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AI and Machine Learning in Nuclear Medicine: Future Perspectives

Robert Seifert, MD,[*,†,‡,§] Manuel Weber, MD,[†,‡,§] Emre Kocakavuk,[†,‡,§] Christoph Rischpler, MD,[†,‡,§] and David Kersting, MD, M.Sc.[†,‡,§]

Artificial intelligence and machine learning based approaches are increasingly finding their way into various areas of nuclear medicine imaging. With the technical development of new methods and the expansion to new fields of application, this trend is likely to become even more pronounced in future. Possible means of application range from automated image reading and classification to correlation with clinical outcomes and to technological applications in image processing and reconstruction.

In the context of tumor imaging, that is, predominantly FDG or PSMA PET imaging but also bone scintigraphy, artificial intelligence approaches can be used to quantify the whole-body tumor volume, for the segmentation and classification of pathological foci or to facilitate the diagnosis of micro-metastases. More advanced applications aim at the correlation of image features that are derived by artificial intelligence with clinical endpoints, for example, whole-body tumor volume with overall survival.

In nuclear medicine imaging of benign diseases, artificial intelligence methods are predominantly used for automated and/or facilitated image classification and clinical decision making. Automated feature selection, segmentation and classification of myocardial perfusion scintigraphy can help in identifying patients that would benefit from intervention and to forecast clinical prognosis. Automated reporting of neurodegenerative diseases such as Alzheimer's disease might be extended to early diagnosis—being of special interest, if targeted treatment options might become available.

Technological approaches include artificial intelligence-based attenuation correction of PET images, image reconstruction or anatomical landmarking. Attenuation correction is of special interest for avoiding the need of a coregistered CT scan, in the process of image reconstruction artefacts might be reduced, or ultra low-dose PET images might be denoised. The development of accurate ultra low-dose PET imaging might broaden the method's applicability, for example, toward oncologic PET screening.

Most artificial intelligence approaches in nuclear medicine imaging are still in early stages of development, further improvements are necessary for broad clinical applications. In this review, we describe the current trends in the context fields of body oncology, cardiac imaging, and neuroimaging while an additional section puts emphasis on technological trends. Our aim is not only to describe currently available methods, but also to place a special focus on the description of possible future developments.

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Introduction

Artificial intelligence (AI) is developing into an integral part of nuclear medicine.[1] It has already been employed for various approaches including image analysis, image pre- and post-processing, prediction of adverse reactions to therapies, and optimization of staging categories. In this article, current concepts and future perspectives of image analysis

*Department of Nuclear Medicine, University Hospital Münster, Münster, Germany.

†Department of Nuclear Medicine, University Hospital Essen, Essen, Germany.

‡West German Cancer Center, Germany.

§German Cancer Consortium (DKTK), Germany.

Address reprint requests to Robert Seifert, Department of Nuclear Medicine, University Hospital Essen, Hufelandstraße 55, D-45147 Essen, Germany. E-mail: robert.seifert@uni-due.de

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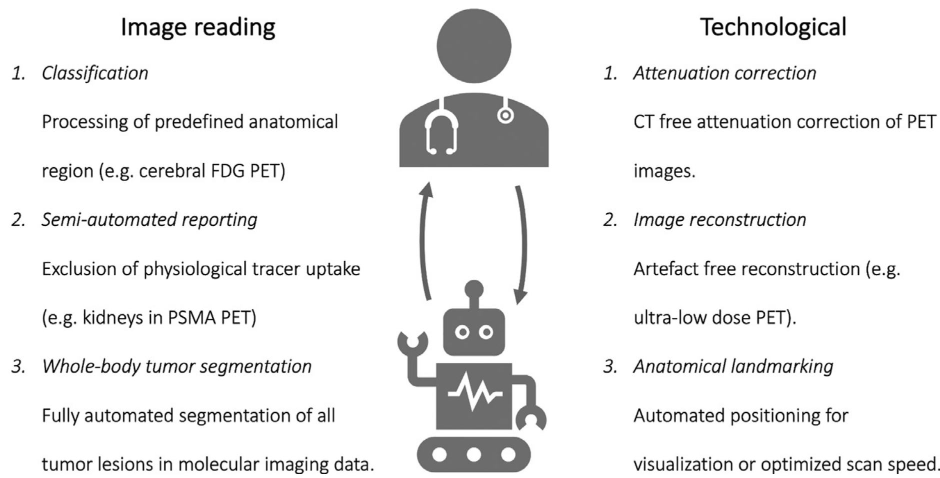

Figure 1 AI-driven image analysis in nuclear medicine.

and image pre- and post-processing were reviewed. This limitation seemed necessary to sketch fundamental trends in AI and review their relevance for future developments in the field of nuclear medicine.

AI-driven image analysis in nuclear medicine can be separated into 3 categories (Fig. 1):

First, AI is employed to characterize manually specified subregions of the body. Generally, this approach is used to process a predefined anatomical section and output a specific label. This is commonly performed on segmented PETs of tumors, aiming at the determination of histological classification by PET data or on cerebral metabolic PET for the diagnosis of neurodegenerative diseases.

Second, AI is employed to assist the nuclear medicine expert in the reading of whole-body acquisitions of nuclear medicine data. This is generally employed to quantify the whole-body tumor volume in PET acquisitions. As PET tracers show physiological uptake, AI is often employed to semi-automatically remove physiological uptake, which facilitates the quantification of a whole-body tumor volume (Fig. 2).

Finally, AI is utilized to process whole body image data to automatically segment all pathological tracer accumulations. This approach is currently emerging and represents the synthesis from the 2 aforementioned trends. It is commonly used in context of oncological examinations, like Fluorodeoxyglucose (FDG-PET), Prostate-specific membrane antigen (PSMA)-PET, or bone scintigraphy. Thereby, patients can be stratified with regard to overall survival, which might facilitate therapy intensification at early time points with improved outcome.

Both the estimation of a pathological status from a predefined anatomical subregion and the fully automated delineation of pathological tracer foci will most likely assert oneself, the first more for the diagnosis of benign diseases (eg, brain PET), the latter more for monitoring of oncological diseases (eg, PSMA PET).

Regarding benign diseases, cardiac nuclear medicine and brain PET for diagnosing neurodegenerative diseases are typical fields of application for AI or machine learning approaches. In addition to automatic classification, the correlation with clinical factors is becoming increasingly examined. AI might aim at identifying individuals who may benefit from certain treatment options. This development goes hand in hand with early diagnosis of benign diseases,

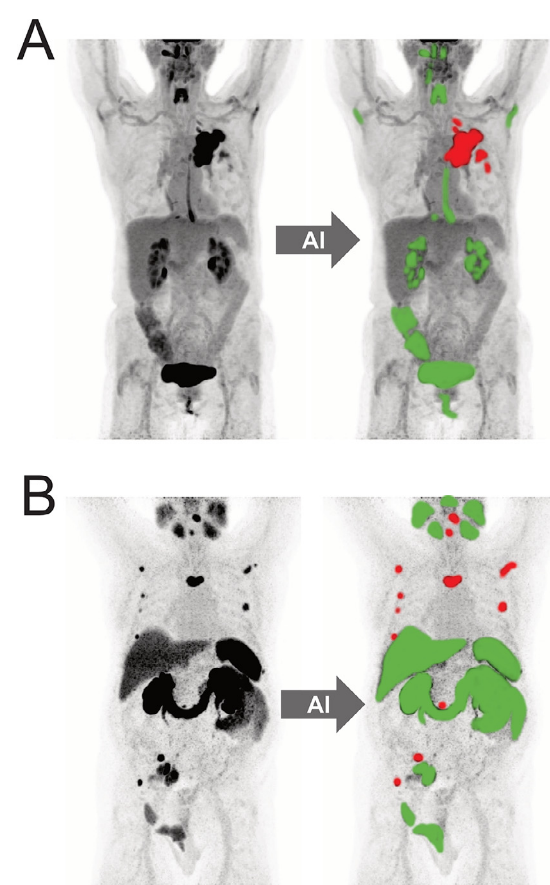

Figure 2 AI for the quantification of a whole-body tumor volume. Segmentation of tumor lesions and of physiological tracer uptake for FDG PET (A shows a patient with lung cancer) or PSMA PET (B shows patient with prostate cancer). Physiological uptake is shown in green color, pathological uptake in red color. Various AI approaches have been proposed to segment pathological tracer uptake.

which might make use of the possibility that AI approaches can evaluate image characteristics that are not obvious for the human interpreter. First studies show results that are superior to a human reader and, as we are still in the beginning of development, we expect future improvements which can lead to important implementations into the clinical routine.

New application possibilities of AI in nuclear medicine go hand in hand with the implementation of novel technical methods. AI-based methods are suitable both for image reconstruction and image pre- and post-processing. Distinct parts of postprocessing might be performed automatically. An example is the process of anatomical landmarking that refers to the automated identification of specific body regions such as the valve plane in cardiac examinations. The information can then be used for further processing such as quantitative evaluation. Moreover, the identification of body parts that are in motion during imaging data acquisition might lead to improvements in image reconstruction and accurate image quantification.

Single preprocessing parts, for example, attenuation correction, or the complete image reconstruction might be performed by AI. These approaches can, on the one hand, be used to reduce the amount of applied tracer activity or avoid a simultaneous computed tomography (CT) acquisition leading to a reduced radiation exposure. On the other hand, the acquisition time might be reduced to increase the number of examinations to be performed per scanner time. As scanner time is limited and radiation exposure is a prominent side effect of nuclear medicine imaging methods, both aspects might play integral parts for the extension of nuclear medicine imaging modalities to larger patient groups.

All in all, we are still at the beginning of an exciting process that might revolutionize the classical way of image acquisition and interpretation and their integration into the clinical workflow. Future developments might focus on:

1. The differentiation of metastatic tumor volume per organ system to adjust for the different aggressiveness of metastases and for tumor heterogeneity.
2. The quantification of the volume change of each metastasis over time (eg, in response to therapy).
3. The combination of different tracers to characterize tumor heterogeneity per lesion in vivo (i.e., integration of FDG and PSMA PET or FAP PET and PSMA PET),
4. The integration of dynamic (ie, 4D) PET acquisitions, which will become increasingly available with the rise of whole-body PET scanners.
5. Image denoising to facilitate “ultra low-dose” PET acquisitions (Fig. 3).

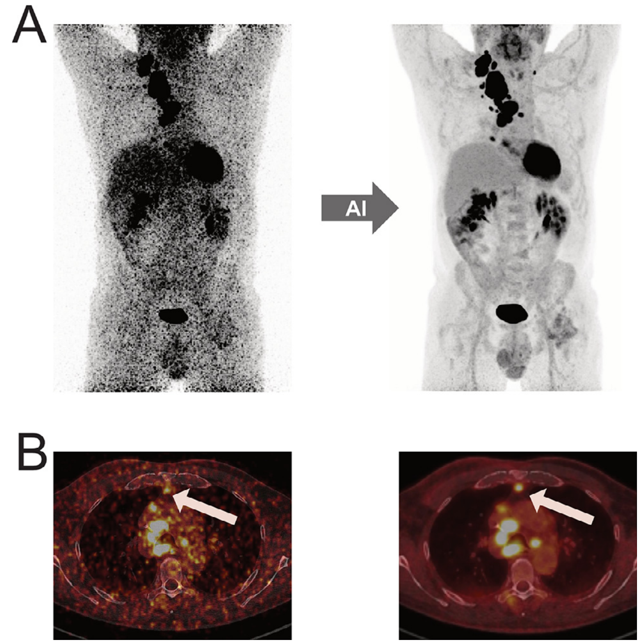

Figure 3 AI for the denoising of PET images. Denoising of FDG-PET imaging might facilitate ultra low-dose image acquisitions. Exemplary case (B cell lymphoma) of an ultra-short emission time FDG-PET is shown as MIP (A) together with the standard acquisition protocol (50 times longer acquisition). AI can be employed to denoise ultra low-dose PET images. Slice-wise visualization shows the impaired lesion detectability in the low-dose acquisition (B, arrow).

Body Oncology

In body oncology (ie, solid tumors excluding the central nervous system), nuclear medicine imaging is predominantly used to assess early therapy responses, to characterize lesions with unclear morphological findings and to quantify the whole-body tumor volume. The quantification of the whole-body tumor volume is a challenging task in the clinical routine, as it would require the delimitation of all metastases in an examination (eg, prostate cancer metastases in PSMA PET/CT). Therefore, PERCIST criteria require the delineation only of a subset of lesions to quantify treatment response.[2] However, this simplification might significantly hamper the response assessment. Therefore, AI is employed to assist or even fully automatize the delineation of all metastases in whole-body examinations.

Bone scintigraphy is a reference standard examination to assess the osseous metastatic spread of prostate cancer patients.[3] The osseous tumor load can be condensed to a single number by the quantification of the bone scan index (BSI), which resamples the fraction of metastatically affected skeleton.[4] The BSI can already be obtained automatically by a trained AI system.[5] Interestingly, the automatically derived BSI is a significant predictor of overall survival time in patients with prostate cancer.[6]

PSMA targeting PET has become the reference standard examination for disease monitoring of prostate cancer patients.[7,8] Several semi-automated approaches have been proposed to quantify the whole-body tumor volume.[9,10] By the use of AI, these approaches enable the facilitated segmentation of all pathologic tracer foci. This is done by the semi-automatic exclusion of tracer foci that are caused by physiological processes. Interestingly, the whole-body tumor volume is a significant negative prognosticator of overall survival time in end stage prostate cancer patients.[9]

Moreover, the segmentation of all metastases enables profiling of the PET uptake patterns.[11] Thereby, end stage prostate cancer patients can be stratified into those with high, intermediate, and low overall survival time.

In contrast to semi-automated approaches for delineation of all pathological PSMAPET foci, Zhao et al.[12] proposed a neural network for the fully automated analysis of PSMA-PET acquisitions. However, this AI is currently only trained for the pelvic area, which prevents testing in whole-body acquisitions.

FDGPET/CT is a reference standard examination for the staging of lung cancer and lymphoma. Sibille et al.[13] have proposed an AI to fully automatically segment all pathological tracer foci in FDGPET/CT acquisitions. The network achieved a high per patient accuracy (AUC 0.98 for lung cancer, AUC 0.98 for lymphoma). Interestingly, the combination of CT and PET images statistically significantly improved the lesion classification accuracy. Capobianco et al.[14] could show that the automatically derived tumor volume is a significant prognosticator of overall survival time in lymphoma patients.

Recent developments in cancer genomics revealed unprecedented insights into the molecular characteristics of primary, recurrent and metastatic tumors with potential implications for cancer imaging.[15-17] In particular, reconstruction of cancer evolutionary trajectories revealed novel insights into mechanisms of metastasis formation. The emergence of metastases has been traditionally accepted to be the final step in cancer evolution. However, Hu et al.[18] recently challenged this assumption and proposed an early occurrence of metastatic seeding even before to the detection limit of the primary tumor was reached. This work underlines the importance of identification of primary and metastatic cancer as early as possible. AI could play an important role solving this issue, in part by diagnosing malignant lesions more accurately and potentially overcoming limitations of PET imaging for detection of micro-metastases.[19] Furthermore, tumor volume, tracer uptake, and additional parameters from nuclear imaging combined with genomic information might help to more accurately dissect the life history of cancers and to precisely time the emergence of malignant lesions, thereby optimizing treatment strategies.

More recently, Reiter et al.[20] revealed different evolutionary bottlenecks for the formation of local (lymph node) vs distant metastases. Accordingly, the clonal composition of anatomically distinct metastases appeared to be fundamentally different, highlighting genetic diversity and tumor heterogeneity. These observations have interesting implications for imaging and the utilization of AI. Via automatic assessment of tumor volume and metabolic activity, it might not only be possible to distinguish between anatomically distinct lesions but also to gain insights into their clonal composition and potentially differentiate between high and low aggressive metastases that lead to different survival outcomes.

Taken together, application of AI in cancer imaging has a great potential to improve personalized cancer detection, therapy and monitoring.

Cardiac Imaging

In nuclear cardiology, imaging is performed regularly in clinical routine with the aim of providing the clinician with significant support in his decision making, for example, in determining whether a coronary stenosis requires intervention. The modalities used include SPECT and PET, which are usually performed as hybrid imaging together with a CT or, in the case of PET, even with an magnetic resonance imaging (MRI) scan. Overall, an increasing number of examinations can be observed. Not only the fact that a large number of examinations are performed, especially in myocardial perfusion scintigraphy, but also the fact that this examination is highly standardized and quantifications are already routinely implemented, make myocardial perfusion scintigraphy one of the most promising tests with regard to the implementation of machine learning and deep learning. Accordingly, AI has made progress in the fields of segmentation of myocardial perfusion imaging data, diagnosis of coronary artery disease (CAD) and prediction of major adverse cardiac events (MACE). For example, there are already approaches that automatically determine the valve plane during the software-based process of segmentation of the left ventricle - one of the most important steps that often requires intervention by the physician when analyzing myocardial perfusion data sets.[21] It has been shown in this paper that these automated evaluations demonstrate a very high correlation with the assessment by experienced nuclear medicine physicians. In a further study of 995 patients who either had coronary angiography ($n = 650$) as a reference method or had a very low pretest likelihood of <5% for coronary artery disease ($n = 345$), it was shown that a fully automated analysis of myocardial perfusion scintigraphy studies has an adequate agreement with experts.[22]

The next step, which was partly touched on in the previous work, is the automated categorization of patients, whether they have a disease, in the case of myocardial perfusion scintigraphy, that is, whether or not stenosing CAD is present. In 1 study with 713 patients who underwent myocardial perfusion scintigraphy and all of whom received a cardiac catheterization with a total of 372 revascularizations during the course of the study were analyzed.[23] Using an automated feature selection algorithm from a total of 33 clinical and quantitative data, only those parameters that represented an information gain were selected. Based on these data, a prediction model was then trained using tenfold cross-validation and the results were compared with the analysis by 2 experienced readers. The machine learning algorithm was comparable or superior to human operators in predicting the need for intervention and was better when only myocardial perfusion scintigraphy data were used. Similar results were obtained in 2 further studies using data of the REFINE-SPECT Registry (Registry of Fast Myocardial Perfusion Imaging with next generation SPECT).[24,25]

Finally, it would be of great interest whether AI can not only diagnose a stenosis requiring intervention, but whether it can also provide a prognosis regarding the course of the disease. Usually, the prognosis of a patient is based on the mere visual or quantitative analysis of image data from myocardial perfusion scintigraphy. Machine learning allows the integration of a large number of variables that humans are not able to oversee. A study has now examined the ability of machine learning to predict the occurrence of MACE in 2,619 patients who underwent SPECT myocardial perfusion scintigraphy.[26] In this algorithm a total of 70 clinical, imaging or electrocardiography (ECG) parameters were taken into account. The prediction of MACE based on machine learning for a combination of the different parameters was significantly better than an algorithm based only on imaging parameters. Furthermore, this machine learning algorithm based on the various parameters was superior to the reading physicians who were aware of patient clinical information and quantitative assessment.

In summary, there are very promising approaches for AI in nuclear cardiology. It is to be expected that in the future, imaging data will be automatically reconstructed by means of AI and that further corrections such as attenuation correction will also be carried out automatically, for example using already existing CT data sets. The segmentation and further processing of the imaging data will also be largely automatic. In addition, AI will support the nuclear physician in making the correct diagnosis and facilitate the evaluation of the individual prognosis of the patient.

Neuroimaging

Glioma

Diffuse gliomas are the most common types of primary brain tumors.[27] Seminal discoveries on genomic, epigenomic, and transcriptomic levels have led to the revised classification of brain tumors integrating prognostically useful molecular features in addition to the classical histological assessment of the tumor.[28]

Imaging of glioma is usually carried out by MRI but can be complemented by PET imaging in some instances. The most commonly used radiotracers are ^{11}C methionine and ^{18}F-fluoroethyl-L-tyrosine (FET), whereas the use of ^{18}F-FDG is limited considerably by the high physiological uptake of the central-nervous system.[29] The joint SNMMI/EANM procedure guidelines identify imaging at primary diagnosis, at (suspected) tumor recurrence, and for therapy monitoring as the main settings for PET imaging[30]:

At primary diagnosis, indications for PET imaging entail the differentiation of grade III/IV vs grade I/II glioma, biopsy planning, tumor delineation, and prognostication:

In this regard, radiomics and genomics approaches were combined to accurately predict the mutational status of gliomas using static FET PET/MRI and MR fingerprinting, with AUCs varying from 76% to 98% for different types of mutations.[31] This study proposes imaging as a non-invasive assessment of molecular characteristics in gliomas requiring further investigation in prospective clinical trials. A different study on the use of machine learning and static ^{11}C methionine PET/MRI for non-invasive glioma subtyping has shown a moderate diagnostic performance for the distinction of isocitrate dehydrogenase (IDH wildtype vs IDH mutant glioma, but low accuracies for exact glioma subtyping.[32] In addition, voxel-based analysis of dynamic FET PET has been shown to identify particularly aggressive subvolumes in gliomas.[33]

To combine longitudinal molecular trajectories with longitudinal imaging of glioma, a multi-institutional group has been established recently.[34] The group aims to identify radiogenomics biomarkers using standardized pipelines for extraction and analysis of imaging features. Prior works on the prognostic relevance of PET radiomics features have identified tumor heterogeneity of FET uptake as a negative predictive factor for the overall survival of glioma patients.[35]

Apart from glioma subtyping and risk stratification, PET can provide a more accurate assessment of spatial tumor extent than standalone MRI,[36] which can impact local treatment planning, such as external beam radiation therapy (EBRT) or surgery. It has also been shown that segmentation of PET positive tumor volume can be automated by implementing a convolutional neural network.[37]

It is of note that tumor response assessment in neurooncology using MRI is highly standardized and protocols are implemented in clinical trials and in the clinical routine.[38,39] In order to further improve the assessment criteria, Kickingereder et al.[40] utilized longitudinal imaging data generated from multiple institutions and performed objective and automated assessment of quantitative tumor response using artificial neural networks. Application of this method decreased inter-observer variability and further opens opportunities for implementation in clinical decision making. In some cases, detection of disease progression is hampered considerably by the occurrence of treatment related changes. For example, pseudoprogression is characterized by an increase in tumor size, typically within the first 3 months of chemoradiation followed by tumor regression. Early differentiation from true tumor progression can be aided by PET imaging.[41] Prior studies have confirmed the high discriminatory power of PET in this context, that can potentially be improved further via the analysis of radiomic features with a random forest classifier.[41,42] In addition to the established conventional quantitative PET parameters, a prior study has also elucidated the promising potential of unsupervised consensus clustering in this context and identified distinct clusters based on textural features that were associated with pseudoprogression.[43]

Neurodegenerative Diseases

Apart from neurooncological diseases, neurodegenerative disorders are a common target of AI-based approaches in nuclear medicine. Inter alia, different neural networks have been applied for automated classification of Alzheimer's disease in FDG PET in combination with T1-weighted MR images, in FDG PET images alone or in amyloid PET images.[44-48] Cerebral accumulation of Aβ amyloid is predicted to precede clinical symptoms of Alzheimer's disease by up to 20 years and treatment options to target cerebral Aβ amyloids, for example, Aducanumab, are clinically tested.[49,50] Albeit until now no pharmaceutical treatment options have been approved, early diagnosis might become extraordinary important with the availability of targeted therapy. In that case, automated evaluation of cerebral PET images might aid in identifying patients who could possibly benefit from therapeutic intervention.

Technological Trends

In addition to the application-oriented field of image analysis, AI-methods are more and more applied in the more fundamental and technical field of pre- and post-processing of nuclear imaging data. PET data require for extended preprocessing and data correction prior to image reconstruction. Inter alia, attenuation correction is a crucial process for quantitative image reconstruction that is performed in current PET/CT systems by using attenuation maps derived from coregistered CT data.[51] Howbeit, attenuation correction is challenging, when no simultaneous CT acquisition is performed like in the case of PET/MRI systems. Typically, atlas-based or segmentation-based approaches (derived from segmented specific MR sequences, for example, the Dixon technique) are used, but can be constrained by quantification errors.[51,52] Moreover, attenuation correction of specific tissues, for example, the lung, can be challenging.[53] Several approaches have been published that aim at using machine learning and AI-based methods to improve attenuation correction in PET/MRI images. These were recently reviewed by Mecheter et al.[54] For instance, Pozaruk et al.[55] report an improved accuracy in PET quantification by estimating μ-maps via an augmented generative adversarial network using MR images as input. It is within the realm of possibility that these or similar techniques may be clinically used in near future to replace conventional methods for PET/MRI attenuation correction, albeit large scale clinical evaluations are yet missing.[54]

One step further, several approaches aim at attenuation correction by using PET data only. Thus, accurate PET imaging may become available without the need for simultaneous CT or MRI acquisition, which is in the case of PET/CT accompanied by an associated radiation exposure and in the case of PET/MRI limited by logistics and availability. For example, Shiri et al. and Arabi et. al.[56,57] used different convolutional neural networks for direct attenuation correction of brain PET images. Accurate image quantification in whole-body PET images that were created using various generative adversarial networks was reported by different groups.[58,59] As sample sizes were small, further evaluations are necessary prior to clinical application. However, the applicability of high-quality PET-only imaging can offer interesting future perspectives and broaden its applicability.

In comparison with radiological imaging techniques, PET data are noisy, especially when low tracer activities are applied, or the acquisition time is short. However, scanning time is limited by availability and high activities lead to higher radiation exposure. Few approaches demonstrated the feasibility of image denoising by AI techniques either as postreconstruction tool or as integral part of the reconstruction algorithms: Gong et. al embedded a convolutional neural network into an iterative image reconstruction framework and achieved a reduction in noise that was accompanied by a visually improved image quality.[60] Kim et. al demonstrated a visual image quality improvement by postprocessing of low-dose reconstructed PET images using a denoising convolutional network.[61] Lu et. al proved an accurate quantification of small lung nodules (SUV_{mean} deviation <15%) in 10 % tracer dosage PET images.[61] These studies can be regarded as proof-of-principles rather than direct starting points for clinical usage, as they use small case numbers or low-dose PET data that are derived from full-dose data by simulation. Large scale studies on real data are still needed beforehand to prove the accuracy of these methods in a clinical context. AI-based methods might then allow for "ultra low-dose" PET imaging after application of minimal tracer activity.

The recent introduction of "digital" (silicon photomultiplier-based) PET systems, that outperform conventional photomultiplier tube-based PET systems by a higher coincidence time resolution and detector sensitivity,[62-66] might play a key role in the development of accurate ultra low-dose PET/CT. These systems are characterized by an optimized signal-to-noise ratio and a consequently improved image quality. In combination with image denoising by AI, clinically evaluable ultra low-dose PET might become available in the future.

If a reduction in radiation exposure into the range of annually accumulated natural radiation might become possible due to AI-based attenuation correction and image reconstruction, the applicability of PET imaging could be extended from evaluation of clinical suspicions to large scale screening. Recently, Lennon et al.[67] demonstrated the feasibility of oncologic screening by a combination of a minimally invasive blood test and subsequent PET/CT: In more than 10,000 women between 65 and 75 years of age, 26 cancers were suspected by blood testing. In this group, additional PET/CT led to an increase in specificity and positive predictive value. Future perspectives might aim at using ultra low-dose FDG PET for oncologic screening. For various tumor entities, inter alia breast, colorectal, and lung cancer, an improved prognosis by screening and subsequent early diagnosis and treatment is a well described phenomenon.[68-72]

For conducting PET examinations on a large scale, an increased availability of examinations would become necessary. Next to increasing the number of PET scanners, a reduction in acquisition time per patient could aim at offering a larger number of examinations per scanner. As decreased imaging time leads to noisy PET images comparable to those after administration of low activities, similar denoising techniques by AI methods could, on the other hand, help in providing the logistics for high examination volumes. These, with increasing population ages and prevalence of oncologic diseases, are supposed to become necessary independent of the applicability of ultra low-dose PET screening.

Conclusion

In this review, future trends of AI in nuclear medicine were contemplated. In the field of nuclear medicine, AI will have a profound impact both on technological aspects and on image reading. In the technological sector, AI is already employed for improved attenuation correction of PET images, artefact-free image reconstruction and anatomical landmarking, which enables a patient specific image acquisition. These developments will ultimately lead to better image quality, shorter acquisition time and lower radiation doses. In the image analysis sector, AI is already used for providing assistance in image reading, fully automated disease classification and fully automated metastases delineation in whole-body acquisitions. By means of these trends, nuclear medicine physicians are finally relieved from routine tasks so that they have more time for patient care and image interpretation. Future patients may therefore benefit from the combination of enhanced image quality and individualized image reporting.

References

1. Nensa F, Demircioglu A, Rischpler C: Artificial intelligence in nuclear medicine. J Nucl Med 60:29S-37S, 2019
2. Wahl RL, Jacene H, Kasamon Y, et al: From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. J Nucl Med 50:122-151, 2009
3. Scher HI, Morris MJ, Stadler WM, et al: Trial design and objectives for castration-resistant prostate cancer: Updated recommendations from the prostate cancer clinical trials working group 3. J Clin Oncol 34:1402-1418, 2016
4. Imbriaco M, Larson SM, Yeung HW, et al: A new parameter for measuring metastatic bone involvement by prostate cancer: The bone scan index. Clin Cancer Res 4:1765-1772, 1998
5. Ulmert D, Kaboteh R, Fox JJ, et al: A novel automated platform for quantifying the extent of skeletal tumour involvement in prostate cancer patients using the bone scan index. Eur Urol 62:78-84, 2012
6. Armstrong AJ, Anand A, Edenbrandt L, et al: Phase 3 assessment of the automated bone scan index as a prognostic imaging biomarker of overall survival in men with metastatic castration-resistant prostate cancer: a secondary analysis of a randomized clinical trial. JAMA Oncol 4:944-951, 2018.
7. Hofman MS, Lawrentschuk N, Francis RJ, et al: Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multi-centre study. Lancet 395:1208-1216, 2020
8. Fendler WP, Calais J, Eiber M, et al: Assessment of 68Ga-PSMA-11 PET accuracy in localizing recurrent prostate cancer: a prospective single-arm clinical trial. JAMA Oncol 5:856-863, 2019
9. Seifert R, Herrmann K, Kleesiek J, et al: Semi-automatically quantified tumor volume using Ga-68-PSMA-11-PET as biomarker for survival in patients with advanced prostate cancer. J Nucl Med 2020. https://doi.org/10.2967/jnumed.120.242057
10. Gafita A, Bieth M, Krönke M, et al: qPSMA: semiautomatic software for whole-body tumor burden assessment in prostate cancer using 68 Ga-PSMA11 PET/CT. J Nucl Med 60:1277-1283, 2019
11. Seifert R, Seitzer K, Herrmann K, et al: Analysis of PSMA expression and outcome in patients with advanced prostate cancer receiving 177Lu-PSMA-617 radioligand therapy. Theranostics 2020
12. Zhao Y, Gafita A, Vollnberg B, et al: Deep neural network for automatic characterization of lesions on 68Ga-PSMA-11 PET/CT. Eur J Nucl Med Mol Imaging 47:603-613, 2020
13. Sibille L, Seifert R, Avramovic N, et al: 18 F-FDG PET/CT uptake classification in lymphoma and lung cancer by using deep convolutional neural networks. Radiology 294:445-452, 2020.
14. Capobianco N, Meignan MA, Cottereau A-S, et al: Deep learning FDG uptake classification enables total metabolic tumor volume estimation in diffuse large B-cell lymphoma. [published online ahead of print, 2020 Jun 12]. J Nucl Med 57, 2020
15. Priestley P, Baber J, Lolkema MP, et al: Pan-cancer whole-genome analyses of metastatic solid tumours. Nature 575:210-216, 2019
16. Campbell PJ, Getz G, Korbel JO, et al: Pan-cancer analysis of whole genomes. Nature 578:82-93, 2020
17. Barthel FP, Johnson KC, Varn FS, et al: Longitudinal molecular trajectories of diffuse glioma in adults. Nature 576:112-120, 2019
18. Hu Z, Ding J, Ma Z, et al: Quantitative evidence for early metastatic seeding in colorectal cancer. Nat Genet 51:1113-1122, 2019
19. Zhu A, Daniel Lee A, Shim H: Metabolic PET Imaging in Cancer Detection and Therapy Response. Semin Oncol 38:55-69, 2011
20. Reiter JG, Hung WT, Lee IH, et al: Lymph node metastases develop through a wider evolutionary bottleneck than distant metastases. Nat Genet 52, 2020
21. Betancur J, Rubeaux M, Fuchs TA, et al: Automatic valve plane localization in myocardial perfusion SPECT/CT by machine learning: anatomic and clinical validation. J Nucl Med 58:961-967, 2017
22. Arsanjani R, Xu Y, Hayes SW, et al: Comparison of fully automated computer analysis and visual scoring for detection of coronary artery disease from myocardial perfusion SPECT in a large population. J Nucl Med 54:221-228, 2013
23. Arsanjani R, Dey D, Khachatryan T, et al: Prediction of revascularization after myocardial perfusion SPECT by machine learning in a large population. J Nucl Cardiol 22:877-884, 2015
24. Betancur J, Commandeur F, Motlagh M, et al: Deep learning for prediction of obstructive disease from fast myocardial perfusion SPECT: a multicenter study. JACC Cardiovasc Imaging 11:1654-1663, 2018
25. Hu LH, Betancur J, Sharir T, et al: Machine learning predicts per-vessel early coronary revascularization after fast myocardial perfusion SPECT: results from multicentre REFINE SPECT registry. Eur Heart J Cardiovasc Imaging 21:549-559, 2020
26. Betancur J, Otaki Y, Motwani M, et al: Prognostic value of combined clinical and myocardial perfusion imaging data using machine learning. JACC Cardiovasc Imaging 11:1000-1009, 2018
27. Weller M, Wick W, Aldape K, et al: Glioma. Nat Rev Dis Prim 1:15017, 2015
28. Louis DN, Perry A, Reifenberger G, et al: The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 131:803-820, 2016
29. La Fougère C, Suchorska B, Bartenstein P, et al: Molecular imaging of gliomas with PET: Opportunities and limitations. Neuro Oncol 13:806-819, 2011
30. Law I, Albert NL, Arbizu J, et al: Joint EANM/EANO/RANO practice guidelines/SNMMI procedure standards for imaging of gliomas using PET with radiolabelled amino acids and [18 F]FDG: version 1.0. Eur J Nucl Med Mol Imaging 46:540-557, 2019
31. Haubold J, Demircioglu A, Gratz M, et al: Non-invasive tumor decoding and phenotyping of cerebral gliomas utilizing multiparametric 18F-FET PET-MRI and MR Fingerprinting. Eur J Nucl Med Mol Imaging 47:1435-1445, 2020
32. Kebir S, Weber M, Lazaridis L, et al: Hybrid 11 C-MET PET/MRI Combined with “machine Learning” in Glioma Diagnosis According to the Revised Glioma WHO Classification 2016. Clin Nucl Med 44:214-220, 2019
33. Vomacka L, Unterrainer M, Holzgreve A, et al: Voxel-wise analysis of dynamic 18F-FET PET: a novel approach for non-invasive glioma characterisation. EJNMMI Res 8:91, 2018.
34. Bakas S, Ormond DR, Alfaro KD, et al: iGLASS: imaging integration into the Glioma Longitudinal AnalySiS Consortium. Neuro Oncol 40:1-30, 2020
35. Pyka T, Gempt J, Hiob D, et al: Textural analysis of pre-therapeutic [18F]-FET-PET and its correlation with tumor grade and patient survival in high-grade gliomas. Eur J Nucl Med Mol Imaging 43:133-141, 2016
36. Song S, Cheng Y, Ma J, et al: Simultaneous FET-PET and contrast-enhanced MRI based on hybrid PET/MR improves delineation of tumor

spatial biodistribution in gliomas: a biopsy validation study. Eur J Nucl Med Mol Imaging 47:1458-1467, 2020
37. Blanc-Durand P, Van Der Gucht A, Schaefer N, et al: Automatic lesion detection and segmentation of18F-FET PET in gliomas: A full 3D U-Net convolutional neural network study. PLoS One 13:1-11, 2018
38. Wen PY, Chang SM, Van den Bent MJ, et al: Response assessment in neuro-oncology clinical trials. J Clin Oncol 35:2439-2449, 2017
39. Thust SC, Heiland S, Falini A, et al: Glioma imaging in Europe: A survey of 220 centres and recommendations for best clinical practice. Eur Radiol 28:3306-3317, 2018
40. Kickingereder P, Isensee F, Tursunova I, et al: Automated quantitative tumour response assessment of MRI in neuro-oncology with artificial neural networks: a multicentre, retrospective study. Lancet Oncol 20:728-740, 2019
41. Galldiks N, Lohmann P, Albert NL, et al: Current status of PET imaging in neuro-oncology. Neuro-Oncology Adv 1:1-11, 2019
42. Hotta M, Minamimoto R, Miwa K: 11C-methionine-PET for differentiating recurrent brain tumor from radiation necrosis: radiomics approach with random forest classifier. Sci Rep 9:1-7, 2019
43. Kebir S, Khurshid Z, Gaertner FC, et al: Unsupervised consensus cluster analysis of [18F]-fluoroethyl- L-tyrosine positron emission tomography identified textural features for the diagnosis of pseudoprogression in high-grade glioma. Oncotarget 8:8294-8304, 2017
44. Huang Y, Xu J, Zhou Y, Tong T, Zhuang X: Alzheimer's disease neuroimaging initiative (ADNI). Diagnosis of alzheimer's disease via multi-modality 3D convolutional neural network. Front Neurosci 13:509, 2019.
45. Lu D, Popuri K, Ding GW, et al: Multiscale deep neural network based analysis of FDG-PET images for the early diagnosis of Alzheimer's disease. Med Image Anal 46:26-34, 2018
46. Lu D, Popuri K, Ding GW, et al: Multimodal and multiscale deep neural networks for the early diagnosis of Alzheimer's Disease using structural MR and FDG-PET images. Sci Rep 8:1-13, 2018
47. Kimura Y, Watanabe A, Yamada T, et al: AI approach of cycle-consistent generative adversarial networks to synthesize PET images to train computer-aided diagnosis algorithm for dementia. Ann Nucl Med 34:512-515, 2020
48. Ozsahin I, Sekeroglu B, Mok GSP: The use of back propagation neural networks and 18F-Florbetapir PET for early detection of Alzheimer's disease using Alzheimer's Disease Neuroimaging Initiative database. PLoS One 14:1-13, 2019
49. Panza F, Lozupone M, Logroscino G, et al: A critical appraisal of amyloid-β-targeting therapies for Alzheimer disease. Nat Rev Neurol 15:73-88, 2019
50. Sevigny J, Chiao P, Bussière T, et al: The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature 537:50-56, 2016
51. Keereman V, Mollet P, Berker Y, et al: Challenges and current methods for attenuation correction in PET/MR. Magn Reson Mater Physics, Biol Med 26:81-98, 2013
52. Mehranian A, Arabi H, Zaidi H: Vision 20/20: Magnetic resonance imaging-guided attenuation correction in PET/MRI: Challenges, solutions, and opportunities. Med Phys 43:1130-1155, 2016
53. Lillington J, Brusaferri L, Kläser K, et al: PET/MRI attenuation estimation in the lung: A review of past, present, and potential techniques. Med Phys 47:790-811, 2020
54. Mecheter I, Alic L, Abbod M, Amira A, Ji J: MR Image-Based Attenuation Correction of Brain PET Imaging: Review of Literature on Machine Learning Approaches for Segmentation. [published online ahead of print]. J Digit Imaging 2020
55. Pozaruk A, Pawar K, Li S, et al: Augmented deep learning model for improved quantitative accuracy of MR-based PET attenuation correction in PSMA PET-MRI prostate imaging. [published online ahead of print]. Eur J Nucl Med Mol Imaging 2020
56. Arabi H, Zaidi H: Deep learning-guided estimation of attenuation correction factors from time-of-flight PET emission data. Med Image Anal 64:101718, 2020
57. Shiri I, Ghafarian P, Geramifar P, et al: Direct attenuation correction of brain PET images using only emission data via a deep convolutional encoder-decoder (Deep-DAC). Eur Radiol 29:6867-6879, 2019
58. Dong X, Lei Y, Wang T, et al: Deep learning-based attenuation correction in the absence of structural information for whole-body positron emission tomography imaging. Phys Med Biol 65:055011, 2020
59. Armanious K, Hepp T, Küstner T, et al: Independent attenuation correction of whole body [18F]FDG-PET using a deep learning approach with Generative Adversarial Networks. EJNMMI Res 10:53, 2020
60. Gong K, Guan J, Kim K, et al: Iterative PET image reconstruction using convolutional neural network representation. IEEE Trans Med Imaging 38:675-685, 2019
61. Lu W, Onofrey JA, Lu Y, et al: An investigation of quantitative accuracy for deep learning based denoising in oncological PET. Phys Med Biol 64:165019, 2019
62. Conti M, Bendriem B: The new opportunities for high time resolution clinical TOF PET. Clin Transl Imaging 7:139-147, 2019
63. Salvadori J, Odille F, Verger A, et al: Head-to-head comparison between digital and analog PET of human and phantom images when optimized for maximizing the signal-to-noise ratio from small lesions. EJNMMI Phys 7:11, 2020
64. Koopman D, van Dalen JA, Stevens H, Slump CH, Knollema S, Jager PL: Performance of digital PET compared to high-resolution conventional PET in patients with cancer [published online ahead of print, 2020 Feb 14]. J Nucl Med 2020
65. Meyer M, Allenbach G, Nicod Lalonde M, et al: Increased 18F-FDG signal recovery from small physiological structures in digital PET/CT and application to the pituitary gland. Sci Rep 10:1-7, 2020
66. López-Mora DA, Flotats A, Fuentes-Ocampo F, et al: Comparison of image quality and lesion detection between digital and analog PET/CT. Eur J Nucl Med Mol Imaging 46:1383-1390, 2019
67. Lennon AM, Buchanan AH, Kinde I, et al: Feasibility of blood testing combined with PET-CT to screen for cancer and guide intervention. Science (80-) 9911:eabb9601, 2020
68. Coleman C: Early detection and screening for breast cancer. Semin Oncol Nurs 33:141-155, 2017
69. Nanavaty P, Alvarez MS, Michael Alberts W: Lung cancer screening: advantages, controversies, and applications. Cancer Control 21:9-14, 2014
70. Brenner H, Jansen L, Ulrich A, et al: Survival of patients with symptom- and screening-detected colorectal cancer. Oncotarget 7:44695-44704, 2016
71. Tabar L, Fagerberg G, Chen H −H, et al: Efficacy of breast cancer screening by age. New results swedish two−county trial. Cancer 75:2507-2517, 1995
72. Schaapveld M, Aleman BMP, van Eggermond AM, et al: Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 365:395-409, 2011