Review Article

Nuclear Medicine Physics: Review of Advanced Technology

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This review aims to provide a brief, comprehensive overview of advanced technologies of nuclear medicine physics, with a focus on recent developments from both hardware and software perspectives. Developments in image acquisition/reconstruction, especially the time-of-flight and point spread function, have potential advantages in the image signal-to-noise ratio and spatial resolution. Modern detector materials and devices (including lutetium oxyorthosilicate, cadmium zinc tellurium, and silicon photomultiplier) as well as modern nuclear medicine imaging systems (including positron emission tomography [PET]/computerized tomography [CT], whole-body PET, PET/magnetic resonance [MR], and digital PET) enable not only high-quality digital image acquisition, but also subsequent image processing, including image reconstruction and post-reconstruction methods. Moreover, theranostics in nuclear medicine extend the usefulness of nuclear medicine physics far more than quantitative image-based diagnosis, playing a key role in personalized/precision medicine by raising the importance of internal radiation dosimetry in nuclear medicine. Now that deep-learning-based image processing can be incorporated in nuclear medicine image acquisition/processing, the aforementioned fields of nuclear medicine physics face the new era of Industry 4.0. Ongoing technological developments in nuclear medicine physics are leading to enhanced image quality and decreased radiation exposure as well as quantitative and personalized healthcare.

Keywords: Nuclear medicine physics, Advanced techniques, Theranostics, Precision medicine, Deep learning, Personalized healthcare

Introduction

1. Overview of nuclear medicine physics

Nuclear medicine physics (NMP) encompasses many research areas, including atomic/nuclear physics (e.g., various radioactivity decay modes), hardware-related fields (e.g., radiation detectors and related electrical instruments), counting statistics/systems, software-related fields (e.g., digital image processing), tracer kinetic modeling, and internal/external radiation dosimetry [1]. Due to the large coverage with limited space and time for the 30th anniversary Progress in Medical Physics (PMP) review series, this review focuses on recent advances of NMP for in vivo NM imaging. Before leaping from the discovery of radioactivity to modern NMP, it is worth summarizing the history of NM and NMP.

2. History of NM and NMP

Radioactivity was discovered by Henri Becquerel in 1896 (one year after the discovery of the X-ray by Roentgen),

and shortly thereafter, Marie Curie (mother of Irene Curie) coined the term *radioactivity* and developed the theory of radioactivity; both were awarded the Nobel Prize in Physics in 1903 [2]. Thereafter, there have been dramatic achievements in many aspects of NMP.

Artificial radioactivity was invented by Irene and Joliot Curie in 1934, and in the meantime, Ernest Lawrence invented the cyclotron (i.e., device for accelerating atoms at high speed to produce radioisotopes) in 1930 and continued to develop the medical cyclotron. These two inventions led to the production of radionuclide for medical use (e.g., I-131 and Tc-99m) [2,3].

Ernest Rutherford identified alpha and beta rays and proposed the nuclear theory of the atom, which is the basis of not only NM therapeutics, but also recent cutting-edge technology of theranostics, and was awarded Nobel Prizes in Chemistry in 1908 and 1919 [4].

NM first gained public recognition through radioactive iodine (RAI) research by Hertz and Roberts [3,5]. For NM imaging, Hans Geiger invented the first practical scintillation detector called the Geiger counter using the Geiger–Muller tube in 1928 [6], which is the basis of modern radiation detection systems and led to the first NM imaging study for mapping thyroid iodine uptake [7]. Cassen et al. [8] developed the first rectilinear scanner with a motor-controlled/collimated radiation detector, and printer, founding the basis of single-photon emission computed tomography (SPECT) and coincidence detection of positron emission tomography (PET) [3,9,10]. The first gamma camera was the scintillation camera developed by Hal Anger [10].

Paul Dirac discovered the existence of annihilation positrons and received the Nobel Prize in Physics in 1933 [3] (PET is based on the coincidence of an opposite-direction 511-keV annihilation photon pair originating from this phenomenon). More recently, PET was invented by Kuhl and Edwards [11] in the early 1950s, who performed a preliminary version of reconstruction followed by coincidence imaging without lead collimation [12]. In the meantime, the concept of emission/transmission tomography was also developed into SPECT [3].

3. Two major branches of NM imaging

Unlike other structural imaging, such as X-ray computerized tomography (CT) or ultrasound, traditional NM imaging (i.e., gamma camera/SPECT) and PET provide images reflecting physiological functions. To this end, both PET and SPECT require a radiopharmaceutical to be distributed into the whole body or organs-of-interest of the subject depending on the purpose of the imaging test.

Although the author will discuss NMP in both modalities, modern NM imaging is dominated more by PET, due in particular to the high image quality in terms of the signal-to-noise ratio (SNR)/spatial resolution. Therefore, the author will focus more on NMP advances of PET. Broadly speaking, most innovative physical methods are first developed for PET imaging and are then incorporated into traditional NM imaging.

4. NM imaging as picomolar−sensitive molecular imaging

Before addressing NMP advances in image acquisition/reconstruction and related hardware/software developments, an overview is provided of PET, which is a major component of modern NM/NMP.

As summarized by Jones [13], PET is a quantitative imaging modality with picomolar sensitivity. Whereas other imaging modalities focus mostly on structural imaging of the human body, NM imaging (PET in particular) focuses on physiology, metabolism, drug distribution, and molecular pathways/targets. At present, PET is widely considered the most sensitive technique available not only for noninvasively studying how the human body functions in terms of physiology, metabolism, and molecular pathways, but also for studying which in vivo pathologies (e.g., amyloid and tau for Alzheimer's disease) are in the human body. In this regard, PET scans sometimes lead other modalities in terms of disease detection and early diagnosis. PET tracers should thus be developed to address clinical research, diagnostic questions, and challenges to properly distribute radiopharmaceuticals in the body (mostly by injection, but sometimes by swallowing and inhalation for organs/tissues of interest).

As mentioned, gamma camera (or SPECT) imaging is another major NM imaging modality. Because most gamma tracers can be easily synthesized using a generator-based radioisotope (mostly for Tc-99m), there are many useful NM imaging tests using this modality. Nonetheless, because many technological aspects are led by PET, the author focuses first on recent advances in PET image acquisition/reconstruction/processing.

5. Limitations and solutions for NM/PET imaging

Although PET is one of the most molecular-sensitive imaging techniques and has significantly better sensitivity and spatial resolution than gamma camera/SPECT owing to collimation-free three-dimensional (3D) imaging, the counting statistics are still intermediate in that PET is a photon-deficient modality compared with other modalities, such as X-ray CT. Therefore, PET has a low SNR and potential limitations in reducing the imaging time and radiation dose. In addition, there are well-known fundamental limitations of PET spatial resolution [14] compared with other structural imaging, such as X-ray CT and magnetic resonance (MR) imaging due to many factors, including the physical size of the detector elements, non-collinearity of the line of response (LOR), and positron range.

To resolve these limitations in PET and PET/CT imaging, NMP has evolved greatly over the last two decades thanks to hardware developments of hybrid imaging [15] free from PET transmission imaging, faster detector systems [16-20], and corresponding software developments [21]. The present standard of PET/CT scanners has incorporated many advanced hardware/software methods in recent decades. First, benefits are provided by the flexible structures of iterative algorithms, including ordered subset expectation–maximization (OSEM) and maximum a posteriori (MAP) algorithms, which have made it possible to achieve a trade-off between SNR and spatial resolution and to further consider noise penalization, respectively. Second, there have been methods for increasing the effective sensitivity of the PET camera, including the time-of-flight (TOF) technique and whole-body PET. Third, there have been methods for improving the spatial resolution of the PET camera: the point-spread function (PSF), depth-of-interaction (DOI),

and partial volume correction (PVC) techniques.

These developments in NMP have led to better image quality in terms of both sensitivity and spatial resolution, and have thus improved small lesion detectability (in tumor imaging, including FDG PET) [22], in vivo pathology detectability (in neurodegenerative disease imaging, including amyloid and tau PET) [23,24], and the general quantification accuracy of PET uptake.

6. Standardized uptake value metric

The Standardized uptake value (SUV) is a well-established (semi-)quantitative measure for PET, playing an especially large role in whole-body oncology PET studies. The SUV is a ratio between concentrations and can be calculated by the activity concentration in a tumor ([Bq/mL]/injected activity [Bq]×body weight [g]; mL: milliliter, Bq: Becquerel). Maximum uptake in a tumor (i.e., SUVmax) is one of the most frequently used metrics not only because it can be easily measured, but also because its diagnostic accuracy is the highest among many FDG PET metrics. Recently, the metabolic tumor volume (MTV) and total metabolic burden (MTV×SUVmean) within the volume called total lesion glycolysis are considered additional useful metrics.

Because SUVmax is sensitive to not only to the PET camera characteristics, but also noise and reconstruction parameters, 1-mL spherical volume-of-interest (VOI)-based maximum uptake is also used and referred to as SUVpeak. PERCIST criteria adopt this as the metric of choice and highly recommend it for tumor assessments between subjects/centers and baseline/follow-up studies [25].

7. Scope of this review

This review offers a brief, comprehensive overview of advanced technologies of NMP to provide knowledge to medical physicists, NM physicians, and researchers. Because NMP has both hardware and software aspects, the author focuses on recent developments/advances in both aspects. Developments in image reconstruction, especially TOF and PSF, have potential advantages in terms of image SNR and spatial resolution. Regarding hardware systems,

modern detector materials and devices, including lutetium oxyorthosilicate (LSO), the silicon photomultiplier (SiPM), and NM imaging systems (PET/CT, PET/MR, digital PET, whole-body PET), will be addressed.

NMP has distinctive characteristics of molecular imaging and multidisciplinary and multicenter study-related physics (in particular, harmonization methods) compared with other MP subspecialties. In this regard, the review also includes current perspectives of cutting-edge NM techniques (e.g., theranostics and deep learning [DL] in NM). For the review specific to the Korean NMP society, the author will discuss future challenges and roles of the Korean NMP society as benchmarking with other NMP societies, and will suggest corresponding perspectives for the Korean NMP society in the Discussion and Perspective section.

NMP Advances in Image Acquisition/Reconstruction

1. Technique for increasing SNR

1) TOF PET

Whereas a conventional PET camera uses coincidence information only for determining the LOR of both opposite-direction annihilation gamma rays, TOF PET resolves the difference in arrival time between both gamma rays to determine the approximate annihilation position on the LOR. By reducing the uncertainty of the annihilation position, TOF PET can improve the effective sensitivity and SNR, which is proportional to the square root of noise equivalent count (NEC) [26], where NEC is reciprocal to the uncertainty. Moreover, TOF PET requires neither massive modification of the PET detector geometry nor other image degradation (e.g., spatial resolution). Rather, the increased SNR permits improved trade-off between SNR and spatial resolution. Therefore, TOF PET has become the standard PET imaging technique.

Although the principle of TOF was proposed earlier, its practical implementation was delayed by several decades [27]. Only prototypes during the 1980s [28-34] used BaF2 or CsF as scintillation crystals for the purpose of reducing decay time compared with high-density scintillation crystals (i.e., bismuth germinate or bismuth germanium oxide [BGO]-based systems). However, these scintillation crystals have limited stopping power and light output; thus, these systems suffered from poor sensitivity and spatial resolution. Therefore, a BGO-based PET camera was the method of choice during that period, and only limited clinical studies and research-based experiments were conducted on TOF PET cameras [28].

LSO became available in the 1990s, thus making it possible to implement practical TOF PET, which requires not only high timing resolution, but also adequate stopping power and energy resolution. The combination of faster detector materials (e.g., LSO or lutetium-yttrium oxyorthosilicate [LYSO]), faster photomultiplier/electrics (i.e., with high temporal resolution), and faster computing power [35] was a critical prerequisite for achieving the clinically useful TOF technique. In addition, list-mode-based iterative reconstruction algorithms played an important role for TOF PET with the assistance of an iterative approach, which has a flexible pipeline in its iterative nature and can thus modify the algorithm to incorporate TOF information.

Due to the patent by Siemens, a similar variation of the lutetium-based scintillation crystal (i.e., LYSO) was introduced in the early 2000s by other vendors. Taken together, TOF PET became the method of choice in the 2000s [16-20], providing a timing resolution of 350–550 ps and a localization uncertainty of 5–8 cm. With improvements in the related electrics, the uncertainly is decreasing daily (~200 ps at present).

2) Whole−body PET

Whole-body PET is the epitome of increased sensitivity in PET. The world's first whole-body PET/CT scanner was developed by Cherry et al. [36]. By increasing the geometric coverage (known as the solid angle in NMP) to encompass the entire body, the sensitivity could be increased by a factor of approximately 40 for whole-body imaging. Moreover, significant advances in the TOF technique arising from ongoing improvements in timing resolution may have contributed to achieve improved effective sensitivity. The overall sensitivity gains are considered to be more than hundreds of times greater than current state-of-the-art (i.e., bed-position-based) PET cameras.

Cherry et al. [36] also demonstrated how this step change

in sensitivity with unprecedented count density affects the way PET is used both in clinical research and patient care. His colleagues also reported the first-in-human imaging study using the 194-cm axial field-of-view (FOV) whole-body PET/CT scanner called the EXPLORER, obtaining the total adult body in a single acquisition, confirming whole-body pharmacokinetic studies with 1-s frame durations [37]. Moreover, they suggested that large gains in sensitivity and SNR can be alternatively used for low-dose (25 MBq or less within the FOV) or short-scan-duration (~1 min or less) PET imaging.

2. Techniques for improving spatial resolution

1) PSF iterative reconstruction and DOI technique

PSF-based iterative reconstruction uses a system matrix to couple coincidence counts along each LOR to activities in neighboring voxels to account for all processes affecting the LOR, including the positron range, photon non-collinearity, and detector geometry-based effects, such as inter-crystal scattering/penetration [22,38]. In this regard, the central LOR with less crystal penetration and the off-central LOR with more crystal penetration are sometimes adopted to illustrate different PSF kernel sizes between central and off-central LORs. PSF can achieve both (transaxial) uniformity and improvement in spatial resolution.

In this regard, PSF can address the limited spatial resolution and also resolve the partial volume effects (PVEs) that affect both the visual and quantitative analysis of PET [39]. Therefore, PSF-based iterative reconstruction is considered to have the most significant impact on SUV measurements. For example, PSF-based reconstruction without post-smoothing can increase SUVmax by approximately 70% in small lesions of breast cancer [40] and lung cancer [41].

However, there is another factor of image resolution degradation: the DOI effect, which is the increase in the LOR location uncertainly mostly due to inter-crystal penetration. Because preclinical imaging has a significantly small relative bore size (compared with the body size of small animals) for a larger solid angle than human PET, this problem becomes more significant as the bore size decreases and the solid angle increases, and there may be a higher probability of an off-centered LOR from distant crystals. With

whole-body PET as the method of choice in the near future, DOI correction is a challenge in both preclinical and clinical PET imaging.

2) PVC

Similar to PSF modeling, PVC can be implemented in both reconstruction and post-reconstruction steps. In addition, there is post-reconstruction-based PSF modeling, such as Philips PSF reconstruction (whereas reconstruction-based PSF modeling is for Siemens HD PET and GE Sharp-IR).

As discussed in a systematic review by Erlandsson et al. [42], there are a variety of PVC methods. In a comprehensive review by Rousset et al. [43], many useful PVC methods were summarized for the combination of post-reconstruction-based/reconstruction-based methods and region-based/voxel-based methods. These methods include the classical recovery coefficient method [44], region-based method of the geometric transfer matrix (GTM) [45,46], voxel-based methods of iterative deconvolution with noise constraints [47-50], and a Bayesian approach [51]. Because the Bayesian approach can penalize noise by *a priori* knowledge in an iterative reconstruction pipeline, it will be addressed in the section '2) MAP algorithm'. Recently, a voxel-wise version of the GTM method called the region-based voxelwise (RBV) PVC method and its extension have been frequently used in literature [23,52] and Freesurfer 6.0.

In a systematic review of PVC in oncology by Cysouw et al. [53], partial volume (PV)-corrected PET may be used as an adjunct (i.e., neither a replacement for PV-uncorrected PET nor a routine application of PVC in standard clinical practice). One major reason for the adjunctive use may be the variety of PVC methods and that oncology PET is usually PV-corrected with voxel-based iterative methods or approximated recovery coefficients estimated by a simpler structure (e.g., sphere).

In contrast, GTM- and RBV-based approaches have been widely used in neuroimaging (in particular, for ADNI cohort PET image analysis) in conjunction with proper cortical parcellation (e.g., Freesurfer software). However, more attention and effort should be paid to potential anatomical image segmentation/registration errors and tissue inhomogeneity [43]. As mentioned in a systematic review by

Erlandsson et al. [42], additional effort should also be made for non-uniform regions [52,54] and correction for tissue fraction [55,56].

For more detailed information, the reader is referred to systematic reviews by Erlandsson et al. [42], Rousset et al. [43], and Cysouw et al. [53].

3. Iterative reconstruction algorithms

1) Expectation–maximization algorithm

There are conventional iterative reconstruction algorithms of the maximum-likelihood expectation–maximization (MLEM) algorithm and its modification for faster convergence called ordered-subset expectation–maximization (OSEM). This class of methods exhibits significant image quality improvement compared with classical analytical methods, such as filtered back-projection.

Expectation–maximization (EM) methods can improve the recovery coefficient of the SUV of lesions as the number of iterations (or iterations×subsets in OSEM) is increased. However, there is a well-known trade-off between the spatial resolution and SNR. Specifically, the image noise level increases with increased iterations, decreasing small lesion detectability and increasing false positive findings.

Due to the flexible structure of iterative reconstruction pipelines, these methods can be optimized in terms of the trade-off of quantitative accuracy and visual lesion detectability for best clinical practice. Specifically, we can reduce the image noise by compromising the SUV accuracy (e.g., slight SUV underestimation in small lesions) by early-stopping iterations.

2) MAP algorithm

As mentioned above, the PSF and increased number of iterations can significantly increase SUV-related quantitative metrics in PET. Due to the goal of PSF iterative reconstruction, reconstructed PET images are usually used as is (with no filtering or all-pass filtering) or with relatively small kernel-based smoothing. To resolve both the potential degradation of SNR and incomplete recovery by early termination by PSF iterative reconstruction, Bayesian penalized likelihood (BPL) iterative reconstruction (a class of MAP algorithms), and the PVC method [51] have recently been

suggested to improve tumor detection and recovery coefficients while maintaining the stability of SUV metrics.

As the name *MAP/BPL* implies, this class of methods takes advantage of prior knowledge of the image for the noise penalty function (e.g., non-negativity, and small image intensity changes between adjacent voxels), such as BPL iterative reconstruction marketed as Q.Clear by GE [39]. As a result, this class of methods permits effective convergence of image accuracy by suppressing noise [38,51]. In this regard, it is not necessary to comprise the iterative reconstruction by early termination due to its robustness against noise, that is, high recovery coefficient with low noise. However, physicians sometimes feel that the resulting images include artificial patterns. Therefore, many institutions that employ MAP reconstruction also perform tandem OSEM reconstruction.

4. NMP technique for SUV harmonization

1) SUV harmonization problems

Although the development of NMP has led to better image quality in a TOF-based and PSF-capable PET scanner, there is an unwanted side effect of not being able to directly compare the quantitative measures between PET camera generations (i.e., non-TOF/non-PSF generation vs. TOF/PSF generation).

Indeed, there are a number of physical factors for the SUV measurement error and difference [57-60] during the entire imaging process. Specifically, these factors include image acquisition/reconstruction parameters, region-of-interest (ROI) or VOI methods, SUV normalization factors (body weight, lean body mass, or liver SUV-based SUV ratio), and image resolutions dominated by PET camera differences (in particular, depending on whether PSF is applied).

2) SUV harmonization solutions

Among many NM societies, the European Association of Nuclear Medicine (EANM) and EANM Research Ltd. (EARL) established a systematic harmonization approach, as reviewed by Boellaard et al. [57-59] and Aide et al. [60]. In this review, among the technical causes of errors and differences in SUV calculation, reconstruction variability has been noted as a prominent factor in the past decades due

to the aforementioned software/hardware improvements in NMP.

Above all, the significantly increased spatial resolution by present PSF corrections is considered the most important factor affecting the scanner differences, making direct comparison more difficult. To better handle the camera differences, EANM suggested producing two reconstructions: one optimized for maximum lesion detection and the other optimized for quantitative analysis [61]. However, performing two reconstructions for every PET/CT scan may be not clinically feasible.

Therefore, there have been several approaches for post-reconstruction-based SUV harmonization. Most harmonization is based on identifying the optimal smoothing kernel for post-reconstruction that matches the recovery coefficient (and bias) of higher-resolution scanners to that of lower resolution scanners.

Joshi et al. [62] performed brain PET image harmonization on the United States Alzheimer Disease Neuroimaging Initiative (US-ADNI) by comparing the optimal smoothing kernel for matching the digital (i.e., bitmap-based) 3D Hoffman phantom to the corresponding PET image. Thereby, one can achieve brain PET SUV harmonization between various PET camera generations. Conversely, this information can be also used for PVC by considering the spatial blurring of real (PVE-free) uptake as the measured PET uptake [23,52].

For whole-body PET, there are a number of studies using anthropomorphic phantoms with a hot cylinder or spheres for post-reconstruction-based recovery-coefficient-matching harmonization [61,63-66]. To this end, the NEMA IQ phantom or Jaszczak cylindrical phantom (equipped with small hot spheres/cylinders) is frequently used with various lesion-to-background ratios (e.g., 2.5:1–8:1). A dedicated post-reconstruction algorithm (marketed as EQ-filter; Siemens Healthineers, Erlangen, Germany) and other third-party tools are also available. There is a report of <7% between-scanner differences by both harmonization methods of post-reconstruction-based methods and double-reconstruction methods [61].

NMP Advances in Detector Elements

1. Development of detector elements in PET (LSO and LYSO)

LSO was first used in small-animal PET [67], in a brain scanner [68,69], and in a whole-body PET scanner [70,71]. As mentioned above, LSO was in the center of TOF PET development due to its superior characteristics in terms of sensitivity, spatial resolution, reduced deadtime (or fast decay time), and random coincidences. Fast photomultiplier tubes (PMTs) and improved electronics led to practical TOF PET systems [72,73]. As mentioned above, LSO- and LYSO-based TOP PET finally became the standard PET method in the 2000s [16-19].

2. Development of detector elements in digital PET and PET/MR (SiPM)

The SiPM will be addressed in PET/MR and Digital PET.

3. Development of detector elements in gamma camera/SPECT (cadmium zinc telluride)

Whereas PET imaging has made a breakthrough with TOF/PSF and SiPM-based digital PET and PET/MR, most gamma camera detectors remained with an NaI(Tl)-based conventional system for many decades. Recently, the cadmium zinc telluride (CZT) solid-state detector-based SPECT camera has emerged and shown potential strength in physical performance, including high sensitivity and spatial resolution, outperforming conventional gamma camera scintillators in terms of energy resolution (i.e., better scatter rejection performance), and high count rate capability (>100 million photons/s/mm^2). CZT is a room-temperature semiconductor detector material that directly converts gamma (and X-ray) photons into electrons and holes.

Moreover, the quantification of myocardial perfusion is an emerging topic in nuclear cardiology with an expected diagnostic/prognostic incremental value, especially in coronary artery disease. Dynamic myocardial perfusion imaging-based coronary flow reserve or myocardial flow

reserve are known to be associated with adverse cardiovascular events independent of luminal angiographic severity [74]. The advent of a new dedicated CZT-based camera created a new opportunity for perfusion quantification in myocardial SPECT. In addition, small-organ imaging, such as breast and brain imaging, has also been attempted.

NMP in Hybrid/Advanced Imaging

1. PET/CT

Since the initial integration of PET/CT by Townsend (2008), hybrid PET/CT imaging has become crucial for clinically feasible routine PET imaging free from the time-consuming transmission PET scan, allowing PET to afford more efforts for emission scan. Moreover, PET/CT allows for essential multimodality imaging, providing both anatomical and metabolic information for oncology, neurology, and cardiology [15,22]. Now that PET/CT has become the standard and most common modality of PET imaging and has been installed worldwide, PET usually refers to PET/CT.

2. PET/MR and digital PET using SiPM

Thanks to the soft-tissue contrast of MR and tremendous technical advances in both PET and MR, the development of hybrid PET/MR systems has been a major focus in the past decade. However, there have been several challenges in the development of PET/MR [75,76]. First, conventional PET photodetectors (i.e., devices for multiplication of light produced by scintillation crystals) are based on PMTs that are susceptible to the strong magnetic fields used in the MR scanner. To avoid this problem, the first integrated PET/MR was implemented using a type of solid-state semiconductor-based photodetector called avalanche photodiodes (APDs). However, APDs (and SiPMs) have much smaller physical dimensions than PMTs; therefore, the remaining bore size (~60 cm) after PET was inserted in the MR was sufficient for patient scanning.

Whereas ordinary APDs have limited amplifier gain and poor timing resolution (~2 ms) and are thus unsuitable for TOF PET, Geiger-mode APDs (also known as SiPMs) are relatively free from these limitations. Therefore, SiPMs have become the current standard for PET/MR photodetectors.

Attenuation correction (AC) is another major physical problem in PET/MR, in contrast to CT-based AC, which is straightforward in older PET/CT systems. AC of bone has remained challenging for many years not only because bone is the critical structure of attenuation of the PET emission signal, but also because it has very low proton density (and thus a very low MR signal).

Several approaches have been proposed, including dedicated fast MR sequence (e.g., Dixon sequence), ultra-short time-to-echo (UTE)/zero time-to-echo (ZTE) MR, and a combination of both, and TOF-based AC [77-80]. However, Dixon sequence-based AC may suffer from bone AC error (>10% AC error and >30% quantification error in osseous structures adjacent to bone [75,81]) due to assigning the same AC coefficients for bone and soft tissue. In addition, UTE/ZTE MR suffers from severe noise.

Alternatively, we can use atlas-based methods [76,82] of retrospectively assigning bone information to the MR AC map. However, this approach has the potential limitation in that it requires previous knowledge for generating the bone template and an appropriate spatial registration (more specifically, spatial normalization and inverse normalization) tool.

In addition, there are potential lung segmentation errors, unrealistic uniform AC, and MR FOV truncation. To fully understand the limitations and perspectives of current PET/MR technology, readers are referred to a systematic review by Boellaard and Quick [75]. The author believes that these challenges can be overcome by DL approaches, as will be discussed in the final section.

Finally, digital SiPM (near one-to-one coupling of SiPM and crystal) has recently been introduced for commercialized digital PET (e.g., GE Signa PET/MR and Discovery MI PET/CT with SiPM, Siemens mMR with APD and Vision PET/CT with SiPM, Philips Vereos with SiPM). Thanks to near one-to-one coupling (2:1–1:1), digital PET can achieve improved spatial resolution and time resolution, permit high maximum count rates [83-85], and demonstrate higher image quality that can also lead to dose reduction [86,87].

3. Whole−body PET

Whole-body PET has already been described in NMP Advances in Image Acquisition/Reconstruction section.

NMP in Precision Medicine

1. NMP in theranostics (also known as theranosis)

1) Theranostics and personalized medicine

Molecular imaging-based personalized/precision medicine and a key technology called theranostics have been a well-established and important concept for individualized therapeutic strategies [88]. To avoid unnecessary/expensive treatments and to optimize patient treatment in terms of target localization and treatment methods, personalized medicine has been a major focus in recent decades [88].

Although theranostics molecular imaging (i.e., RAI-131) was introduced long ago (first performed in 1946), the term "theranostics", which has been used in recent decades (first used in the early 1990s), refers to a technique for a specific molecular-targeted therapy by combined diagnostic testing and therapeutic modalities, mostly based on PET or SPECT diagnostic imaging using the same molecule with therapeutics or a very similar molecule (also known as an analogue) as a therapeutic radiopharmaceutical [88-90].

Theranostics is performed mainly for individualized therapeutic decision-making, for attaining high efficacy, and for reducing adverse effects in a patient-specific manner. In this regard, theranostics is the epitome and key technology of personalized medicine [88].

Diagnostic imaging-based visualization/localization of therapeutic targets indicating which sites require treatment (diagnostic scan [90]) can help treatment outcome prediction and monitoring, confirming that the sites have been treated (post-therapy scan [90]), as well as help determine the best treatment strategy. By its nature, a tumor is heterogeneous within a subject as well as between subjects, and there are thus many challenges in the execution of targeted therapy in cancer [90]. In this context, a whole-body imaging-based approach may be beneficial; for example, a single tumor biopsy cannot capture all tumor heterogeneity without underestimating the genetic mutational burden,

subsequently contributing to treatment failure or drug resistance [88-90].

As the medical specialty of theranostics is well established as a molecular imaging-based personalized (i.e., specific molecular-targeted) therapy and has been for three-quarters of a century [88], we must focus on this new area of NMP. Theranostics for thyroid by RAI has been performed for differentiated thyroid cancer, contributing to modern tailored personalized management by providing a high therapeutic effect and by avoiding significant adverse effects [88,91,92]. SPECT/CT, which can provide the SUV by appropriate sensitivity calibration, can significantly improve the precision and sensitivity of whole-body iodine scintigraphy and in turn contribute to improved precision medicine [90].

Recently, somatostatin receptor-based theranostics has been studied for neuroendocrine tumors (NETs), for example, Lu-177 DOTATOC and DOTATATE-based treatment in conjunction with Ga-68-based diagnostic imaging [89]. In South Korea, several institutions have also established or practiced theranostics of NETs. In addition, Lu-177-based SPECT/CT imaging can be used for radiation dosimetry for assessing the therapeutic efficiency and unwanted radiation exposure to critical organs (e.g., kidney/bladder/red marrow).

For metastatic prostate cancer, for example, we have prostate-specific membrane antigen (PSMA) diagnostic ligands, including Ga-68 PSMA series for PET imaging and therapeutic ligands, including Lu-177 J-591 and Lu-177-PSMA-617 [89].

2) NMP perspective: dosimetry for theranostics

Because theranostics other than RAI is at the beginning stage, its role in NMP is not yet clear. However, the aforementioned internal dosimetry (e.g., Lu-177-based SPECT/CT for Lu-177 DOTATOC or DOTATATE-based treatment) has become much more important than conventional diagnostic PET or SPECT imaging due to its direct association with therapeutics per the nature of theranostics. General dosimetry may require whole-body organ delineation and multiple serial whole-body PET scans [93]. However, this may be intractable as routine practice for theranostics due to the much longer half-life of the therapeutic radioisotope

(e.g. Lu-177) than of F-18. Recently, the single time imaging-based dosimetry method [94] has reported low variability from more rigorous methods (i.e., multi-time-point-based exponential fitting for residence time calculation).

Because internal dosimetry is closely related to the estimation of external radiation, dosimetry may be the main NMP part in theranostics. Thanks to the development of related DL technique, we can also consider automatic delineation of target lesions and critical organs.

2. DL in NM precision medicine

1) Artificial intelligence, machine learning, and DL
Before discussing DL in NM, Artificial intelligence (AI)/ machine learning (ML)/DL must be explained. DL is a specific type of ML using a deep network (i.e., artificial neural network [ANN] with more than one hidden layer), and both are AI concepts [95]. For the history of ML, common algorithms, and reasons for using machine learning, readers are referred to the systematic review by Uribe et al. [96], which emphasizes traditional ML techniques, including naïve Bayes classification, linear regression, support vector machine (SVM), random forest, principal component analysis, k-means/hierarchical clustering, and ANN.

Although the principles of AI and ML have been proposed much earlier (first described in 1956), their practical implementation was delayed by several decades. In particular, DL suffered from a larger delay because higher computing power and sophisticated training algorithms [97] were required for the significantly larger number of training parameters than for the traditional ML algorithm.

In traditional medical image processing (as other biomedical research), only a specific algorithm provided by humans was used for learning features from medical imaging. Therefore, the performance was highly dependent on the domain knowledge and expertise of the user or programmer. In AI/ML, computers can learn features from observations (e.g., medical imaging data) based on a mathematical model and cost function by training unknown variables (e.g., weights in ANN and SVM), and further make statistical inferences from learning [96].

Unlike traditional ML, DL can learn features from data by training a deep ANN (in NM imaging, mostly based on a convolutional neural network [CNN]) without or with very little domain knowledge. Each layer of the CNN has multiple channels of convolution kernels that can learn specific filters that can extract hidden features from an image. As the layer becomes deeper, the extracted information is integrated into a higher level of the hierarchy (or larger scale) information. Thereby, deep learning can extract a large amount of useful information for classification, regression by convolution-based encoding, and image generation by further transposed convolution-based decoding (e.g., U-NET).

For more information on AI/ML, readers are referred to the aforementioned reviews by Visvikis et al. [95] and Uribe et al. [96]. For more information on DL, readers are referred to reviews by Visvikis et al. [95] and Choi [98].

2) Rise of ML/DL algorithms
The amount of biomedical data (medical imaging and radiomics/radiogenomic-related data) is rapidly increasing, thus forming availability of big data, which is the key ingredient for training ML and is particularly important for DL [98,99]. Advances in the theory of stochastic gradient (in an analogy of MLEM and OSEM) [97] made it possible to train ML with big data by faster convergence, which enabled us to train DL with a more complex structure more efficiently. Computing hardware development (including the central processing unit [CPU], graphics processing unit [GPU], and neural network Tensor Processing Unit [TPU] [35]) made it possible to train ML/DL epochs with big data, especially for sufficient epochs to converge the DL network.

3) ML/DL algorithms in medical imaging
Many systematic reviews [95-98] have indicated that recent advances in DL have impacted various scientific fields and demonstrated successful results in many areas. In particular, there is growing research and clinical interest in automatic medical image analysis, including radiomics and radiogenomics [100-116] that may reveal additional information that is not accessible even by experts [95].

4) ML/DL algorithms in NM imaging
As radiomics and radiogenomics have been the most representative approach for imaging-based precision medicine

in recent decades, the main objective of this evolution (also known as Industry 4.0) may be to assign medical imaging a larger role [95] as follows. Medical imaging should produce more useful information from imaging studies for precision medicine. More importantly, NM imaging should move beyond diagnosis (as addressed in the section of Theranostics) to be an essential integrative part covering all clinical decision-making systems (e.g., therapy planning/monitoring/assessment, predictive modeling, and stratification). With sufficient understanding of the rationale of DL in NM, the author would like to discuss more specific applications as follows.

5) DL application in NM 1: classification

Classification is one of the oldest and most extensively researched ML areas in NM (e.g., disease group classification or diagnosis/differential diagnosis, including automatic diagnosis of neurodegenerative diseases, such as Alzheimer's disease [24,107,108] and Parkinson's disease [109], and brain perfusion reserve decreases [110]). These methods can be easily extended for precision medicine, as the promising diagnostic accuracy (area-under-the-curve>0.9) may lead to automatic classification of the genotype and phenotype of tumors with higher accuracy than conventional methods, thus aiding decision-making for personalized medicine in an extended line of recent radiomics and radiogenomics studies [100-106].

6) DL application in NM 2: automatic segmentation and quantification

Precise and accurate automatic segmentation of lesion VOIs is a prerequisite not only for quantitative analysis, but also for precision medicine, as the accuracy of VOI can dominate the accuracy of subsequent quantification and decision-making. Indeed, many useful radiomics and radiogenomics features are extracted from well-delineated VOIs [100-106].

Although manual delineation may be the gold standard for this task, it is labor-intensive to delineate many VOIs for research or routine quantification purposes. Moreover, differences between raters and their expertise may lead to high inter-rater variability. CNN-based DL is considered one of the best solutions for accuracy and inter-rater reliability. Therefore, there have been a number of CNN-based segmentation studies for PET or CT segmentation for quantitative PET analysis [111-113], and CT segmentation for quantitative SPECT analysis [114]. Interestingly, U-NET has been extensively used in most studies as the generator for automatic segmentation. This may be due to the strength of U-NET in the automatic encoding of multi-scale features by combinations of convolution and strided-pooling layers, and in residual learning by skip connection between the encoding and decoding parts of the CNN.

7) DL application in NM 3: image generation

Image generation is a unique area of DL in which traditional ML technology and/or radiomics/radiogenomics technology cannot compete. Although the ordinary structure of a CNN may be sufficient for generating a binary mask of VOI segmented, recent image generation tasks are more complex (e.g., increasing SNR of low-dose PET [115,116], increasing spatial resolution of PET [117], and generating an MR-like mask from amyloid PET [118]). In this situation, a generative adversarial network (GAN) [104] architecture is useful and has thus been used by many previous studies [115-118]. It should be noted that the conditional GAN, which uses a realistic image as the input for CNN unlike the original (noise-based) GAN [97], is used for the purpose of medical image generation. Thereby, image generation can solve many of the aforementioned complex and seemingly impossible problems by conventional signal processing and ML on the basis of big data.

Interestingly, DL-based image generation can also be used to help image reconstruction. There have been several studies using U-NET or autoencoder-based CNN for generating a CT AC map using a TOF-based MLAA map not only for brain PET [119], but also for whole-body PET [120]. In addition, Gong et al. [121] performed Dixon and UTE MR-based AC map generation for PET/MR.

Discussion and Perspectives

1. Limitations of this review for in vitro NM

In addition to NM imaging, in vitro NM (mostly based on radioligand binding assay or radioimmunoassay) is worthy

of consideration as another component of NM. Although there also are NMP-related parts, including the gamma counting-based system in in vitro NM, they are not addressed in this review for the sake of brevity.

2. Limitations of this review on tracer kinetic modeling

Tracer kinetic modeling (TKIN) is a promising technique for NMP and NM image processing that can provide quantitative kinetic model parameters and that has an enormous number of subfields, including graphical analyses and tissue compartment models. In this context, the SUV is sometime called a semi-quantitative measure, even though it is quantitative measure of molecular imaging that other modalities cannot achieve.

Although they are quantitative by nature, NM images in most clinical publications and routine practice have been analyzed mostly visually or by the SUV [95], largely due to difficulties of performing TKIN in routine clinical practice. In this context, this important area of NMP is not discussed in the main text.

However, routine TKIN may become a key part of NM/NMP in the near future thanks to whole-body PET and PET/MR, as noted by Cherry et al. [36] and Cabello and Ziegler [76]. Moreover, DL-based and/or PET/MR-based automatic delineation of VOI also has potential to facilitate subsequent TKIN (e.g., one for arterial input function extraction [76]).

3. Convergence between multiple disciplines and multiple centers

As noted by Jones [13], to meet the goals of converging molecular imaging with molecular biology and molecular medicine, we must collaborate between multiple disciplines and between academia and industries. Moreover, randomized/controlled multicenter clinical trials are now requisite for the successful development of pharmaceutical and therapeutic methods for patient healthcare.

As mentioned by Aide et al. [60], NM and NMP societies should focus on ensuring exchangeability or pooling of quantitative results in a multicenter setting for this purpose,

which can also be beneficial to derive diagnostic criteria for routine PET/CT metrics. In this context, NM imaging standardization and harmonization is a crucial step for the Korean NMP society as well and will be discussed in the next section.

Theranostics and DL may be pivotal in current NM and NMP. In this context, multidiscipline convergence and multicenter clinical trials will facilitate theranostics and DL, both of which demand (well-labeled) big data. Now that many Korean studies have also been published in this area, the Korean NMP society should exert more effort in contributing to Korean NM/MP, precision medicine, and patient welfare.

4. Standardization, harmonization, and beyond

As mentioned, EANM and EARL have established systematic reviews/guidelines/ systems for multicenter NM image standardization and harmonization. These developments have influenced oncological/neurological/cardiological diagnosis and disease staging, as well as therapy response monitoring and planning [60].

In addition, greater efforts by the NMP society for quality control/quality assurance (QC/QA) of NM imaging should be made. Indeed, most of the aforementioned standardization and harmonization of NM imaging is inevitably related to QC/QA, including calibration and corrective action for QC errors. Moreover, many useful metrics for NM imaging harmonization are from routine QC/QA (e.g., NEMA/ACR phantom-based quarterly QC for recovery coefficient measurements).

In this context, Korean NMP society members should also benchmark themselves with the American College of Radiology (ACR) accreditation and EANM guidelines and EARL accreditation for FDG PET/CT tumor imaging, and should align with them and proceed to establish their own accreditation system.

Based on the aforementioned guidelines, EANM/EARL launched a PET/CT QC program in 2010 aiming to harmonize image quality and quantification across sites and cameras [60]. Both the EARL program and ACR accreditation recommend using a specific set of QC experiments. EARL accreditation established the acceptance limits for SUV bias

and recovery coefficients based on the results of a feasibility study performed on PET/CT systems currently used in clinical practice. Similar PET scanner qualification is also performed as part of the ACR accreditation and in ACRIN PET scanner qualification.

At present, many Korean institutions are accredited or qualified by these systems; for example, one Korean institution (Asan Medical Center) is continually accredited by both ACR PET accreditation and ACR NM accreditation, and several institutions are continually qualified for their PET scanner by ACRIN PET qualification. In addition, many Korean studies on standardized/harmonized NM imaging data have also been published in this important area. Therefore, it is time for the Korean NMP society to establish the perspective for the PET/NM center accreditation and PET/SPECT scanner qualification.

Concluding Remarks

In this paper, the author provided a brief and comprehensive review of advanced technologies of NMP. The advances are in various areas of NMP, including image acquisition/reconstruction, detector material/devices, hybrid/advanced imaging, precision medicine, and DL, and have led to high-quality digital imaging of invaluable in vivo whole-body molecular information for NM and NMP. Owing to these strengths and currents trends of convergence/consilience with other imaging modalities and disciplines, the author believes that NMP can contribute to enhanced image quality and decreased radiation exposure, and consequently, quantitative and personalized healthcare.

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Conflicts of Interest

The authors have nothing to disclose.

Availability of Data and Materials

All relevant data are within the paper and its Supporting Information files.

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