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Molecular Imaging in Oncology and Immuno-Oncology

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ABSTRACT

Molecular imaging is commonly used to improve the diagnosis and treatment of cancer. Nuclear medicine offers cutting-edge procedures and instruments, computers and radiopharmaceuticals for the diagnosis and treatment for various diseases, including oncology indications. The detailed images provided by positron emission tomography (PET) can accurately image biochemical or physiologic/pathologic phenomena. Because of this, PET offers substantial advantages over anatomic imaging modalities in oncologic imaging. There are several key considerations in the chemical and radiochemical synthesis and clinical translation of PET radiotracers. In this review article, we will discuss recent insights in molecular imaging research in oncology and immuno-oncology provided by PET radiopharmaceuticals, with a focus on development strategies and clinical utilities, using breast cancer as an example. This mini-review is intended to be a primer for newcomers to the field of molecular imaging and to give insight into the development of PET radiopharmaceuticals for cancer indications.

Keywords: Molecular Imaging; PET: Positron Emission Tomography; Radiopharmaceuticals; Oncology; Immuno-Oncology; Breast Cancer

Introduction

Molecular Imaging has been defined on the website of the Society of Nuclear Medicine and Molecular Imaging (SNMMI) as a type of medical imaging that provides detailed pictures of what is happening inside the body at the molecular and cellular level [1]. This is especially important in the era of personalized medicine, where much more refined diagnostic testing is used to identify the exact disease, monitor disease progression, tailor treatments based on precise disease patterns, and enhance our knowledge of pathophysiology. Furthermore, the introduction and validation of quantitative molecular imaging continues to drive and optimize the field of oncology diagnostics. Current clinical molecular imaging approaches primarily use PET- or single photon emission computed tomography (SPECT)-based techniques [2]. PET involves the use of small amounts of radioactive materials (radiopharmaceuticals) to help diagnose and guide cancer treatment. PET is by nature a quantitative imaging tool [3]; the radiopharmaceuticals are detect ed by specialized cameras and computer analysis to provide very precise pictures of the area of the body being imaged. In this invited mini-review we focus on PET imaging. Over the years PET imaging has emerged as an important molecular imaging technique with useful clinical applications in oncology, driven by its two well-grounded foundations: targeting vectors and quantification. Specifically, we provide examples from translational science and oncology/immuno-oncology clinical care of the utilization of PET imaging, with a particular focus on the use of PET imaging to guide and improve patient management for breast cancer.

PET Technology

PET is the gold standard for sensitivity in clinical molecular imaging [4]. PET is a functional imaging technique that uses radioactive substances known as positron emitter labeled radiophar-

maceuticals (often referred to as radiotracers) to visualize and measure physiological and pathological processes. Positrons are the antiparticles of electrons that are emitted from the nucleus of radionuclides. When a positron-emitting radionuclide decays, a positron (positively-charged electron) is emitted from the nucleus and almost immediately collides with a nearby orbital electron. After the collision and subsequent annihilation, two 511 keV gamma ray photons are produced emitting at 180° to each other [4,5]. This emission can be detected by a PET scanner with an array of coincidence detectors. These detectors are configured in rings and contain high density crystals which convert the simultaneously emitted gamma rays to electrical signals thereby encoding the position of the positron emission along a "line of response". When a positron-emitting radionuclide labeled compound is introduced into the body as a tracer (or a radioligand to a receptor), the tracer reports back from the body as the emission signal to indicate the location of the labeled compound. PET imaging uses these signals to reconstruct the tracer's in vivo distribution as three-dimensional tomography [4]. In theory, PET can track in vivo movement and distribution of any molecules as long as the molecule can be radiolabeled by a positron-emitting radionuclide such as ^{11}C (T1/2 = 20 min), ^{68}Ga (T1/2 = 68 min) and ^{18}F (T1/2 = 110 min) [4,6]. After introduction into the body, most often intravenously, the tracer is subjected to distribution, accumulation to target tissue, metabolism, and clearance. Selective target accumulation reflects the specific molecular interaction of the tracer and its target. A dynamic PET imaging study can, if needed, track the distribution of a positron-labeled compound at any location in the body over time and provide tissue pharmacokinetics as time-activity curves [6].

With the rapid increase in the number of target-specific radiotracers in the last few years, PET technology has also advanced in spatial resolution, image quality and sensitivity. The gain is in part due to significant advances in detector technology [7], where the original crystal and analogue photomultipliers are being replaced by block crystal detectors. These blocks are machined to produce an array of crystal elements each a few millimeters in dimension [7]. These are coupled directly to micro arrays of silicon avalanche photodiodes, resulting in high-speed, high-resolution detection [8]. The geometry of PET scanners is evolving also. Modern PET scanners include a CT scanner [6] and with the advent of the solid-state detectors PET-MR scanners are also available [9]. The detector blocks are assembled in rings in these scanners and these rings are stacked to cover an axial field of view (FOV) of 20 to 30cm. These detect emissions in a 3D configuration such that a subject may be scanned by sequentially advancing the patient through the detection FOV.

Very recently, the major vendors of PET scanners are now introducing large FOV detector configurations with up to 200 cm coverage reducing or eliminating the need to advance the subject FOV. Larger fields of view allow for greatly increased sensitivities meaning that imaging times can be considerably reduced or greater signal to noise can be obtained, or injected radioactivity is reduced – this is particularly valuable when repeat dosing or when multiple tracers are used because complementary information is desired, for example, in tracking therapy response [10]. There are also healthcare economics cost saving aspects as halving the time to scan a patient with one large FOV PET scanner is likely less expensive than obtaining two shorter field of view PET scanners both in purchase and staff costs. Image reconstruction of the PET image from the gamma ray events has also evolved. Iterative reconstruction has replaced filtered back projection and greater detection of "time of flight" temporal resolution has resulted in greater localization of each event along the line of response, decreasing the effective noise in the reconstruction [11]. Also, Bayesian reconstruction methods are available which minimize pixel to pixel noise while preserving spatial resolution [12] and retaining accuracy of quantitation. PET vendors are also introducing artificial intelligence (AI) through deep learning algorithms which can further improve images with lower injected activity or shorter acquisition times. The combination of these advances has resulted in high signal to noise, high-definition images with increased sensitivity in lesion detection and better patient throughput with modern PET scanner technology.

PET Targeting Vector

A PET radiopharmaceutical is a pharmacophore that is labeled with a positron-emitting radionuclide. Pharmacophores include, but are not limited to, small molecules, affibodies, aptamers, amino acids, peptides, antibodies, antibody mimetics, and nanoparticles [13]. These molecules can target cancer biomarkers or biological processes. We provide examples of PET radiopharmaceuticals that have been evaluated in the clinic for oncology and immuno-oncology indications. Antibody-based PET imaging using high-affinity monoclonal antibodies (mAbs) such as in cancer therapeutics trastuzumab and pertuzumab, has been studied as proof-of-concept. Results show that in vivo molecular imaging of the Human Epidermal Growth Factor Receptor 2 (HER2) status in breast cancer using zirconium-89 labeled trastuzumab (^{89}Zr-trastuzumab) and ^{89}Zr-pertuzumab is feasible and safe in humans [5], though the optimal time interval between the intravenous injection of ^{89}Zr-trastuzumab and PET imaging for a high tumor to background contrast is 4–8 days [14]. Same-day imaging, as is done in daily practice with ^{18}F-FDG PET, would be optimal and can only be accomplished with shorter half-life radionuclides such as ^{68}Ga or ^{18}F [15]. This raises one key question: "How does one select the appropriate radioisotope and radiolabeling strategy for a pharmacophore?" The most straightforward answer would be to select a radiolabel with a radioactive half-life that is compatible with the bioactivity of the pharmacophore [13]. In addition to other factors such as high binding affinity, high specificity, and imaging favorable pharmacokinetics (e.g., fast clearance, high imaging contrast at early time points) [13].

^{18}F-Fluoroestradiol (FES)

On the molecular level, breast cancer is a heterogeneous disease; molecular features include the activation of HER2, activation of hormone receptors (estrogen receptor (ER) and progesterone receptor (PR)) and/or BRCA mutations. Treatment strategies differ according to molecular subtype [16]. The majority (more than 70%) of breast tumors express ER [17]. ER functions as a transcription factor. After estrogen binding, ER undergoes a conformational change, forms a dimer, and subsequently binds to DNA. At the DNA level, under the influence of several co-regulatory proteins, the transcription of estrogen-responsive genes takes place [18]. In breast cancer, transcription of estrogen-responsive genes results in proliferation and cell survival. Endocrine therapy can be used to interfere with this process by depleting circulating estrogens (via inhibition of aromatase), by competitive antagonism (e.g., tamoxifen), or by decreasing ER expression (e.g., fulvestrant) [18]. A novel way to determine ER activity is by PET imaging of the ER (ERα and ERβ) with the tracer 16α [^{18}F]fluoro-17β-estradiol (^{18}F-FES) [11]. [^{18}F] fluoroestradiol (FES), also known as Cerianna™, is the first FDA-approved PET imaging agent specifically indicated for use in patients with recurrent or metastatic breast cancer (MBC) as an adjunct to biopsy [19]. This tracer has the potential to visualize and quantify ER expression in multiple lesions non-invasively within an individual patient [19]. In a prospective multicenter trial, 200 patients with newly diagnosed MBC underwent extensive workup including ^{18}F-FES-PET imaging. For the analysis, ER expression in the biopsied metastasis was related to qualitative whole-body ^{18}F-FES-PET evaluation and quantitative ^{18}F-FES uptake in the corresponding metastasis. Whole-body ^{18}F-FES-PET assessment predicted ER expression in the biopsied metastasis with good accuracy: a sensitivity of 95%, a specificity of 80%, a positive predictive value (PPV) of 93%, and a negative predictive value (NPV) of 85% in 181 of 200 evaluable patients [20].

SNMMI convened an expert workgroup to comprehensively review the published literature for ^{18}F-FES-PET in patients with ER-positive breast cancer and establish appropriate use criteria (AUC) for ^{18}F-FES-PET. This AUC summarizes the findings and discussions of the SNMMI ^{18}F-FES workgroup. Of the clinical scenarios evaluated, the workgroup concluded that until now the most appropriate uses of ^{18}F-FES-PET are as follows: to assess for ER functionality when clinicians are considering endocrine therapy either at initial diagnosis of metastatic breast cancer or after progression on a prior line of endocrine therapy, to assess ER status of lesions that are difficult or dangerous to biopsy, and to assess ER status in lesions when other imaging tests are inconclusive [21]. The SNMMI ^{18}F-FES workgroup hopes that this document will support the appropriate clinical use of ^{18}F-FES-PET, promote investigation into areas requiring further research, and lead to more efficient approval of FES use by payers [21]. Although there is robust evidence that ^{18}F-FES-PET/CT offers the functional readout of ER status compared to conventional imaging such as CT/bone scan/^{18}F-FDG-PET, there is a paucity of literature on whether ^{18}F-FES-PET-guided management ultimately translates into improvement in patient reported outcome or survival, thus a prospective multicenter trial is warranted. Further, staging and restaging have been mentioned as potential indications for ^{18}F-FES-PET besides ER heterogeneity in MBC [22].

Several active clinical trials (some multicenter) are currently evaluating the predictive value of ^{18}F-FES-PET, often together with ^{18}F-FDG-PET or other targeted imaging agents, for its ability to identify metastases and intra-patient heterogeneity (NCT01957332), (NCT02398773), (NCT03726931), and (EUDRACT 2013-000-287-29) [19]. Further, the clinical utility of ^{18}F-FES-PET/CT in metastatic breast cancer patients after progression on first line hormonal therapy is being investigated in two multicenter clinical trials, with a primary objective to evaluate a change in therapeutic management plan assessed by comparing pre/post-^{18}F-FES-PET/CT treatment selection (NCT05068726), (NCT05486182). In short, evidence generation strategies have been developed as one of the key elements to boost adoption of ^{18}F-FES-PET/CT into real-world clinical practice.

HER2 PET

Besides ^{18}F-FES (Cerianna™), an FDA approved radiopharmaceutical, multiple HER2 PET radiopharmaceuticals are under clinical development [6]. Instead of hormone receptor expression, HER2 is used for breast cancer classification [23]. HER2 is a 185 kDa protein receptor expressed on the cell membrane of breast cancer cells. HER2 is a member of the epidermal growth factor receptor family. Activation of HER2 leads to homodimerization or heterodimerization with other epidermal growth factor receptor family members. This leads to downstream activation of the mitogen activated protein kinase and serine/threonine kinase pathways that ultimately results in cell proliferation and sustained survival [23]. HER2 is overexpressed in approximately 15-20% of breast cancers [24], conferring a worse prognosis for clinical outcomes and survival, and is a target for anti-HER2 therapies [23]. Breast cancers with HER2 overexpression in primary or metastatic sites will benefit from HER2-targeted therapies such as the monoclonal antibody, trastuzumab, resulting in a clear survival advantage [23]. A clear unmet need now exists for accurate noninvasive in vivo profiling of HER2 expression in patients with metastatic breast cancer so that the treatment regimen with the greatest prospect of improving patient survival can be selected [24]. However, all tested mAb or HER2-targeted antibody fragment radiopharmaceuticals labeled with ^{89}Zr, have a common feature that HER2-positive tumors would be imaged at 24 hours after injection, since tumor uptake increases up to 24 hours post-injection of the ^{89}Zr-PET radiopharmaceutical

before reaching a plateau [6]. The long waiting time for imaging of intact radiolabeled antibodies can be solved by using radiolabeled Fab fragments.

Due to their small size and high affinity, nanobodies can penetrate tumor tissues and bind antigens with high specificity, making them a suitable therapeutic and diagnostic tool [6,24]. Similarly, Affibody® molecules have a triple helix structure, which is also called an "artificial antibody". In contrast to antibodies, the smaller Affibody molecules have relatively fast uptake and clearance rates. In addition, the Affibody molecules have high affinity and stability, and thus, they are very well suited for molecular imaging. Multiple HER2-targeted Affibody molecules, have been investigated in clinical trials [6]. To date, most of the reported studies of radiolabeled Affibody molecules in the literature have used analogs of the HER2-specific Affibody molecules ZHER2:342 labeled with radiometals [6,25]. Recently, re-engineering of this Affibody molecules led to an optimized scaffold containing 11 amino acid substitutions in the nonbinding surface of the Affibody molecules removing similarity to the original protein A domain—ZHER2:2891 [25]. Further, to increase potential for automated site-specific good manufacturing practice-grade manufacture and allow broad clinical access to a HER2-imaging agent, ZHER2:2891 has improved thermal and chemical stability by avoiding deamidation, as well as increased hydrophilicity of the nonbinding surface; positive attributes for ease of peptide synthesis and in vivo pharmacokinetics [25]. The latter property is desirable to permit imaging within 1- to 2-hours post radiopharmaceutical injection [25]. The ZHER2:2891 Affibody molecules is the pharmacophore used for [68Ga] ABY-025 and [^{18}F] GE-226 [6,25].

[^{18}F]GE-226 binds to the HER2 receptor with high affinity to a different epitope than the target for the HER2 targeted anti-cancer therapies, trastuzumab and pertuzumab [26]. The active molecule is a 61–amino-acid peptide that is modified site to allow labelling with [18F]4-fluorobenzaldehyde. The radiopharmaceutical has been shown to bind selectively to tumors expressing HER2 in nonclinical [25] and clinical settings [27]. Because of its small size, this compound has advantages such as fast blood clearance and rapid uptake by tumors. Nonclinical studies suggest that HER2 targeted therapy does not affect tumor uptake, and therefore imaging efficacy of [^{18}F]GE-226 [25]. The efficacy of [^{18}F]GE-226 as the only Affibody molecules labeled with ^{18}F has been investigated in a First in human (FIH) clinical study (NCT03827317) [27] in determining the expression of HER2 in MBC patients. PET imaging with [^{18}F]GE-226 was able to differentiate HER2-positive from HER2-negative breast tumors, as well as differentiating HER2-positive from HER2-negative metastatic lesions in lymph nodes and bones. However, liver metastases were often vague and hard to identify because of high background uptake in the liver. In studies of other radiotracers, this problem has been attributed to a "sink effect" that can be addressed by increasing the mass dose of the peptide [28].

Whilst the importance of correct HER2 assessment becomes important with the increasing use of trastuzumab emtansine [24], which affects only HER2-overexpressing cancer cells, HER2-low disease has attracted significant attention [29]. Until recently, only people with breast cancers whose tumor cells express high levels of HER2, known as HER2-positive breast cancer, had been shown to benefit from drugs that target HER2; however, only about 15% to 20% of people with breast cancer have HER2-positive tumors. The rest have no detectable HER2 or low levels. The newly designated HER2-low form of MBC has traditionally been challenging to treat. The classification for HER2-low that is used in most clinical trials [29] is defined by a score of 1+ on immunohistochemistry (IHC) analysis or by an IHC score of 2+ and negative in situ hybridization (ISH) results. The recent study DESTINY-Breast04 [29] enrolled patients with metastatic or inoperable HER2-low breast cancer. Nearly 90% of the participants had hormone receptor–positive disease. Efficacy and safety of trastuzumab deruxtecan (T-DXd) versus treatment of physician's choice were compared in patients with HER2-low MBC treated with 1 to 2 prior lines of chemotherapy in the metastatic setting. In the group receiving T-DXd, progression-free survival was about 10 months, compared with 5 months in the chemotherapy group. The median overall survival was 23.4 months for subjects who received T-DXd and 16.8 months for subjects in the chemotherapy group. The numbers were similar when the researchers looked specifically at study subjects who had hormone receptor–positive disease. T-DXd is the first HER2-targeted therapy shown to provide clinically meaningful improvement in progression-free and overall survival compared with standard chemotherapy in people with HER2-low MBC [29]. These study findings are expected to change how metastatic HER2-low disease breast cancer is diagnosed and treated and it is fundamentally changing the way breast cancers are classified in patients with metastatic disease [30]. With additional HER2-targeted antibody–drug conjugates expected to become available in the coming years, novel, more accurate, and sensitive ways of assessing a tumor's HER2 status warrant development.

It is known that HER2-low expression is highly unstable during disease evolution, mostly driven by cases switching from HER2-0 to HER2-low. The overall rate of HER2 discordance was 38.0%, represented by HER2-0 switching to HER2-low (15%) and HER2-low switching to HER2-0 (14%) [31]. A recent study [32] found that pathologists did not always agree when it came to distinguishing between HER2-low and HER2-0 breast cancers using IHC. Only a 26% concordance between 0 and 1+ compared with a 58% concordance between 2+ and 3+ was reported [32]. In addition, HER2-low assessment using 2 of the market's leading IHC tests (Dako Herceptest and Ventana 4B5) may provide different results [33]. Reports of clinical activity using the next generation of HER2-targeting antibody-drug conjugates in HER2-low breast cancers suggest that some strategies of targeting HER2 could be effective in this patient population while raising considerable concerns over limitations

in our current testing methodologies and our ability to accurately identify such patients [34]. Researchers are developing new tests that can detect lower HER2 levels, but these are not yet ready for use in everyday patient care.

A phase II study of [68Ga]ABY-025 PET for non-invasive quantification of HER2-status in solid tumors is ongoing (NCT05619016). The goal of this phase II clinical trial is to improve the selection of patients with solid tumors including HER2-low advanced breast cancer who would benefit from effective treatment with HER2 targeted drugs. The feasibility of using HER2 PET for the detection of HER2-low tumors warrants investigation for its potential large clinical impact where it estimates that at least 50% of people with breast cancer fall into HER2-low category—including some patients who have either hormone receptor–positive breast cancer or triple-negative disease, who will now have a new strategy to target and treat their disease [29]. In short, multiple novel HER2 radiopharmaceuticals, which are under active investigation with more clinical studies planned to further characterize their diagnostic performance [6]. Defining their clinical utility will be of key importance from a translational strategic view.

Immunotherapy & Molecular Imaging

William Bradley Coley is known today as the Father of Immunotherapy, as he first attempted to harness the immune system to treat bone cancer in 1891 [35]. More recently, with advances in the understanding of tumor biology, evasion of immune destruction has been established as one of the hallmarks of cancer [36]. In addition to cancer cells, tumors exhibit another dimension of complexity: they contain a repertoire of recruited, seemingly normal cells that contribute to the acquisition of hallmark traits by creating the ''tumor microenvironment.'' [36]. The emergence of immunotherapy, in the form of immune checkpoint inhibitors (ICI), has irrevocably altered the paradigm of cancer treatment over the past decade, with several drugs already approved by the FDA for multiple cancer types including breast cancer [35]. Despite the successful application of cancer immunotherapy across a broad range of human cancers, only a minority of patients benefit from these therapies. This likely reflects the complex and highly regulated nature of the immune system [37]. The top 10 challenges in cancer immunotherapy have been outlined [37] and maximizing personalized approaches through composite biomarkers has emphasized and highlighted the importance of developing immuno-oncology biomarkers with good spatial and temporal resolution, so that the complexity in immune dynamic response to immunotherapy is better understood. There are over 3,000 ongoing clinical trials of immunotherapy agents, either alone or in combination with standard of care or other targeted agents [38]. ''What is the right therapeutic approach for their specific disease?'' Today, diagnostic testing for cancer patients is not fully embedded into clinical practice [37]. New molecular imaging tracers allow for whole-body visualization with PET of tumor and immune cell characteristics and drug distribution, which might guide treatment decision making [39]. They are emerging as a valuable method to understand the complexity of the tumor immune microenvironment. Here, we summarize some recent developments in molecular imaging for immuno-oncology, such as PD-L1, CD8, and Granzyme B.

Diagnostic tests based on biopsy PD-L1 immunohistochemistry (IHC) have been approved to predict the likelihood of patient response to ICIs, but response rates remain low. A first-in-human PD-L1 PET imaging study was performed with ^{89}Zr-atezolizumab in 22 patients with metastatic non-small-cell lung cancer, bladder cancer, and triple-negative breast cancer [40] for a whole-body assessment of this immune checkpoint molecule. While ^{89}Zr-atezolizumab PET imaging demonstrated the proof-of-principle in terms of safety and efficacy in various solid tumors, the optimal time interval between the intravenous injection of ^{89}Zr-mAb and PET imaging for a high tumor to background contrast is a few days [14,40], which limits its temporal resolution. In this small study, clinical responses in patients were better correlated with pre-treatment PET signal than with IHC, and the results showed heterogeneity of PD-L1 expression both within and between tumor lesions. Adnectin -based PET tracers have also been evaluated for PD-L1 PET imaging. The first tracer evaluated in humans was [^{18}F] BMS-986192, a fluorine-18 labeled anti-PD-L1 adnectin, where image scans were acquired 1 hour after tracer injection [15].

Another immune biomarker that has been evaluated with PET imaging is CD8, which is expressed on the surface of CD8+ T cells. These cells are central to immunotherapy efficacy and when activated following ICI treatment, they secrete the effector molecule Granzyme B, to mediate tumor cell death via apoptosis [39]. In a first-in-human CD8 PET imaging study, ^{89}Zr-Df-IAB22M2C, an anti-CD8 minibody, evaluated the tumor distribution of CD8+ T cells [41]. Recently, whole-body CD8+ T cell distribution was assessed in cancer patients before and during ICI treatment with 89ZED88082A, an ^{89}Zr labeled one-armed antibody [NCT04029181]. The study confirmed that CD8+ T cell presence in tumor lesions imaged before ICI treatment could be predictive for patient overall survival, highlighting the potential of CD8 imaging as a predictive biomarker to personalize treatment for patients receiving immunotherapy [42]. Moreover, whole-body imaging data from this pivotal study illustrated the complexity of the dynamics of intra-tumoral CD8 expression during ICI treatment, which differed between patients and between lesions, highlighting the limitation of single-lesion biopsies. The results provide a strong rationale for the use of CD8-specific PET tracers labelled with fluorine-18 to allow repeat imaging following initiation of immunotherapy with shorter frame sequential imaging, to track spatio-temporal changes in CD8+ T cells, increasing the chance of capturing a more complete time course.

Granzyme B is a serine-protease released by activated T-cells as well as natural killer cells for eliminating target cells [39]. Visualization of Granzyme B might therefore allow early assessment of response to ICI therapy [39].

Interim analysis of a studying imaging patients with [^{68}Ga-NOTA]-hGZP (CSB-111), a small peptide tracer specific for human Granzyme B supports the potential of this biomarker to monitor response to immunotherapy [NCT04169321] [43]. In the first eight patients imaged in this study, as well as establishing the tracer was safe and well tolerated, tracer uptake in lesions with respect to blood pool, correlated with their response to ICI. Another Granzyme B targeted tracer, ^{68}Ga-grazytracer, resulted similar findings in the first 5 patients undergoing ICI treatment [44]. While none of the molecular imaging radiopharmaceuticals are FDA-approved biomarkers to select patients for immunotherapy, there is a lot of academic and industry endeavors to develop novel PET tracer for immuno-oncology, as the understanding of the immune-resistant mechanisms is essential to improve current cancer immunotherapies [45]. As tumor biology understanding continues to evolve, PET tracers to facilitate immuno-oncology therapy development and to guide treatment selection and monitor patient responses, may expand to include tracers specific for other immune cell types including B cells and macrophages, and/or other tumor microenvironment markers such as stromal cell, hypoxia and metabolic targets.

The Role of Artificial Intelligence

With the growth of targeted PET tracers and approval of these tracers by regulatory authorities, there is a need for software tools to aid the transition of these tracers from academic sites into more routine clinical use. Image interpretation involves both detection and quantitation tasks. When there are multiple diagnostic scans, either at the same time point or over multiple time points, or a patient has many metastases, the time required to fully complete these tasks can quickly become challenging or even infeasible for research and clinical studies. In the case of response evaluation, the compromise has been the adoption of response criteria like Response Evaluation Criteria in Solid Tumors (RECIST) or Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST), where only a handful of lesions are tracked quantitatively over time [46]. Additionally, iRECIST (iRECIST is based on RECIST 1.1. Responses assigned using iRECIST have a prefix of "i" (ie, immune)) has been developed to allow more standardized assessment of response under immunotherapy, where pseudo-progression can be a confounding factor [47,48]. Despite the widespread adoption of current response criteria, they should be applied with caution, and there remains opportunity for exploring alternative means of measuring and assessing therapy response. A clear opportunity lies in development of software tools with artificial intelligence (AI), where the burden of the complete evaluation of a patient's disease may provide a new level of decision-making support. To start, automated image annotations and generation of reports removes reader variability to provide consistent quantitative assessments, which can then inform and assist clinicians in making faster and more confident patient management decisions. The next step is to combine imaging biomarkers with other biomarkers and comparing historical patient data to predict the response to a given therapy. In both cases, there is a clear need to characterize whole-body disease heterogeneity, as disease progression is often driven by areas of therapy resistance, as is the case for endocrine resistance in breast cancer [49]. Software tools are well-situated for this task through automated registration between images and time points followed by lesion identification, segmentation, and analysis.

Two example software solutions that have FDA clearance, are PYLARIFY AI by Lantheus and TRAQinform IQ by AIQ Solutions. PYLARIFY AI is an AI platform developed to assist in standardized quantification of PSMA PET/CT scans, through automated segmentation and quantitation, localization and characterization of disease (by lesion type, location, volume, and SUV), and generation of a standardized quantitative report [50,51]. TRAQinform IQ also uses AI to identify regions of interest in PET/CT scans to compare differences and evaluate quantitative changes, thus providing comprehensive information about how a patient's cancer is responding to treatment [52,53]. Software solutions such as these will continue to be developed and will ultimately enable more efficient clinical workflows, especially for newer PET radiotracers, for which normal and diseased uptake patterns may be unfamiliar. The future will see continued growth of software tools with expansions of more radiomics features for the interpretation of PET/CT and PET/MR studies. Decision guides for patient care will hopefully lead to improved patient outcomes.

Perspectives and Summary

Molecular imaging is a quickly evolving field. Since 2012, nine novel PET radiotracers received FDA approval for cancer indications, in comparison to only two new PET/SPECT tracers between 2000 and 2009 [54]. We anticipate this accelerating trend to continue as more groups contribute to their development. New treatment schemes call for a more precise stratification of patients which requires PET molecular imaging [55]. The commercial development of molecular imaging agents can be as challenging as the development of therapeutics. In fact, the development of radiopharmaceuticals shares much in common with standard drug discovery and development practices. Partnering between academia, pharma, and imaging companies has been advocated as the parallel paths for the development of therapeutic drugs and diagnostic agents, raising exciting opportunities for technology convergence, where applications from both domains converge and technologies from one domain can accelerate processes in the other [54].

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