and, therefore, the studies are divided in SN related studies and primary tumour localisations.

Sentinel lymph node biopsy

Prognosis and survival is in many tumour types dependent on tumour stage, in which assessment of locoregional lymph nodes is highly important. For this purpose, lymphatic mapping and SN biopsy have been incorporated into the standard of care in patients. SNs are the first lymph nodes to receive detached tumour cells by direct lymph drainage with the potential to grow into metastasis. The application of AR-based navigation within this setting to detect lymph nodes and guide biopsies is quite new.
Breast cancer
The first reports on the application of SN biopsies were for melanoma patients and it was regarded as a less invasive technique compared to a complete axillary lymph node dissection. Since the introduction by Morton et al., the SN procedure has been adapted also for other indications like early stage breast cancer. [13-15] The introduction and application of a 3D navigation technique to localize the SNs in breast cancer has been described in 5 different studies. The additional value of freehand-SPECT compared to the conventional gamma probe was studied in 2 case reports and in 2 studies with 40 and 85 patients, respectively. [16-19] Freehand-SPECT, achieving real-time three-dimensional nuclear image acquisition, proved feasible for these procedures and detected more SNs compared to the conventional gamma probe, however, it detected less SNs compared to planar lymphoscintigraphy mainly due to merging of spots. Its use resulted in changed surgical management in 10.5% of all cases by a postoperative freehand-SPECT scan where still a considerable amount or remaining activity was detected after resection, possibly coming from second echelon nodes. [19] In a recent technical and clinical evaluation from Engelen et al. a combination of a portable gamma camera with freehand-SPECT was described. It was hypothesized and proven that a portable gamma camera is superior to a gamma probe for image acquisition in terms of sensitivity and SN resolvability. Furthermore, the same set-up was used for preoperative SN imaging of 10 patients scheduled for a SN procedure. [20]

Head and Neck cancer
SN mapping for head and neck cancer in melanoma and Merkel cell cancer is widely used since the introduction of SN biopsies. In addition, oral cavity cancer SN biopsies (arising from squamous cell carcinomas mainly) are also increasingly performed for adequate lymph node staging. [21, 22] In tumours developing at this site, locoregional evaluation is highly important to minimize tumour recurrence rate, but also to avoid extensive mutilating surgical procedures when cure cannot be achieved anymore. Head and neck cancer SN procedures are therefore highly important, but it has to be realized that this procedure is performed in an area with complex anatomy. Indeed, there are many critical structures, such as nerves and blood vessels, and relatively large amounts of small lymph nodes. SN staging is performed to avoid extensive surgery and the accompanying morbidly needed for complete lymph node dissections. To guide this complex surgical SN localisation, real-time 3D navigation by means of freehand-SPECT has been introduced for both melanoma and oral cancer SN procedure. A study for SN
mapping in oral cancer with 23 patients demonstrated good results, in terms of accurate intraoperative visualisation, in all but 1 case in oral cavity SN procedures. [23] The study noted that freehand-SPECT overcomes the shine-through phenomenon (meaning radiation detected from a deeper or contralateral structure which could indicate false SN localisations), one of the most important limitations of SN procedures, and thereby confirmed the importance of SN procedures using 3D navigation in patients with cN0 oral cancer.

In a larger study by Heuveling et al., the use of this modality, previously described in a case series for oral cancer SN mapping, was extended to 66 patients and concluded that freehand-SPECT based navigation is feasible in the intraoperative detection of SNs in early stage oral cancer. [22, 24] Freehand-SPECT provided helpful information in order to find the SN in a quarter of cases based on the surgeon’s opinion. However, SNs located in the vicinity of the injection site caused problems with localisation resulting in the non-visualisation of 9 nodes (out of 146).

Two other studies including small numbers of patients for SN procedures in early oral squamous cell carcinoma and head and neck cancer reported comparable results [25, 26].

Urogenital cancers

SN procedures for urologic malignancies are still quite controversial. The safety and reduction in morbidity of this technique have not been proven and studies are still ongoing to assess its benefits. A SN procedure can reduce patient morbidity by avoiding a lymph node dissection thus it is important to explore the possibilities in doing so. However, SN procedures in these areas are complex because of drainage to various lymph node levels and a complex anatomy of the pelvis region. The first SN procedure for prostate cancer using SPECT/CT navigation was performed in a proof of principle study. [27] At that stage, it was difficult to perform a high quality freehand-SPECT scan in a laparoscopic setting because of the limited possibilities for gamma probe movement within the abdominal cavity. Therefore, the use of preoperative SPECT/CT images superimposed onto the patient was preferred. To accomplish this an optical reference target had to be positioned on a static part of the patient during the SPECT/CT-scan as well as during the surgical procedure at the exact same place by means of a skin mark. Subsequently, the generated SPECT/CT was superimposed over the patient to create a mixed-reality environment aimed to facilitate navigation. A disadvantage of the method is the potential mismatch between the reference target
placement and the positioning of the patient during the procedure compared to the position during the SPECT/CT scan.

In SN procedures for penile cancer SPECT/CT navigation was used in 10 patients based on the same approach as described in the prostate case. The SPECT/CT-scan was superimposed on the patient during surgery and proved to be a feasible method to translate 3D functional SPECT/CT images to the operating room. [28] This study demonstrated a relatively good correlation (±5mm error) with the projected SNs and the location where the SNs were detected with the gamma probe or the depth measured at the SPECT/CT scan.

**Melanoma**

SN melanoma is, together with breast cancer, the most prevalent indication for a SN procedure. In this respect, lymph node involvement is the most important prognostic factor for disease-free survival in stage I-II melanoma, indicating the importance of the SN biopsy procedure. [29] Additional intraoperative imaging by means of freehand-SPECT might further improve this procedure in terms of SN localisation and validation of complete excision of all SNs, which would benefit procedures in complex areas.

Two case reports and two feasibility studies with 25 patients in total demonstrated the value of freehand-SPECT in the SN procedures for melanoma. The studies described better guidance towards SNs and precise pinpointing of the SN location. The feasibility study from Freesmeyer et al. described cases of both melanoma and breast cancer SN procedures in a setting where the nodes were assessed by means of ultrasonography after localisation with freehand-SPECT. [30-33] The fusion concept by combining SN information with ultrasound images proved to be feasible and technically successful. However, significant technical limitations were shown in freehand-SPECT quality as compared to SPECT/CT and fusion precision (registration error 0-20mm).
Figure 3: StealthStation as example of a surgical navigation system to provide surgeons the ability to visualize and track in real-time their surgical instruments relative to a patient’s specific anatomy.

Primary tumour localisation
In addition to AR for SN procedures, the freehand-SPECT application that combines real-time imaging with preoperative images or navigation, has also been used for primary tumour localisation as described in this paragraph.

Radioactive seed localisation
Radioactive seed localisation (RSL) is used to mark primary and neoadjuvant systemically treated breast tumours or lymph nodes. A radioactive $^{125}$Iodine ($^{125}$I) seed of approximately 8 MBq is implanted in the tumour as marker using ultrasound or stereotaxic guidance. This enables radioguided tumour excision with a gamma probe and replaces the wire-guided tumour localisation. Freehand-SPECT has been used for RSL in the Netherlands Cancer Institute to localize $^{125}$I-seeds and to measure the marker depth. This modality was introduced in different phases where first in the preoperative setting the $^{125}$I-seeds were localized to facilitate an intratumoural tracer injection for the SN procedure. In a subsequent study, ex vivo breast cancer specimen
were evaluated to assess the accuracy of localizing the seeds within the specimen. [34, 35] Currently, an in vivo study is in progress that aims to assess the possibilities for intraoperative freehand-SPECT use. The accuracy of the reconstruction depends on various factors and can be more or less accurate (i.e. marker depth, marker radioactivity) but it is mostly within 5mm.

Thyroid and parathyroid surgery

Freehand-SPECT was first used for thyroid disease in a feasibility study using both freehand-SPECT images and real-time superimposition on the ultrasound images in Jena University Hospital, Germany. This study had as purpose to report on the initial experiences regarding freehand-SPECT/US fusion. All examinations were technically successful and in 18 of 34 examinations the automatic co-registration and image fusion showed no discrepancy. No discrepancy means that there was no mismatch between the SPECT image of the thyroid and the ultrasound image of the thyroid. Only minor limitations in fusion offset occurred in 16 patients (mean offset 6.7mm SD 3mm, Range 2-10mm). [36]

Another study demonstrated the feasibility of 3D mapping in patients with parathyroid adenomas. A total of five parathyroid adenomas were successfully located with SPECT/CT using approximately 750 MBq $^{99m}$Tc-SestaMIBI as tracer. Freehand-SPECT allowed intraoperative detection of all adenomas, and subsequently successful parathyroidectomy was accomplished. Parathyroid hormone level decreased intraoperatively in all three patients. This preliminary study demonstrated that intraoperative localisation of parathyroid adenomas is feasible using the freehand-SPECT technology, thus allowing an image-guided parathyroidectomy. [37] Another study performed in Valencia, Spain reported about 2 parathyroid adenomas where freehand-SPECT provided useful information about the depth of the lesions to provide minimal invasive radioguided surgery [38].

Paraganglioma

In paraganglioma, the use of freehand-SPECT was reported in only one single case. A patient showed 2 foci of uptake of I-123-MIBG next to the left renal vein in a diagnostic scan, corresponding to paragangliomas. In the operating room, freehand-SPECT guided the surgeon to the resection of both lesions. The system was of additional value in planning the operative access to the region of interest and in determining the depth of one lesion for precise and more rapid extirpation. Furthermore, it confirmed no residues in the operating field after resection of the tumours. [39]
Neurosurgery or neuroradiation therapy

Neurosurgery is one of the most demanding surgical specialties in terms of precision requirements and surgical field limitations. [40] The brain has the advantage compared to other areas that it is a relatively fixed structure within the bones of the skull. Consequently, neuronavigation gained popularity in an earliest phase in the introduction of navigation for medical purposes.

In 2002, seven patients were included for a study to visualize speech-eloquent areas during neurosurgery with the use of preoperative PET and functional-MRI. Functional 2-[18F]-2-desoxy-D-glucose (FDG) PET images were integrated into the MRI-based neuronavigational system of BrainLAB (VectorVision) and could be transferred exactly to the operative field. Preoperative functional images indicated the speech eloquent areas by imaging under stimulation of the specific task-related neuron networks during image acquisition. A star shaped tool was attached to the headrest as a rigid reference point during surgery to achieve real-time imaging. The relative position of the pointing probe and the specific areas in the brain were real-time visualized and enabled navigation. This study demonstrated a method where preoperative functional imaging could be used to define specific areas, this is usually performed by keeping the patient awake during the procedure and have the patient perform specific tasks. [11]

Head and Neck tumour resection

As mentioned before, surgery in the head and neck area is highly complex due to all the critical structures. A study from Feichtinger et al. presented a new method of matching FDG PET and CT datasets on a commercially available navigation system for image-guided intraoperative navigation (StealthMerge, Medtronic, Louisville, USA) in the head and neck area. Six patients with a primary T4b oral cavity carcinoma with extension to the pterygoid muscles and pterygoid plates or primary T4a carcinoma of the maxillary sinus and nasal cavity with invasion of pterygoid plates, infratemporal fossa or sphenoid were included. StealthStation TREON plus was used for navigation and image fusion was done on the workstation monitor using the software of the navigation system StealthMerge. (Figure 3) This study aimed for clear resection margins, which was validated by cryosection analysis. Additional image-guided resection of tissue was performed to reach a minimal tumour distance of 5mm. In this limited number of patients it seemed useful to use image-guided PET/CT navigation during these procedures, although further clinical trials are required. [12]
Limitations

Optical imaging and navigation do have some general limitations. The first thing that users should be aware of is that there is always a line of sight required between the fiducials and the optical tracking system, commonly a pair of stereo infrared cameras. When there is an obstruction of this line of sight, for example caused by blood on the fiducials or a person/instrument, tracking fails. A second point of attention is mismatch of the AR view and the patient’s anatomy due to registration error and patient movement/deformation. The registration error of the preoperative imaging data and the optical image was described in two studies. [27, 28] This is described for mismatch of the preoperative SPECT/CT on the patient by means of tracker misplacement. This mismatch could result in confusion on the location of the SN. The mismatch in projection of the SPECT image on the patient originates in the registration step of the 3D radioactivity map with the optical image by an optical tracking target placed on the patient both during image acquisition and 3D navigation/visualisation. This tracker placement should be very precise because a small angular or translational misplacement of the tracker might result in relatively large errors. In the urological setting logistical challenges were encountered that needed further optimisation, such as the positioning of the probe tracker and the positioning of the target tracker relative to the patient and the endoscope. It was recommended that further studies are needed in order to determine the overall accuracy and sources of error so that the process can be optimized for routine use. [27] The errors are also caused by tissue deformations or movements of the patient during or after the scanning process resulting in a mismatch between anatomical structures and the reconstruction. If such artefacts occur because of patient movement, instrument navigation towards targets will be inaccurate. In this setup counting with an intraoperative image modality that can acquire images any time during the procedure like freehand-SPECT improves guidance. [23] For example in breast cancer the tissue is highly deformable and movement can easily occur, and accordingly, requires several image acquisitions during a surgery. [37]

A study from Wendler et al. in 2010 addressed several technical required improvements. The freehand nature of the acquisition of freehand-SPECT still yielded at that time false-negative and false-positive findings. Accordingly, further research was directed at optimizing methods to classify good and bad acquisitions and thus provide better feedback on the quality of the scan. A problem that was experienced was the proximity to the injection site that apparently played an important role in the false-
negative findings of the validation study. Unfortunately at this time, neither changing the thresholds nor altering the defined filter range made it possible to separate the SN from the injection site. [16] Over the years more advanced reconstruction algorithms have been incorporated and results have improved gradually, whereas know continuous image reconstructions are provided to real-time guide image acquisition.

Inter and intraobserver variation also needs to be assessed. It was noted by Bluemel et al. that in that particular study for two patients out of 40 patients the scanning process had to be repeated because of poor image acquisition. In this respect, the surgeon did not follow the scanning protocol properly and moved the gamma probe too fast over the region of interest. It is important to mention that in this study all freehand-SPECT users were previously trained in the clinical use of the freehand-SPECT system, resulting in an average scanning time of 2 min per imaging procedure. [19] A different study further assessed the influence of training novice users on scanning accuracy, and concluded that an intensive short training would be sufficient for accurate results. [41]

Neuronavigation does have significantly less influence of tracker or target movement thanks to the rigid structure of the skull. However, as soon as the skull is opened the brains are moved (brain shift). Further during the surgery there is risk of movement of the areas of interest. Unfortunately no new imaging is possible because only preoperative images are used in the navigation setting. To date, no mobile intraoperative PET system is available, but work has been done in this direction. [42]

The variety of clinical AR applications is wide-ranging. In general, studies reported in the present review conclude and underline that the technique is feasible and promising. However, the application in small patient groups in combination with preliminary data requires additional studying and improvement of this technique. Indeed, major limitations are related to the fact that a significant part of the data is acquired in the learning phase of using the technique and that the sample size is not sufficient to demonstrate significant improvements in clinical outcome for patients. We believe that larger multicentre studies are needed to demonstrate the additional clinical value of implementing freehand-SPECT, or the preoperative image-guided surgery options.

Developments

General developments

A completely different approach not included in this review is total body intraoperative imaging with navigational options. The expenses of such surgical solutions are currently very high but the options extend the possibilities with the mobile AR methods. An
An overview of intraoperative PET/CT using Advanced Multimodal Image-Guided Operating (AMIGO) suite is provided by Tempany et al. [43] This method allows navigation using MRI, CT, or PET scans acquired at the operating room.

Other mobile devices, like Percunav (Philips, Best, The Netherlands) or the Logiq E9 (GE, Milwaukee, WI, USA), also enables augmented reality. These devices have the option to combine PET/CT scans with the real-time ultrasound images by electromagnetic tracking. However, currently there are no publications and results of this technique available.

In addition to augmented reality solutions based on 3D data for radioguided surgery there are other alternatives to aid these specific surgical procedures. These devices generate AR visualisations by merging two 2D images and thus they do supply similar functionalities with a (small) overlay error due to the dimensionality of the images used. A portable gamma camera (Sentinella, Oncovision, Valencia, Spain) can also be equipped with a stereo optical camera attached to the site of the gamma camera and a software algorithm projects the optical image on the scintigraphic image. [44] The hybrid portable gamma camera proposed by Lees et al. uses a mirror to reflect the optical image form within the pinhole collimator to a CCD chip and visualizes in this way two aligned images onto top of each other (scintigraphic and optical image) [45, 46] These devices also aim for more accurate and clear intraoperative guidance comparable to the devices described in this overview. Fluorescence is another (non radioactive) imaging method currently used for various indications with the advantage of high resolution close up imaging (optical imaging). Recently, it was introduced as a hybrid approach in the combined form of indocyanine green-99mTc-nanocolloid (ICG-99mTc-nanocolloid). Based on its radioactive signature such hybrid tracers preserve the possibility for perioperative imaging using conventional gamma cameras, SPECT/CT, and portable devices. At the same time the added fluorescent signature leads to an improved SN detectability during surgery. [47, 48]

**AR guided SN Biopsies**

In more recent publications on freehand-SPECT, the use of a portable gamma camera for SPECT acquisition in combination with an ultrasound device for real-time fusion of the two modalities has been described. [49] This development enables radioguidance to the target or the structure of interest and high-resolution imaging by means of ultrasound to visualize the exact anatomical structure. In theory, this development allows higher resolution acquisitions in a shorter time interval. [50, 51] And in practice,
this method allows image-guided core needle biopsies or fine needle aspiration cytology guided by freehand-SPECT imaging together with ultrasonography. [32, 36, 52] In the study from Freesmeyer et al, the initial results of real-time ultrasonography and freehand-SPECT fusion was evaluated and proved technical feasible. [36] The indications for freehand-SPECT are mostly in the surgical field but a shift might occur towards radiological interventional procedures. If this proves feasible, one of the basic requirements of introducing AR described by Sielhorst et al. is met. It provides a significant benefit for a particular phase in the total workflow. We believe that treatment options where a surgical procedure can be omitted by introducing a radioguided interventional procedure will show a clear beneficial aspect of this type of AR in the clinical workflow and therefore its introduction could gain significant momentum.

Neurosurgery
For neurosurgery one of the most important aspects is limiting damage while removing the target lesions. To improve surgery there is a trend towards integration of multimodal imaging more functional information during surgery. Functional MRI and PET can guide surgeons in surgery by displaying functional information during surgery. Augmented reality surgery for brain surgery can register multimodal patient data with atlases and potentially improve surgical outcome in terms of morbidity by providing a fused visualisation of several modalities and sorts of information. [53]

Conclusion
AR is quickly adapted and developed for nuclear medicine. Combining different modalities demonstrate useful applications for clinical applications in both interventions and surgery although larger studies are required for prove of real clinical benefit.
Table 1: All relevant publications where AR is described in the field of nuclear medicine and molecular imaging using mobile devices.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Indication</th>
<th>Patients</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
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<td>2007</td>
<td>Technical</td>
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<td>Freehand-SPECT w/gamma probe</td>
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<tr>
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<td>SN Oral Cancer</td>
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<td>Parathyroid</td>
<td>3</td>
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<td>Technical</td>
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<td>SN Breast</td>
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<td>Freehand-SPECT w/gamma probe</td>
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<tr>
<td>Gardiazaabal et al. [56]</td>
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*RSL: Radioactive seed localisation, SN: Sentinel node*
References

1. Milgram P, Kishino F. A taxonomy of mixed reality visual displays. Trans Inf Syst. 2015;E77-D:12.


