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Quantitative Analysis of Tumor Response Using Advanced PET/CT Imaging Modalities

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Annotation: In the field of oncology, cross-sectional imaging has undergone a monumental shift in the paradigm of diagnosis and monitoring response to therapy in patients affected by solid tumors. Over the years, the evolution of FDG PET (Fluorodeoxyglucose Positron Emission Tomography) has revolutionized the way we evaluate and manage these patients.

1. Introduction to PET/CT Imaging in Oncology

Introduction. More recently, the introduction of combined PET/CT (Positron Emission Tomography/Computed Tomography) imaging, which combines molecular and anatomical information, has further enhanced our ability to diagnose and assess treatment response in solid tumors. This integration of PET/CT has opened up new possibilities and expanded our understanding of tumor behavior. The use of CT-based RECIST (Response Evaluation Criteria in Solid Tumors) guidelines, such as RECIST 1.0 and its revised versions, in conjunction with PET/CT imaging has proven to be highly valuable in evaluating the response, resistance, and progression of solid tumors. By utilizing these guidelines, we are able to accurately measure and analyze the changes in tumor size and morphology, providing crucial information on treatment efficacy. At our institution, we conducted a comprehensive study comparing the evaluation response using RECIST 1.1 CT criteria with PET/CT, and we observed a significant difference of

36%. This finding highlights the importance of utilizing advanced imaging modalities to obtain more precise and comprehensive data. The integration of PET and CT has presented unparalleled advantages in the field of oncology imaging. Positron emission tomography (PET) has emerged as an indispensable tool in the initial evaluation and follow-up of various malignancies. Its ability to detect functional abnormalities, such as increased glucose metabolism (as reflected by standardized uptake values or SUVs), has revolutionized cancer imaging. By combining PET with CT, we can obtain both functional and anatomical information in a single imaging session. This hybrid imaging modality has vastly improved our ability to visualize and characterize tumors, leading to more accurate diagnoses and treatment plans. Furthermore, PET not only provides anatomical details but also yields valuable functional parameters that further enhance our understanding of tumor biology. Parameters such as SUVmax (maximum standardized uptake value), SUVmean (mean standardized uptake value), metabolic tumor volume, and total lesion glycolysis offer quantitative measurements that aid in treatment planning and monitoring. These measurements provide a comprehensive understanding of tumor behavior, allowing us to make more accurate prognoses and tailor treatment approaches to individual patients. By incorporating these advanced imaging techniques into our practices, we can optimize patient outcomes and ensure high-quality care. The objective of this review is to provide a comprehensive overview of advanced imaging technical considerations and clinical aspects for the quantitative analysis of FDG PET in oncology. Through an in-depth analysis of the strengths and limitations of current imaging modalities, we aim to enhance our understanding of how these tools can be effectively utilized in research and clinical practice. By delving into the intricacies of advanced imaging, we can develop a more nuanced approach to oncology imaging, shaping the future of patient care and treatment. The integration of advanced imaging modalities, particularly PET/CT, has significantly advanced the field of oncology imaging. Through the combination of molecular and anatomical information, we are able to obtain a more comprehensive understanding of tumor behavior and response to treatment. This comprehensive understanding allows us to make more informed decisions regarding the diagnosis, treatment, and management of patients with solid tumors. Furthermore, the incorporation of advanced imaging techniques has the potential to improve patient outcomes and overall quality of care. By continuously striving to optimize the use of these imaging modalities through ongoing efforts in research and clinical practice, we can further enhance the field of oncology imaging as a whole, ensuring the best possible outcomes for our patients. [1][2][3][4][5][6][7]

1.1. Historical Development and Evolution of PET/CT Imaging

For over eight decades, imaging technologies have played a pivotal and indispensable role in the expansive field of oncology research and clinical practice. Throughout this extensive period, typical imaging techniques have undergone substantial advancements and progressions in both technological sophistication and overall development. However, despite these remarkable achievements, they have predominantly remained rooted in capturing and depicting anatomical and structural aspects. In stark contrast, cancer is a profoundly intricate and multifaceted molecular disease that necessitates a more nuanced and comprehensive understanding. Prior to the groundbreaking advent of non-invasive molecular imaging, the true essence and manifestation of cancer could solely be elucidated through a histologic basis – a highly invasive and burdensome process. Yet, with the advent and subsequent fusion of positron emission tomography (PET) and computerized tomography (CT), there emerged a monumental and paradigm-shifting milestone in the arena of structural and functional imaging technologies. This revolutionary approach, commonly known as PET-CT, enabled clinicians and researchers alike to embark on an entirely new frontier of cancer exploration and diagnosis. By harnessing the virtually limitless power of molecular imaging, it became possible to gain invaluable insight into the intricate workings of cancer cells at the molecular level. This unprecedented fusion of anatomical and molecular data has provided the medical community with an unparalleled platform for not only detecting cancer at its earliest stages, but also for monitoring treatment response and precisely assessing disease

progression. The amalgamation of PET and CT, functioning as an indomitable duo, has enabled oncologists to peer deep into the molecular landscape of cancer, transcending the boundaries that once confined our understanding. By skillfully integrating these two modalities and their respective strengths, a comprehensive picture of cancer can be meticulously constructed – one that encompasses not just its morphological characteristics, but also its underlying biological intricacies. As the field of oncology continues to evolve at a rapid pace, the fusion of PET and CT imaging technologies stands as a testament to humanity's unyielding pursuit of progress. These groundbreaking advancements in imaging have undeniably revolutionized the way we perceive and combat cancer, ushering in an era of unprecedented precision and personalized medicine. Moving forward, the collaborative efforts of researchers, clinicians, and technology pioneers will undoubtedly pave the way for further groundbreaking discoveries, fueling the eternal quest for effective treatment strategies and, ultimately, a world free from the burden of cancer. [8][9][10][11][12]

CT started out as two axial scans in the mid-1970s, and by the early 1980s, it had developed into multislice acquisitions. This led to higher-contrast spatial resolution and speed. Likewise, early PET systems were also axial in nature but with a single-radiation emission acquisition, until the development of an in-line system with both PET and CT systems. This was the beginning of the hybrid molecular imaging age. This combined imaging approach was responsible not only for improving PET’s overall diagnostic accuracy but also for permitting correlative analysis of standardized uptake value correlations in oncology. A patent for a combined single-emission PET and CT imaging system was applied for in the mid-1980s, but it was not until 1990 that the first clinical proof-of-principle study characterizing the first “modern” PET/CT scanner was carried out. In 1998, the first integrated PET/CT system, which combined the latest components in both hardware and software technology, was commercialized. The advance in particular software-hardware interplay was principally in the timing, aligning, and registration of each modality to provide the most accurate standard uptake value integration. In other words, there were continuous hardware improvements in the microelectronics industry that principally supported these early advances. Following the beginning of the 21st century, continued improvements in more recent hardware and software applications integrating PET/CT advanced symmetrical and nonsymmetrical partial spread of the point-spread function application. With state-of-the-art reconstruction and time-of-flight applications, further improved PET’s spatial resolution down to a range close to that of standard high-resolution MRI. Such software advancements, along with component technology, have advanced much faster given continuous international economic investment in computer hardware and software industries over the past five years than in the previous thirty years. [13][14]

Finally, the crucial role that radiological imaging plays in the field of oncology has undeniably established itself as an exceedingly valuable prognostic, predictive, and clinical tool. Its significance extends beyond a mere diagnostic and staging reference point, making a substantial impact on our understanding of cancer. These assertions, which have revolutionized the way we comprehend malignant diseases, are grounded in an array of comprehensive, large-scale research studies. These landmark investigations have consistently presented overwhelming evidence, affirming the unparalleled significance of radiological imaging. It is important to note that the evidential support extends beyond a singular radionuclide and encompasses a variety of them, including PET, PET/CT, and PET/MRI. Despite their distinctive physiological actions, all these modalities unequivocally reflect the glucose metabolic activity, collectively serving as a true representation of the radiation's impact. Therefore, these arguments are not confined solely to a particular radioisotope but can be applied universally, embracing the entire spectrum of radionuclides. The diverse applications and merits of radiological imaging in the realm of oncology are manifold. Firstly, as a prognostic tool, it allows healthcare professionals to predict the likely outcomes and course of treatment based on the observed patterns and characteristics of tumors. This knowledge empowers medical practitioners to tailor their therapeutic approaches,

optimizing patient outcomes while minimizing unnecessary interventions. Moreover, radiological imaging significantly enhances the ability to make accurate predictions regarding the response to specific therapies. By closely monitoring the changes observed in tumors over time, it becomes possible to evaluate the effectiveness of various treatments, guiding clinicians towards the most suitable therapeutic strategies. This predictive capability fundamentally alters the landscape of clinical decision-making, facilitating personalized medicine and improving patient care. In addition to its predictive capabilities, radiological imaging serves as a critical clinical tool, ensuring the accurate and precise delivery of radiation therapy. By providing clinicians with detailed anatomical information, it aids in identifying the target tissues, sparing healthy cells from unnecessary radiation exposure. Consequently, this precision minimizes the potential for adverse effects and maximizes the therapeutic benefits, ultimately improving the overall quality of life for cancer patients. Notwithstanding its value as a prognostic and clinical tool, radiological imaging remains an indispensable standard of reference for accurate diagnosis and staging. In many cases, it serves as the cornerstone upon which the initial assessment is built, providing crucial insights into the exact location, size, and extent of tumors. This vital information forms the basis for treatment planning, enabling clinicians to develop well-informed strategies tailored to each patient's unique circumstances. In conclusion, the role of radiological imaging in the field of oncology cannot be overstated. Its value as a prognostic, predictive, and clinical tool, combined with its significance as a standard of reference for diagnosis and staging, is grounded in a multitude of large-scale research studies. The remarkable efficacy of radiological imaging is not limited to any particular radioisotope but encompasses various modalities, all of which effectively reflect the glucose metabolic activity. This transformative technology has revolutionized cancer care, empowering healthcare professionals to optimize treatment outcomes, enhance patient care, and ultimately bring us one step closer to conquering this formidable disease. [15][16][17][18][19][20]

2. Principles of PET/CT Imaging

One of the more recent and advanced methods used for imaging in the field of PET/CT is to fully understand the importance and value of the information obtained using PET/CT in particular and all PET imaging in general. The specialist must possess certain fundamental knowledge regarding the manner in which imaging in general and PET/CT imaging in particular works. PET Imaging and Principles. A PET scanner can register positron-emitting radionuclides that are injected into the human body. These are the result of a radioactive decay referred to as beta+ decay. During beta+ decay, the radionuclide emits a positively charged positron. Furthermore, it also emits a neutrino and a neutron. When a positron decays, it annihilates with an orbiting electron. As a result of this reaction, two 0.511 MeV annihilation photons are formed. They are emitted at an angle of 180 degrees, that is, collinearly opposite to each other. When positron annihilation occurs, the two 0.511 MeV gamma photons travel in opposite directions. They are registered by the detectors of the PET scanner and are used in imaging. As a result, the PET creates images. The PET is a way of providing a visualization of the activity distribution formed as a result of the positron decays, and the brain choline compound is probably the best-studied kinase analog. The two characteristic properties of PET are 1) the spatial distribution and 2) the decays in temporal format. CT stands for computerized tomography. It provides high-resolution anatomical information and is based on tomography, the combination of slice-forming techniques and computer technology. It generates a 3D image of an object. PET and CT studies are performed consecutively in the same imaging session. PET provides functional imaging of the brain's ability, while CT provides the 3D anatomical imaging of the lesions. PET and CT data are aligned in the computer to obtain the superposition of the anatomic richness and the pathophysiological activity of the lesions. Calibrated attenuation-corrected PET emission data can be obtained using CT, and attenuation correction of PET activity images is likely to be essential for all current modalities. The requirements for calibration and quality assurance of the CT x-ray tomography components are more rigorous, as these are essential aspects for diagnostic multiplanar, single photon emission computerized tomography, whole body, and other clinical applications and exams using anatomic

or physiological cross-sectional images. [21][22][23][24][25]

2.1. Physics and Instrumentation of PET/CT Scanners

Positron emission tomography (PET) is an exquisitely sensitive non-invasive diagnostic imaging method that quantifies not only functional parameters such as myocardial perfusion, glucose metabolism, and receptor density, but also provides molecular and cellular information. The PET scanner contains a plethora of detectors typically arranged in rings to form a large ring-like structure that surrounds the patient when placed inside the scanner's bore. PET scanners have three major components: detection system, collimation, and image reconstruction. The PET scanner requires a dedicated ring of detectors. The main component of the detection system is a pair, or more, of detectors that are placed exactly opposite each other across the diameter of the ring. Types of detectors used in PET are Anger-logic scintillation cameras and position-sensitive photomultiplier tubes. [26]

When the positron interacts with an electron within the body, it is converted into two high-energy gamma rays that travel in opposite directions. These gamma rays are the "coincidence photons." They are emitted rapidly. Many nuclear medicine examinations are based on the detection and analysis of these "coincidence" gamma rays or positrons, and the reconstruction of their paths as they move through the body. The CT component is a standard diagnostic CT used to obtain anatomic information for localizing PET abnormalities within the PET body. CT uses an x-ray source and detector array to generate multiple cross-sectional images or many single-slice images of a region of the body. The spatial resolution of PET/CT is directly dependent on the spatial resolution of the PET and CT systems. Scanners differ in maximum axial and transaxial field of view, the distance between the array of detectors and the patient enabling increasing positioning from part to part of the bed. The urgent demands for high performance, low noise, and fast imaging time with increasing spatial and temporal resolution are an important issue in the PET/CT community. It should become simpler, faster, versatile, and user-friendly. [27]

3. Quantitative Analysis in Oncology Imaging

It is now widely appreciated in the medical community that qualitative assessments alone are insufficient for accurately predicting how a tumor will respond to treatment. Therefore, there exists a strong motivation to develop quantitative metrics that can better capture the physiological and biological attributes of tumors. This paradigm shift in tumor response evaluations has prompted the creation and advancement of software tools designed to facilitate the rapid analysis of captured images. By utilizing these innovative software tools, medical professionals can generate precise tumor metrics that have the potential to greatly enhance patient treatment. These metrics serve as critical data points that aid clinicians in making well-informed decisions regarding their patients. With access to these comprehensive metrics, clinicians are empowered to provide more effective and tailored treatments, ultimately improving patient outcomes and overall quality of care. [28][29]

Standard uptake values are traditional indicators measuring metabolic activity. In the field of oncology, these values play a crucial role in assessing the physiological characteristics of tumors. However, with the advancement of technology and the introduction of dynamic data acquisition and compartmental models, a more accurate estimation of tumor metabolic or physiologic features has become possible. To keep up with these advancements, the development of imaging modalities and sophisticated methodologies has been necessary. This includes the creation of best-practice frameworks that encompass the acquisition and normalization of image data. Additionally, considerations such as subject motion, blood glucose levels, and body size or composition have to be taken into account to ensure reliable and accurate results. Quantitative imaging techniques have also expanded beyond basic metabolic measurements. They now encompass the extraction of higher-level information, delving into tumor heterogeneity through the assessment of entropy or texture. The ultimate goal of these efforts is to improve the predictive capability of assessments and enhance the understanding of tumor behavior. One of the primary advantages of employing

these quantitative approaches is their reduced subjectivity. By minimizing the reliance on subjective interpretations, the reproducibility and comparability of results across studies are significantly enhanced. This emphasizes the importance of consistency in measuring tumoral sites of glucose metabolism over a short time period, as it can serve as a reliable indicator of tumor aggression or malignancy. While staging a tumor based on these measurements remains a valuable application, their true significance lies in their potential to predict patient prognosis. By analyzing the metabolic activity of tumors, healthcare professionals can gain insights into the likely course of the disease and make informed decisions regarding treatment strategies. In conclusion, the utilization of quantitative imaging techniques and the exploration of tumor heterogeneity through higher-level information extraction have revolutionized the field of oncology. By incorporating dynamic data acquisition, compartmental models, and best-practice frameworks, we can obtain more accurate estimations of tumor characteristics. These approaches not only enhance reproducibility and comparability but also provide valuable predictive capabilities for patient prognosis. [30][31][32][9][33]

A plethora of tumor response assessment criteria now exist that will consider the positron emission tomography data to stage tumors, whether on a visual or quantitative basis. The measurement of tumors has also been widely reported to be highly useful in the context of tumors expressing biomarkers. Perhaps one of the simplest and most straightforward ways to comprehensively analyze treatment response in tumor imaging studies may be as a percentage change calculated from the baseline quantitative parameters. However, the task of determining whether significant differences exist within the individual patients may pose a considerable challenge, thereby requiring the establishment of adequate statistical procedures. In the pursuit of developing innovative imaging protocols to effectively characterize intracellular correlations, there may be a pressing need to carefully mitigate high receptor expression. Furthermore, it is important to acknowledge that the successful interpretation of quantitative data at the therapeutic level continues to present ongoing challenges and complexities. [34][35][36][37][38]

3.1. Basic Principles of Quantitative Analysis

In oncology imaging, cancer growth can broadly be measured as the change in tumor size based on established criteria, but these morphometric measurements cannot truly reflect early changes in tumor cell viability. Quantitative tumor response criteria using PET/CT images analyze either regional uptake or SUV in dynamic sequences in PET images. To accurately measure the change in the metabolic rate of cancer, we must measure the rate of change in the availability of the metabolic substrate, and this can be done using dynamic PET studies involving radiolabeled glucose. Dynamic PET measures the arterial input function for FDG and the rate of tumor uptake and clearance. Tracer infusion levels and scheduling are done based on pharmacokinetic modeling or computerized algorithms that adjust infusion rates automatically based on imaging analysis. Quantitative analysis of PET involves modeling time-activity curves using compartmental models or using derived voxel values from parameters calculated through analysis of the entire time-activity curve multiplied by appropriate scaling factors. A dynamic FDG PET procedure is very complex, involves patient sedation in part, and has not yet enjoyed widespread clinical applicability in cancer therapy management, but it has been performed successfully, especially for tumors in the brain. [39][40][41][42][43][44][45][46]

The performance of mathematical operations in defining quantified measures on images is done using statistical methods that guarantee both precision and accuracy. Precision refers to the ability to generate repeatable and reproducible measurements over time in the same patient, the same imager, and between different imagers. Accuracy of a given measurement is its agreement with a true or accepted value for a quantity of interest in the field. A lack of standard calibration procedures can make complex imaging of an individual using the same machines appear to have different results if measured at different imaging sites, with differences of large magnitude obtained between imaging instruments and interobserver reading differences showing a coefficient of variation of 15%. Calibration of imaging instruments is improved by the use of polymers of

known density and volume and the use of a lung simulator. To calibrate individual imaging procedures, by the use of internal reference standards, one must measure the radioactivity and X-rays based on CT number prior to image capture and hold machine settings constant each time an image is collected before analyzing it. Quantitative techniques are also limited when comparing different imaging protocols for the same body part, with small changes seen in serial body imaging taken with positioning checks by simple landmarks such as major arteries being hard to define, baseline variations of up to 20% being found in the initial analysis for some imaging features.

Overall, for many features for serial body images in the low-resolution images, tumor changes of less than 30% in tumor volume were difficult to quantify. Tumor lesions have to measure greater than about 20% different to be confident that a change in the lesion has occurred. In recent research, efforts have been made to improve the precision and accuracy of mathematical operations in defining quantified measures on images. Advanced statistical methods have been developed to enhance the precision of measurements over time, ensuring repeatability and reproducibility. Furthermore, new calibration procedures have been established to address the issue of variations between imaging instruments and interobserver reading differences. The use of polymers with known density and volume, along with the implementation of a lung simulator, has significantly enhanced the calibration of imaging instruments. These advancements have revolutionized the field, allowing for more consistent and reliable measurements. Moreover, internal reference standards have been introduced to calibrate individual imaging procedures effectively. By measuring the radioactivity and X-rays based on CT number prior to image capture and maintaining consistent machine settings, the accuracy of measurements has greatly improved. This has paved the way for more precise and reliable quantitative techniques. However, challenges still persist when comparing different imaging protocols for the same body part. Minor changes observed in serial body imaging, especially when relying on positioning checks by simple landmarks, such as major arteries, can be arduous to define accurately. Baseline variations of up to 20% have been identified during the initial analysis of certain imaging features. These challenges highlight the need for further research and development to refine the quantification of these features. Particularly in low-resolution images, quantifying tumor changes of less than 30% in tumor volume remains a complex task. To be confident in identifying changes in tumor lesions, a significant difference of approximately 20% in measurements is required. While progress has been made, continued efforts are necessary to advance the precision and accuracy of mathematical operations in the context of defining quantified measures on images. By addressing the current limitations and refining the existing techniques, the field can progress towards more precise and reliable measurements, leading to improved diagnoses and treatment planning. [47][48][49][50][51][52][53]

4. Advanced PET/CT Imaging Modalities

Introduction. It is widely recognized and acknowledged that positron emission tomography (PET) imaging offers superior sensitivity when compared to multi-detector computed tomography (MDCT). However, the use of 18F-fluorodeoxyglucose PET/CT (18F-FDG PET/CT) has shown limitations in terms of specificity in the staging and monitoring of tumor response to therapy. This is primarily due to its ability to visualize both inflammatory and metabolic changes in organs or tumor lesions, thereby presenting challenges in accurately distinguishing between benign and malignant lesions. Within the realm of advanced PET/CT imaging modalities, there exists an opportunity to achieve more precise diagnoses, incorporating the ability to differentiate between various lesions, both benign and malignant, by harnessing the complex biological constellation. Consequently, the significance of advanced imaging modalities in the current PET/CT landscape cannot be overstated. These advanced PET/CT imaging modalities encompass novel imaging techniques that operate beyond the realm of anatomical and physiological process imaging. They have demonstrated the ability to enhance specificity and sensitivity, surpassing the capabilities of conventional imaging methods alone. The advantages associated with these advanced imaging modalities extend beyond the mere imaging of physiological and molecular information. They also

include the precise grading of cancer, achieved through tissue characterization, including the arduous task of sarcomeric differentiation, as well as the detection and differentiation of various types of tumors. The utilization of these advanced modalities has led to improvements in patient management, wherein personalized treatment plans are tailored based on accurate diagnosis and evaluation of treatment effects. Consequently, it is crucial to conduct extensive and comprehensive research in order to foster the development of an integrated diagnostic approach, further enhancing and refining these techniques. Within the confines of this review, our primary focus will be on the discussion of four advanced modalities of 18F-FDG PET/CT. We aim to provide a comprehensive overview of their diagnostic capabilities in various tumor detection scenarios, shed light on recent research trends associated with each modality, and ultimately highlight their potential impact on clinical practice. Through this undertaking, we hope to introduce the evolutionary advancements in clinical tumor diagnosis and the evaluation of new treatment methods, emphasizing the pivotal role played by advanced imaging modalities in improving patient outcomes. [54][55][56][57]

4.1. Novel Radiotracers for PET Imaging

A radiotracer is a compound labeled with a radionuclide that can be used to trace the metabolism and location of compounds in the body. Development of novel radiotracers is important because a good radiotracer can improve the resolution, contrast, and image quality, and can also facilitate metabolic assessment. Over the last decade, a variety of radiotracers have been developed. They usually target tumor blood vessels or related molecules of tumor angiogenesis, such as vascular epithelial growth factor or its receptor. In contrast to these tracers, radiotracers targeting tumor cells or their constituents that have upregulated expression in the tumor compared with normal tissue have emerged. These targets or building blocks include familial adenomatous polyposis coli, prostate-specific membrane antigen, and somatostatin receptors. Most tumors overexpress surface proteins, receptors, or enzymes. This hyperaccumulation can be exploited by radiolabeled peptides or antibodies for imaging and often also for radionuclide therapy. [58]

Moreover, the radiotracers used in PET are selected mainly because they tend to target a specific biological pathway such as cell metabolism, proliferation, or the use of amino acids in cancer, overcoming some of the diagnostic dilemmas that conventional PET/CT cannot clarify. Another reason for their use is that pathological cells usually overexpress specific markers, hence the uptake of radiotracers. Therefore, after administration of these radiotracers, they will be selectively concentrated in the targeted cells and washed out from the normal cells. The selective uptake can make the subsequent images provide a clear view of the specific cells that uptake the radiotracers. Of course, it will take a sequence acquisition protocol to obtain these images. The half-life of the radionuclide used to label the radiopharmaceutical must also be longer than needed to traverse, i.e., the duration of tracer uptake reaching the equilibrium state in the tissue and organs. Currently, one of the problems for new PET radiopharmaceuticals is advanced synthesis, to obtain high targeting specificity and high binding affinity, as well as long shelf life and good selectivity in clinical use. [59]

5. Tumor Response Assessment Criteria

Evaluating treatment response plays a critical role in evidence-based oncologic practice. Improving patient care relies on standardized classifications and endpoints. The treatment of cancer patients increasingly involves complex protocols. The evaluation of these protocols is not only more complex, but impacts both patient treatment planning and the resulting research. Inherent to these voluminous changes is concern and debate about whether the traditional criteria remain valid. Bringing these debates to patients and the oncologic community requires the support and joint action of all the stakeholders within and across the research and regulatory domains. [60]

Tumor response assessment using CT/MRI is currently based on widely accepted standard criteria. Although widely accepted and utilized in clinical trials, these criteria are based only on tumor size measurements without considering other criteria of tumor response such as functional, cellular, molecular, or biologic features. Response assessment with PET-CT is currently based on two

major classification criteria, on the basis of uptake six weeks after completion of the treatment. Therefore, no standardized time point for assessment of therapy must be established, and multiple time points in a PET study can better describe the complete patient response. The largest prospective data are in accordance with established criteria with an overall scale of PET-CT. Although the routine use of molecular imaging techniques to monitor tumor response to therapy still remains limited to a small number of centers, it is strongly increasing, and molecular imaging will be crucial to personalize single patient therapy, to design anti-cancer drugs, and also for patient radiation treatment planning. [61]

5.1. RECIST Criteria in Oncology

The Response Evaluation Criteria in Solid Tumors (RECIST) were introduced in the year 2000 as a comprehensive and standardized framework for assessing the response to treatment in cases of solid tumors. This groundbreaking set of criteria brought forth guidelines that were specifically designed to ensure the accurate and reliable measurement of a tumor's longest diameter. The development of the unidimensional approach towards measuring disease has proven to be highly valuable and indispensable in both the realm of clinical practice as well as in research endeavors. RECIST 1.0, the initial iteration of these criteria, precisely defines progressive disease (PD) as an absolute increase in the sum of tumor diameters by at least 20%, with the smallest sum being at least 5 mm. Moreover, this increase must take place within the target tumor volume and can involve either the growth of a new lesion or the reappearance of a previously treated or untreated lesion. [62]

Partial response (PR) is defined as a 30% geometric percent decrease in the sum diameters of marker lesions. Complete response (CR) remains the absence of disease, with the same minimum of five millimeter rule as noted for PD. Stable disease (SD) is defined as less than 20% but not qualifying for either PD or response, with the same minimum of five millimeter rule. These guidelines for responding, or not responding, to treatments have been widely adopted to date, both for clinical trials. As both targeted and cytotoxic anti-cancer agents have been developed over recent years, their differing mechanisms of action have caused major changes in the quality and speed of the antitumor response. In 2008, changes were made because of rapid changes and the discrepancy in time to progression in some patients immunologically. To clarify issues noted, emphasis was placed on the detection of PD at multiple time points, with a minimum of four to six weeks between scans. RECIST has continued to be the standard for solid tumors as a result of issues related to other competing criteria. For example, whereas a need for a 3D reconstruction of disease was issued, that did not end up as criteria. Both RECIST 1.1 and 1.0 have been shown to be effective in detecting PD and assessing partial response, stable disease, and progression. One of the major issues for using RECIST 1.1 to assess tumors is that it can only be used for solid lesions and not lymph nodes. So, in certain disease types, these criteria fail and need to be modified accordingly. RECIST 1.1 primarily relies on bi-dimensional assessment of disease, which is mainly based on measuring the longest diameter along with normal reference fields of organs or viscera as noted in the very first RECIST 1.0 guidelines. [63]

6. Clinical Applications of Advanced PET/CT Imaging

Most advanced PET/CT imaging systems used in oncology focus primarily on early diagnosis, staging, prognosis, and monitoring of treatment regimens. In particular, various imaging techniques have been judiciously combined to comprehensively evaluate diverse tumor properties including glucose metabolism, non-glucose metabolism properties, and additional inherent biomarkers. This innovative and highly effective technique predates the emergence of the biomarker market, underlining its substantial impact on the field of oncology. Furthermore, it emerges as an indispensable asset, significantly contributing to paramount decision-making processes concerning patient management, encompassing both real-world practice and clinical trials. Such invaluable information aids clinicians in determining optimal dosages of therapeutic molecules, ultimately driving more efficient allocation of human and economic resources.

Cancerous diseases, regarded as one of the most prevalent forms of malignancy globally, underscore the urgency and significance of employing these cutting-edge imaging systems. [64][1]

In the field of oncology, there are various approaches available for the initial assessment of tumor response. These methods include size-based morphological imaging, the utilization of the standard uptake value obtained from positron emission tomography (PET) scans, and the implementation of newly developed imaging sequences or texture analysis techniques such as the contrast-enhanced computed tomography (CECT) or the utilization of multifunctional T2-weighted turbo inversion recovery magnitude (T2w-TIRM) sequences in magnetic resonance imaging (MRI). The incorporation of these advanced medical imaging modalities greatly enhances the ability to accurately differentiate between tumor recurrence and post-treatment inflammatory phenomena, which conventional images often fail to achieve. As a result, there has been significant progress in therapeutic advancements leading to early reduction in tumor volume and improved patient survival rates. Notably, the delayed acquisition of both MRI and PET scans has shown substantial improvement in the specificity, positive predictive value, negative likelihood ratio, and recurrence identification rate. Consequently, these commendable practices have been effectively integrated into the most recent cancer management plans. Moreover, numerous clinical applications are currently being explored within the realm of multi-center clinical research studies. [65][66][67]

6.1. Monitoring Treatment Response in Solid Tumors

Patients with solid tumors are evaluated by imaging studies using established guidelines for patient follow-up at specific intervals and at the end of treatment to assess the evolution of the tumor. These systems are based on objective methodology to assess tumor burden through a priori definition of measurable lesions typically assessed by computed tomography. Treatment response is generally defined as a requirement for size changes of lymph nodes and/or non-nodal structures. Furthermore, heterogeneity in tumor blood flow, proliferation, necrosis, and apoptosis during treatment may be associated with active treatment rather than progressive disease. Thus, imaging strategies should become more sophisticated and take into account multiple complementary methodologies for more accurate evaluation of changes in tumor characteristics during treatment. Advanced variables that predict treatment response also provide surrogate markers for relating individual signal intensity with the clinical outcome. Changes in imaging parameters occur very early in contrast to the anatomic response, and provide important information regarding patient outcome. Moreover, clinical data suggest that patients evaluated by imaging are able to start an alternative therapy earlier than patients evaluated by anatomic response, reducing any potential damage of manifest disease. The implementation of these imaging strategies has led to significant improvements in the management of solid tumors. The ability to accurately assess tumor burden and treatment response has allowed for more personalized and effective treatment plans. By utilizing multiple complementary methodologies, healthcare professionals can gain a comprehensive understanding of the changes in tumor characteristics during treatment. This allows for a more accurate evaluation of treatment effectiveness and the ability to tailor therapies to individual patients. In addition to providing valuable information regarding treatment response, advanced imaging variables also serve as surrogate markers for clinical outcomes. By observing changes in signal intensity, healthcare professionals can predict the efficacy of treatment and adjust interventions accordingly. This not only improves patient outcomes but also reduces the potential damage caused by manifest disease. By identifying treatment response at an early stage, alternative therapies can be initiated promptly, providing patients with a better chance of successful outcomes. Furthermore, the use of imaging studies in patient evaluation has revolutionized the field of oncology. It has enabled healthcare professionals to detect changes in tumor parameters that occur much earlier than anatomic responses. This early identification allows for prompt intervention and the implementation of alternative therapies, ultimately improving patient prognosis. The future of imaging strategies in the evaluation of solid tumors looks promising. As technology advances, more sophisticated methodologies can be utilized to further enhance the accuracy and reliability of tumor assessment. By incorporating advanced imaging techniques, such as functional imaging

and molecular imaging, healthcare professionals will have a more comprehensive understanding of tumor characteristics, allowing for more targeted and effective treatment plans. In conclusion, imaging studies play a crucial role in the evaluation and management of patients with solid tumors. By following established guidelines and utilizing multiple complementary methodologies, healthcare professionals can accurately assess tumor burden, treatment response, and predict clinical outcomes. The early identification of treatment response through imaging studies enables the prompt initiation of alternative therapies, leading to improved patient outcomes. As imaging technology continues to advance, the future holds exciting possibilities for further refining tumor assessment and tailoring treatments to individual patients. [68][69][9][70][71][72]

7. Challenges and Limitations in Quantitative Analysis

Quantitative analysis is necessary, not only in demonstrated responses but also in cases where a qualitative assessment is the usual approach. The main sources of variability responsible for suboptimal measurement accuracy are patient-related ones, resulting in inconsistency among repeated measurements in the same patient, and technical issues leading to divergence among studies or laboratories. In particular, regarding small lesions, the impact of lesion-related factors on the reproducibility or trending ability of data across the change of lesion status has gained growing interest. Variability is present in data, and up to now, the treadmill approach is the more reasonable criterion to state whether a significant change in the tumor feature has actually occurred, ruling out misinterpretation related to pure technical vulnerability of the data or of imaging protocols and processing. There are still uncertain issues concerning data interpretation across different types of tumors and imaging. [73][74]

Quantitative analysis in imaging has some intrinsic limitations. Recent advancements have led to more effective imaging protocols providing improved data quality, but the intrinsic properties of the imaging equipment and the methodologies remain substantially the same. A great part of the limitations of current imaging for quantitative analysis comes from the nature of PET and CT scans. Technical and physical limitations of both modalities determine a series of possible discomforting factors, which need to be dealt with as much as possible by optimizing protocols, improving software employed to deal with data, and harmonizing procedures in clinical practice. Advances outside of the realm of instrumentation may mitigate limitations. For example, using advances in machine learning and natural language processing to retool medical literature may help leverage past publications and opinions to substantiate and validate medical outcomes on the basis of new investigations. These advancements will increase our power of interpretation and increase certainty of interrogation, negating some of the challenges regarding heterogeneity in data interpretation. [34][75]

7.1. Variability in Quantitative Measurements

High variability is often observed in the quantitation of imaging data in oncology. Variability can arise from multiple sources, including scanner calibration, patient preparation, data acquisition, image reconstruction and processing, radiotracer production, and metabolite determination. Population variability from patient characteristics and pathology also adds to these effects. Techniques are standardized in routine clinical studies as much as possible to minimize these effects and obtain reliable interpretation of disease for multicentric and multicountry clinical trials. The variability in measurements is associated with many problems in clinical oncology, such as improving the patient's diagnosis and staging, patient treatment or monitoring treatment responses, and in difficult cases, providing a prognosis. Variability in measurements may be responsible for decisions in clinical trials, especially for studies focusing on establishing survival rates. The problem of measurement variability in oncological imaging has attracted increasing attention, including a number of studies highlighting the issue. Many factors are responsible for the variability in the deposition of FDG in tissue and the difficulty of quantitating true deposition from PET images. Test-retest studies demonstrate a plethora of sources of variability, some of which are difficult to control by conventional imaging methods. Variability appears good when well-

defined, tightly controlled imaging conditions are used. Variability is high and appears poorly reproducible in the presence of uncertainty about imaging preparation, imaging apparatus, and image-processing techniques. Overall, PET FDG global tumor uptake measurement agreement may be as good as 0.8–1.0 SUV, but only if conditions are very tightly controlled. This suggests that a simple one-size-fits-all SUV measurement may give high agreement in FDG studies. [76][77]

8. Future Directions in PET/CT Imaging Research

Emerging methodologies and technologies hold great potential for many future research avenues. A rapidly evolving set of molecular biology and molecular genetics tools will directly result in novel cancer therapies. There is an urgent need to detect early in the dawn of malignant cellular evolution, let alone the phenotypic emergence of cancer, to finally detect emergent tumors, and subsequently achieve constraints of early initiation to the personalized therapy window. Imaging within oncology is in ongoing rapid development, with new radiopharmaceuticals, image processing algorithms, and synergizing multimodality imaging strategies. The rapidly developing technologies that are bumping up against each other are based on the marriage of these multiple evolving technologies and methodologies, offering sizeable new potential, research questions, pitfalls, and challenges all continually emerging. [9]

New possibilities regarding the imaging of oncologic molecular targets and microenvironments progress the development of new and better PET/CT imaging agents applicable in a clinical environment. Image processing in everyday routines, as well as imaging research statistics, may be potential areas of involvement through the innovation of AI and machine learning. Larger imaging databases on imaging studies permitting real-time links to clinical outcomes will allow both statistical analyses and individualized pattern detection. The future of PET/CT imaging will likely also involve multimodality imaging, testing the molecular cancer environment as well as measuring structural and functional presentations. To achieve high clinical confidence in image interpretation and study conclusions regarding treatment effects, we recommend at least radionuclide producers, imaging equipment developers, image processing algorithm researchers, and database and big data expertise in multi-disciplinary collaboration. [78][9]

8.1. Emerging Technologies and Trends in PET/CT

8.1.1. Detector Technologies ■ Solid-state detectors. Examples are silicon photomultipliers (SiPMs) with improved sensitivity; they can be a promising alternative to avalanche photodiodes (APDs) for timing measurements, which allows for better coincidence-timing resolution in PET. Depth-encoding geometries can be constructed as scatter-angulation devices, allowing separation of true from scattered events in the object. One such example is time-of-flight (ToF) encoded patients, which can reduce the imaging time required to achieve noise-equivalent count rates (NECR) by a factor of 3.5 over a standard whole-body PET system. ■ Crystal scintillators. Another approach to achieve cost-effective ToF PET is to couple SiPM detectors with a fast and large single crystal, so that the pulse height of annihilation gamma energy is encoded by a varying light output, thus allowing a time reference to be added to each photon detection. Emerging cerium-doped lutetium yttrium orthosilicate (LYSO, Ce) crystals exhibit a distinct pulse-shape discrimination allowing for 300 ps coincidence-time resolution, which directly translates into a high sensitivity for identifying scattered events. Alternatively, having very fast detector systems can enable real-time imaging of dynamic processes from several seconds down to the millisecond. 8.1.2. Automation and Consolidation of Image Processing and Quantification Techniques For quantifying uptake of 18F-NaF in bone metastases, computational models combined with Monte Carlo simulation of the scanner using pre-recorded scans were used to correct for the bone signal bleeding a significant amount of activity from the VOIs in the fit parameters. Using whole-body MRI as a reference, the 18F-NaF activities were compared between lesions below, normal, and above background activity, with consistent results. Future work with at least 30 patients will investigate the dynamics of bone metastasis using 60-minute dynamic whole-body protocols. It is

anticipated that MRI data may inform the estimation of compensatory arterial blood activity in capillary-tumor exchange models. [79][80][81][82]

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