Molecular Imaging in Positron Emission Tomography

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Molecular imaging has become widely used in many diseases, with a particular focus on cancer care. It refers to the in vivo characterization and measurement of key biomolecules and molecular events underlying malignant conditions. Positron Emission Tomography (PET) is the gold standard in clinical molecular imaging because it possesses the high sensitivity required for deep tissue penetration and visualization of most interactions between physiological targets and ligands.

precision medicine molecular imaging radionuclides

1. Introduction

Hippocrates of Kos (c. 460—ca. 370 BC) stated that it is more important to understand the type of person with a disease than to identify the type of disease the patient has. This statement by the father of modern medicine is considered the platform of personalized medicine (PM). The term “personalized medicine” refers to a relatively new field of medicine that aims to enhance diagnostic precision and reduce therapeutic failures. There is wide use of molecular imaging modalities in screening, diagnosis, treatment, assessment of disease heterogeneity, progression planning, molecular characteristics, and long-term follow-up for various diseases. As opposed to conventional imaging techniques, molecular imaging approaches images as data that can be mined and used to extract additional information as well as assess large populations of patients [1][2].

Significant rapid advances in molecular biology, cancer biomarkers, and radio-genomics help to have a better understanding of cancer, resulting in developing personalized medicine and molecular imaging since both are strongly dependent on the collaboration of different clinical disciplines. Personalized medicine is a comparatively new emerging practice of medicine that focuses on providing the tumor genetic profile to proffer individual prevention, diagnosis, and treatment, which reflects on cancer treatment by improving the anti-cancer therapeutic efficiency and reducing the adverse effects. Molecular imaging is used widely in screening, detection and diagnosis, treatment, assessing disease heterogeneity and progression planning, molecular characteristics, and long-term follow-up. Moreover, it is able to detect very tiny tumors and assess their activity numerically, which makes molecular imaging one of the most scientific reasons that contributes greatly to expanding and developing the personalized medicine, research, clinical trials, and medical practice of cancer fields, evolving a new generation of platforms with greater accuracy and sensitivity for in vivo quantification and characterization of various biological processes [3][4][5][6][7][8][9][10].

2. Positron Emission Tomography (PET)

PET is the gold standard in clinical molecular imaging because it possesses the high sensitivity required for deep tissue penetration and visualization of most interactions between physiological targets and ligands. Due to this, non-invasive detection up to the picomolar level is achievable. By producing quantitative images and 3D morphological images at quick scan times, which enables dynamic imaging (time-resolved images to be generated), it has become the fastest-growing clinical imaging technology and is now a current tool in cancer diagnoses and cancer treatment planning. The basis of the PET technique is the phenomenon of positron–electron annihilation, resulting in the formation of two high-energy photons (511 keV) emitted in opposite directions (180°). PET using biomarkers are labelled with positron (a positively charged electron)-emitting radioisotopes, primarily nitrogen, oxygen, carbon, and fluorine, which are short-lived elements (2–110 min) used to image the molecular interaction of biological processes such as cell proliferation, glucose metabolism, amino acid uptake, and membrane biosynthesis. They also deliver information about biomarker expression and tissue biochemical characteristics, provide the exact location of a lesion frequently before symptoms arise, determine molecular phenotypes, provide valuable molecular, functional, and metabolic information, and aid in determining the tumor biology of neoplasms by creating quantitative imaging that is capable of transforming collected gamma rays into quantitative terms. These quantitative images support safer surgical resections that minimize morbidity and mortality as well as increase the cost-effectiveness of healthcare with a measurable return on investment. They also aid in the diagnosis, optimization, and personalization of treatment for a variety of diseases. Moreover, the use of several tracers in PET technology is one of the technique's distinctive advantages. Over the past decade, the clinical use of PET has increased dramatically. The most often used glucose analog is 18F-fluorodeoxyglucose (FDG). Some novel receptor-active peptides have found usage in the transport and phosphorylation of FDG, but then the FDG is stuck [2][3][8][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27][28].

Due to the special characteristics of PET and the quick development and growth of hybrid PET in recent decades, the scope of PET clinical applications has increased. By advancing the clinical use of PM, PET clinical applications will continue to support the role of molecular imaging in the era of personalized medicine. PET has been used in oncology using antimetabolic image information for diagnosis and identifying undetected distant metastases, stages, and volume in cancers and the presence of inflammatory infiltrate. By providing personalized medicine, such as personalized chemotherapy, immunotherapy, targeted therapy, and dosage, as well as personalized evaluation of response early in treatment due to changes in glucose metabolism and evaluation of the antiangiogenic therapeutic result, PET scanning can improve cancer management. PET scans have many advantages in toxicology studies because they are an important tool in personalized drug discovery and development, screening, identifying new drug candidates, and evaluating individual patient susceptibility to treatment by nanocarrier systems. PET imaging is ideal for radiopharmaceutical micro-dosing research and drug therapy development. Additionally, it contributes to minimizing expenditure on medication development and animal use in preclinical toxicological research. In order to determine whether the drug concentration delivered to the target is sufficient to elicit a pharmacologic response, the PET imaging protocol can be used to measure both AR levels (in the sense of a predictive biomarker for estimating response to therapy and monitoring drug-target engagement) and AR activity using a PD biomarker [1][10][14][21][22][24][27][28][29][30][31][32][33][34][35].

2.1. PET-US

Hybrid imaging adds value to imaging data and provides efficient diagnosis, radiogenomics, and therapy planning. PET combined with various modalities such as US, MRI, optical imaging systems, immune probes, and CT, are most commonly used in clinical settings today. PET-US uses radiolabelled microbubble shells such as 18F-labeled, albumin-shelled, and VEGFR2-targeted, which have a short half-life and are several micrometres in size. This modality can be used for investigating the biodistribution of microbubbles after i.v. injection and offers better quantification, which is particularly true in biodistribution analyses and can be used for targeted drug delivery, such as delivering VEGFR2 in breast cancer [2][36][37][38].

2.2. PET-MRI

PET-MR units are currently in development and being used in pre-clinical environments. This dual modality allows high spatial resolution, temporal resolution and accuracy, superior soft tissue contrast and multi-planar capabilities, and less ionizing radiation exposure. These features allow it to perform translational research from a cell culture setting to pre-clinical animal models to clinical applications, which is advantageous for the drug discovery and evaluation process that could help optimize the development of new drugs non-invasively and develop radiotracers. Additionally, it has been used to measure processes as diverse as blood flow and volume, tissue oxygenation, tissue pH, protein synthesis, cellular proliferation, enzyme kinetics, endogenous metabolite concentration, water diffusion, tissue anisotropy, vascular permeability, and better treatment response, providing information on downstream effects from multiple pathways, even though it is more limited with respect to the number of molecular processes that can be imaged, and provides additional opportunities for facilitating targeted biopsy and the determination of its efficacy. Hybrid PET/MR systems provide complementary multi-modal information about perfusion, metabolism, receptor status, and function, together with excellent high-contrast soft tissue visualization without the need to expose the patient to additional radiation, which makes them very useful for precision medicine cancer care in cardiac sarcoidosis, degenerative diseases such as Alzheimer's disease, and cancers such as pharyngeal and ovarian cancer [2][10][11][14][24][25][26][30][36][38][39][40][41][42][43].

2.3. Positron Emission Tomography-Optical Imaging (PET-OI)

PET and optical imaging have been combined and demonstrated in vitro, ex vivo, or in vivo in recent years. The principal benefits are related to the combination of increased tissue penetration of radiation from positron emitter radionuclides that enables non-invasive quantitative imaging and tumor detection and light generated by the fluorescent probe for optical imaging during surgery, in particular, robotic surgery. This allows for effective, targeted drug delivery in vivo without causing systemic toxicity, and both the administered dose and therapeutic efficacy can be precisely monitored non-invasively over time. In order to image and evaluate the concentration and function of the target without having an impact on it, the probe is utilized in extremely low mass amounts during PET imaging (tissue concentrations of around femtolitres per gram of tissue). Similarly to PET/MRI, this dual imaging is used in the drug development process to identify, accurately measure, and assess medications' performance in vivo in

mice models and human patients. This will make it possible to discover drugs more successfully using a systems-based approach that is driven by molecular imaging and diagnostic techniques [2][43][44].

2.4. Immuno-PET

Despite not being fully realized, the combination of radiation therapy and immunotherapy has the potential to change the field of oncology. Immuno-PET imaging could play a critical role in providing the crucial information required to help understand this sophisticated connection. Nowadays, immuno-PET is a safe multimodality treatment strategy that helps to move toward precision medicine using radio-labelled antibodies and targets that combine with the high sensitivity and quantitative potential of PET non-invasively to provide quantitative, high quality, high spatial, and temporal resolution images that help to estimate the antigenic expression level of immuno-PET such as immune checkpoints and effector molecules, or the detection and tracking of immune cell populations such as T-cell subsets and chimeric antigen receptor T-cells, in identifying diseases and stages, responses to therapy, and whole-body bio-distribution in real-time, which leads to improvement in cancer patient management. In contrast, the long half-life of intact antibodies hampers their use as imaging agents due to the several days required for blood and background clearance in order to achieve a good signal-to-noise ratio. These emerging methods in PET may improve patient selection and target delineation and, ultimately, may become a useful tool for adaptive radiation planning as we collectively strive toward personalized medicine in radiation oncology [32][35].

2.5. PET-CT

The most widely available and widest molecular imaging modality used in oncology is PET-CT due to its non-invasive nature and high accuracy in its application and management in oncology. PET-CT is a quantitative technique that provides information about morphologically relevant, physiologic, and pathologic processes at the molecular level, as well as biodistribution, dosimetry, the limiting or critical organ or tissue, and the maximum tolerated dose (MTD). It could detect and quantify abnormal molecular activity throughout the body and have high accuracy in differentiating malignant tumors from benign ones. It can also be used to evaluate the response rates of chemotherapy to allow easy management and early detection of tumor recurrences. This is useful in order to identify non-responders as soon as possible and to modify treatment. Furthermore, radiation planning with a PET-CT scan can be more beneficial by modifying the radiation dose for patients with situs dose deposition in the tumor. It has the ability to determine the more active and metabolic areas within the tumor to direct more aggressive radiation to reduce the chance of converting to more aggression, which fulfils the potential of personalized medicine. Moreover, there are also dynamic PET/CT scans, which are a new technology of PET/CT scan that allows new opportunities for personalized nuclear medicine by providing better image quality in a short scan time that can be used to optimize administered radioactivity and for pediatric patients and sick patients who cannot remain still for long periods [2][24][40][44][45].

PET-CT scans have high sensitivity and specificity, allowing them to use radiopharmaceutical tracers such as F-18 fluorocholine, Ga-68, and C-11 methionine to measure cellular characterization and biological processes in a tumor at the molecular and cellular level. The ability to quantify the disease at a molecular level, tumor hypoxia, and bone

metastases may help assess the global inhibitory effect of such multi-targeted therapeutic approaches. Notwithstanding, there is a lack of personalized radiotracers in PET-CT radiotracers, which presents a major limitation to the molecular imaging role in personalized medicine [9][21][40][45][46][47].

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