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Imaging for response assessment in cancer clinical trials:

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Abstract

The use of biomarkers is integral to the routine management of cancer patients, including diagnosis of disease, clinical staging and response to therapeutic intervention. Advanced imaging metrics with CT, MRI, and PET are used to assess response during new drug development and in cancer research for predictive metrics of response. Key components and challenges to identifying an appropriate imaging biomarker are selection of integral versus integrated biomarkers, choosing an appropriate endpoint and modality, and standardization of the imaging biomarkers for cooperative and multicenter trials. Imaging biomarkers lean on the original proposed quantified metrics derived from imaging such as tumor size or longest dimension, with the most commonly implemented metrics in clinical trials coming from the RECIST criteria, and then adapted versions such as iRECIST and PERCIST for immunotherapy response and PET imaging, respectively. There have been many widely adopted biomarkers in clinical trials derived from MRI including metrics that describe cellularity and vascularity from DW-MRI (ADC) and DSC or DCE-MRI

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(K^{trans} , rCBV), respectively. Furthermore, FDG-, FLT- and FMISO- PET imaging, which describe molecular markers of glucose metabolism, proliferation and hypoxia have been implemented into various cancer types to assess therapeutic response to a wide variety of targeted- and chemotherapy. Recently, there have been many functional and molecular novel imaging biomarkers that are being developed that are rapidly being integrated into clinical trials (with anticipated of being implemented into clinical workflow), such as AI and machine learning computational strategies, antibody and peptide specific molecular imaging, advanced diffusion MRI. These include PSMA- and trastuzumab-PET, vascular tumor burden extracted from contrast-enhanced CT, diffusion kurtosis imaging, CD8 or Granzyme B PET imaging. Further excitement surrounds theranostic procedures such as the combination of $^{68}\text{Ga}/^{111}\text{In}$ - and ^{177}Lu -DOTATATE to use integral biomarkers to direct care and personalize therapy. However, there are many challenges in the implementation of imaging biomarkers that remains, including understand the accuracy, repeatability and reproducibility of both acquisition and analysis of these imaging biomarkers. Despite the challenges associated with the biological and technical validation of novel imaging biomarkers, a distinct roadmap has been created that is being implemented into many clinical trials to advance the development and implementation to create specific and sensitive novel imaging biomarkers of therapeutic response to continue to transform medical oncology.

1. Challenges and standardization of imaging biomarkers of therapeutic response in oncology

1.1 Integrated and integral imaging biomarkers in oncology clinical trials

Imaging is an integral component of cancer care and has transformed clinical decision making in medicine[1]. A biomarker, qualitative or quantitative, is a defined characteristic that is distinctly positive or negative and measured as an indicator of normal or pathogenic biological processes or in response to an exposure or intervention[2, 3]. The use of biomarkers, both imaging and specimen-derived, are integral to the routine management of cancer patients, including diagnosis of disease, clinical staging and stratification, and assessment of response to therapeutic interventions[4]. Additionally, there are many advanced imaging metrics with computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and ultrasound that are used extensively in new drug development and in cancer research. O'Connor et al has published a high-profile paper describing an overview of the roadmap for imaging biomarkers into clinical integration in which the first steps to create an appropriate imaging biomarker is to assess technical, biological and clinical validation in animals and in humans[4]. Technical validation ensures that an imaging biomarker can be standardized and performed, agnostic of location and vendor, and provide comparable quantitative data to be utilized longitudinally. Biological and clinical validation ensure that the information extracted is related to underlying biology and is associated with a specific clinical outcome. Next, the imaging biomarker must provide reliable measures to test a hypothesis in clinical cancer research tested as an integrated metric that is evaluated parallel to cancer care to provide diagnostic assessment or prediction of response. Finally, after validation in an integrated setting, the imaging biomarker can be applied as an integral metric into the clinical decision making and management of patients with cancer.

1.2 Selection of endpoint and modality

A clinically meaningful endpoint is commonly defined as an outcome that directly measures how a patient feels, functions, or survives. In oncology, the most common examples include overall survival (i.e., time from diagnosis until death), progression free survival (i.e., time from diagnosis until disease condition gets worse), overall response rate (i.e., fraction of patients who have a partial or complete response), and duration of response (i.e., length of time a tumor is responsive to therapy). While the interpretation of overall survival is clear, a methodology for assessing the last three had to be developed. As described more completely below in section 1.4, the Response Evaluation Criteria in Solid Tumors (RECIST;[5]) provides a practical method for summarizing anatomical changes to report on the latter three endpoints. Briefly, RECIST divides treatment response into four categories: 1) Complete response (CR)—disappearance of all target lesions, 2) Partial response (PR)—30% decrease in the sum of the longest diameter of the target lesions, 3) Progressive disease (PD)—20% increase in the sum of the longest diameter of the target lesions, and 4) Stable Disease (SD)—small changes that do not meet the above criteria.

It is well recognized that this approach needs to be significantly improved for a number of reasons. For example, the metric for positive response is based on one dimensional changes (i.e., changes in the sum of the longest diameters) which can be grossly misleading in trying to describe a complex object that is almost certainly changing in all three spatial dimensions. Furthermore, RECIST is based on anatomical and morphological changes which are only (temporally) downstream manifestations of the underlying physiological, cellular, and molecular changes. What is needed are methods to characterize those underlying changes as they are significantly more likely to offer early and specific response to treatment indices than changes in longest dimensions. Thus, the imaging community has long sought to develop biomarkers that can report on the downstream effects of particular therapies. For example, if a particular therapy is designed to affect vascular properties, then contrast enhanced x-ray CT or contrast enhanced MRI may be indicated as they are sensitive to change in vascular properties. If a therapeutic approach is designed to reduce cellular proliferation or induce cell death, then fluorodeoxythymidine (FLT) PET or diffusion weighted (DW)- MRI, respectively, may be the proper measurement technique.

1.3 Standardization of imaging biomarkers in cooperative and multicenter trials

In the context of multicenter trials where imaging is used for evaluation of therapeutic efficacy, it is imperative to implement standardized protocols to limit scan to scan variability. In terms of image acquisition, investigators must predefine specifications and institute a site qualification process to ensure correct implementation across a range of imaging platforms. Depending on the circumstances and study goals, this may require tradeoffs – such as simplifying to ‘lowest common denominator’ minimum requirements that are widely generalizable across many sites with varying equipment, or limiting the participating sites to only those with capabilities to perform a more sophisticated approach (which will in turn limit accrual rates). Site qualification prior to data collection should entail centralized review of test scans for both imaging phantoms with known properties, as well as representative in vivo cases. For highest rigor in deriving quantitative imaging biomarkers for clinical trials, centralized image analysis should be performed by a core lab to ensure standardization of

post-processing and measurement (e.g. ACRIN trials [6]). Also, this would allow for centralized review of protocol compliance and data quality, and enable investigators to provide timely feedback to the site to address any issues that may be identified during the course of the study. Alternatively, it may be more feasible in some trials to deploy standardized measurement software tools and/or interpretation strategy at the individual site level, with adequate training of site investigators, to avoid the need for immediate submission and central review of imaging data and clinical metadata. Examples of this include ISPY-2 and ECOG-ACRIN EA1141[7]

Regardless of the method of acquisition or analysis for imaging biomarkers, a central need in moving these techniques from single site, specialty centers into broadly employed practices is establishing their repeatability and reproducibility. Indeed, there has been much recent effort in this area (see, e.g.,[8]), including in the community setting[9].

1.4 RECIST/PERCIST measurements in clinical trials

RECIST criteria, which was originally published in 2000 and updated in 2009, is a set of guidelines that focuses on lesion size when assessing response to therapy.[10] The division of RECIST criteria for lesion response to therapy includes the following classifications: complete response, partial response, progressive disease, and stable disease. A 2016 update clarified specific aspects of RECIST, including frequency of monitoring, small lesions (under 5 mm), specific of target lesions, tumor number, lymph node size and management, and other issues regarding measurements.[5] Tumor size for RECIST measurements is measured using CT or MRI (slice thickness of less than or equal to 5 mm) and the minimum size is less than 10 mm (20 mm for chest x-ray).¹ The RECIST criteria has been criticized for various reasons. One such issue involves certain tumors that do not have significant size changes after treatment using “cytostatic” mechanisms that have been proven to yield long term therapeutic benefits. Other problems include variability in measurements across readers and concerns of volumetric versus one dimensional measurements.[11]

In 2009, the Positron Emission tomography Response Criteria in Solid Tumors (PERCIST) version 1.0 was introduced to address some of the shortcomings of RECIST 1.1 criteria for standardization and objective assessment of metabolic response utilizing [¹⁸F]FDG-PET/CT. [11] Notable, RECIST 1.1 criteria is limited in evaluation of novel therapies aimed to stabilize, and not necessarily cure, disease. PERCIST criteria, on the other hand, measures metabolic expression of tumor with classifications in the following manner: complete metabolic response, partial metabolic response, progressive metabolic disease, and stable metabolic disease.[11] Generally, PERCIST utilizes measurements of standardized uptake values (SUV) corrected for lean body mass (SUL) to assess metabolic tumor activity during the course of therapy. The PERCIST criteria was later revised to Practical PERCIST in 2016 to address and clarify several issues with the original PERCIST criteria.[12] The value of utilizing PERCIST as a response criteria (rather than RECIST 1.1 or other established criteria) has been demonstrated in multiple different cancer types, including esophageal, lung, colorectal, pancreatic, head and neck, and lymphoma.[13–20] Many of these studies demonstrate the ability of PERCIST to predict progression-free survival, response to therapy, and overall survival when compared to other response criteria.[13–20] Some

limitations of the PERCIST criteria include ensuring exams are technically adequate, SUV calculated appropriately, and time constraints are observed when performing the FDG-PET/CT exam with regard to the timeframe of chemotherapy administration.

Despite many advancements and adaptations for improvement, widespread adoption of PERCIST as a response criterion in clinical trials has been limited. Most important, many therapeutic clinical trials are written for RECIST 1.1 or immune-RECIST (iRECIST) criteria and may utilize a FDG-PET/CT at baseline and to confirm progressive disease. In these patients, frequently standard-of-care clinical qualitative reads are sufficient to provide the required information to the investigator. In a direct comparison between RECIST and PERCIST, one study demonstrated only moderate agreement between RECIST and PERCIST criteria with almost 38% discordance between response characterization and overall response rates.[21] In patients with lung cancer who underwent combination chemotherapy and radiation therapy, PERCIST provided higher overall agreement between observers when compared to a qualitative evaluation in evaluating early response to therapy. [22] However, a separate study which directly compared PERCIST to EORTC, Peter Mac Criteria, and Deauville criteria for survival prediction in patients with non-small cell lung cancer who underwent curative chemoradiation demonstrated similar performance among criteria for prediction of overall survival, but found that visual criteria had greater interobserver agreement and stronger discrimination between complete metabolic responders and non-complete metabolic responders.[23] This highlighted the importance of visual assessment of radiation pneumonitis and other factors in assessment of response. Additionally, while some studies suggest improved prediction of local control and progression-free survival utilizing PERCIST/RECIST response criteria compared to SUVmax, little data exists to support PERCIST's superiority over SUVmax as a response metric.[24]

1.5 Current challenges with imaging biomarkers for response assessment

Current challenges with imaging biomarkers for response assessment are 1) accuracy or validation, 2) repeatability and 3) reproducibility in both acquisition and analysis. Many quantitative imaging biomarkers require advanced image processing techniques that are often complex [25, 26]. Extensive standardization and validation is often needed prior to deployment in a clinical setting. As previously mentioned standardization for both individual sites and multisite trials can be very challenging. Furthermore, it is important to further standardize across multiple vendors, as it is impractical in large medical centers to ensure that an individual patient will be scanned with the same scanner for each evaluation of disease response. In addition to achieving high accuracy, a full metrology analysis is typically needed to assess linearity, bias, precision, repeatability conditions, reproducibility conditions, test-retest repeatability, inter-observer agreement, and other metrics. Ideally, an imaging biomarker has a broad range of applications and is vendor neutral, easy to deploy, and has high accuracy and precision; however, most imaging biomarkers have a narrow scope of clinical utility and should only be applied conditionally. In addition to the challenges with acquisition of data, the numerous quantitative analysis codes developed (or implementation of the same code by different individuals) have shown how the same imaging metrics can be solved differently (one example in [27]).

The final challenge will be true implementation into clinical workflow to ensure rapid computation and integration into electronic health records to allow all physicians integrated into oncology-care (radiologists, oncologists, radiation-oncologists, surgeons, etc) to be able to clearer and accurately understand the biomarker metric and interpretation of that metric. A major limitation of quantitative imaging biomarkers is integration of the measurement techniques into commonly used clinical imaging platforms. There are many barriers to integration into routine clinical image scanners and/or viewing workstations including cost, difficulty and timing of software upgrades, intellectual property rights, vendor interest, etc. Most imaging biomarkers must first be deployed in independent platforms and must be clinically and commercially successful to attract the attention of larger distribution vendors who have a broader deployment base. This development cycle is perhaps even more challenging for quantitative imaging biomarkers that involve machine learning algorithms, due to the requirement for additional hardware and software requirements.

2. Modality-specific imaging biomarkers to assess response in current therapeutic oncology clinical trials

2.1 Magnetic Resonance Imaging

2.1.1 Contrast-enhanced and DCE-MRI—Contrast enhanced MRI is an umbrella term used to describe a myriad of dynamic MRI acquisition and analysis techniques[28]. On the acquisition side, contrast enhanced MRI can provide either high spatial resolution data or high temporal resolution data, though more recent efforts have sought to balance both of these demands[29, 30]. Regardless of the data required, all approaches obtain serial, T_1 -weighted images before and after the injection of a paramagnetic contrast agent. As the contrast agent perfuses (or diffuses) into the tumor, the measured signal intensity will change to a degree based on the accumulation, retention, an elimination of the agent which is, in turn, a due to a complicated mixture of vascular and extravascular features. If the data is acquired at high temporal resolution, then these dynamics can be characterized with pharmacokinetic models to return estimates of physiological interest including (for example) K^{trans} (the volume transfer rate), v_p (plasma fraction), v_e (extravascular extracellular volume fraction), and k_{ep} (the efflux constant). To accomplish this task, three main data types are required: a pre-contrast T_1 map, the dynamic T_1 -weighted data acquired before and after the administration of the contrast agent, estimation of the time rate of change of the concentration of contrast agent in the blood (i.e., the arterial input function). Then, a pharmacokinetic model to analyze the resulting data can be utilized to extract these imaging metrics. Currently, high temporal resolution acquisition during contrast injection, and the subsequent quantitative analysis, is typically only performed in the research setting.

Conversely, in the standard-of-care setting, obtaining contrast enhanced MRI data at high spatial resolution [31] is most valued, and this necessitates acquiring data with a lower temporal resolution so that the resulting time series data can only be analyzed qualitatively or semi-quantitatively to characterize general curve shape features. In this approach, the curve shape is placed into one of three categories: curves showing washout dynamics (i.e., rapid washin and washout; frequently associated with malignancy), persistent dynamics (i.e., a time course that continually increases with time; frequently associated with benign cysts),

and plateau dynamics (i.e., a time course that initially rises and then levels off with minimal washout during the measurement). Such low temporal resolution can also be analyzed semi-quantitatively with the signal enhancement ratio (SER; [32]); a method that has been very successful in the I-SPY trials for breast cancer.

2.1.2 DSC-MRI—The abnormal perfusion and vascular characteristics that accompany malignant brain tumor growth provide a highly sensitive biological marker of tumor status and treatment response. Dynamic Susceptibility Contrast (DSC) MRI is a well-established approach to interrogate these hemodynamic features and relies upon tracking the dynamic passage of an exogenously administered contrast agent. Analysis of such data provides maps of relative cerebral blood volume (rCBV), flow (rCBF), and mean transit time (1). Studies have demonstrated the utility of DSC-MRI measures of rCBV to differentiate glioma grades, tumor types and identify tumor components in non-enhancing glioma (2–5), distinguish tumor recurrence from post-treatment effects (6–9), and predict tumor response and patient survival after molecularly targeted therapy (10, 11).

In the context of therapeutic clinical trials, DSC-MRI is able to overcome the known limitations of conventional MRI techniques to reliably, and efficiently, discern therapeutic response. In a Phase II clinical trial of temozolomide, paclitaxel poliglumex, and concurrent radiation, the mean rCBV measured at initial progressive enhancement and the change in rCBV after therapy were characterized in high grade glioma patients who exhibited radiologic pseudoprogression and progressive disease (12). While single time point, post-therapy rCBV values were similar between the two patient groups, the post-treatment changes derived from multiple follow-up exams were significantly different between the pseudoprogression and progressive disease groups (−0.84 and 0.84, respectively, $p = 0.001$). The predictive potential of DSC-MRI in glioblastoma patients was also demonstrated in a multicenter, randomized, phase II trial (ACRIN 6677/RTOG 0625) of bevacizumab with irinotecan or temozolomide (11). Patients with a decrease in rCBV measured before and two weeks after therapy exhibited an overall survival greater than one year, whereas patients with increases in tumor rCBV were found to have significantly shorter OS. Such trials highlight the potential of DSC-MRI as a prognostic biomarker of treatment response.

2.1.3 DW-MRI—In recent years, diffusion weighted (DW)-MRI has emerged as a valuable imaging modality for assessment of cancer and is increasingly being incorporated as a marker of response in clinical trials [33]. DW-MRI reflects the mobility of water molecules diffusing in tissues, revealing tissue organization at the microscopic level. Whereas pure water exhibits random isotropic molecular diffusion, the motion of water molecules in vivo is restricted by cell membranes and other hindrances within intracellular and extracellular compartments. As a result, DW MRI is sensitive to microstructural tissue properties including cell density, cellular organization, and cell membrane integrity. With DW MRI, the rate of diffusion is typically quantified by the apparent diffusion coefficient (ADC). ADC is defined as the average area occupied by a water molecule per unit time (in mm^2/sec) and can be calculated using a monoexponential equation that describes the relationship between the signal intensity with diffusion-weighting, the signal intensity without diffusion weighting, and the diffusion sensitization factor (b-values, reflecting the

degree of diffusion weighting, in sec/mm^2) [34]: Within days to weeks after initiation of effective cytotoxic therapy, cellular necrosis develops in the tumor, and associated reductions in cell membrane integrity and cellularity cause a relative increase in ADC. Such cytotoxic changes likely precede changes in tumor size or perfusion, suggesting DW MRI has unique potential to provide early indication of treatment efficacy [35]. This has motivated incorporation of DW-MRI into oncologic trials across numerous disease sites (including brain, breast, prostate, and liver) and treatments (including chemotherapy and radiation therapy) where ADC has shown predictive value as a marker to differentiate responders and non-responders [36]. Figure 1 shows changes in ADC in response to therapy in a multisite breast imaging trial.

Beyond the capability to measure important tissue microstructural characteristics, other advantages of DW-MRI as an imaging biomarker include high intrinsic image contrast that does not require externally administered agents, short scan time (several minutes), ease of implementation across different vendor platforms and field-strengths, and robust reproducibility and repeatability of ADC measurements when using standardized protocols [37]. One issue is that image quality in DW MRI is susceptible to a variety of factors, particularly for imaging areas outside the brain, although technical advances in acquisitions and post-processing are helping to overcome some of these challenges [38]. Future studies aimed to improve the standardization of approach and consistency of image quality in multicenter trials are essential for further advancement of DW MRI biomarkers [6, 39].

While ADC is by far the most common metric derived from DW MRI, several advanced modeling techniques may further improve sensitivity for characterizing therapeutic effects [40]. Diffusion kurtosis imaging (with derived apparent kurtosis metric, K_{app}) allows measurement of structural complexity and may better reflect treatment-induced alterations in tumor intracellular microstructure such as nuclear-cytoplasmic ratio [41]. Intravoxel incoherent motion (IVIM) modeling allows characterization of effects on microcirculation (through metrics reflecting perfusion fraction, f_p , and rate, D^*) as well as tissue diffusivity (D). Further exploration of these and other advanced diffusion models is likely enhance the value of DW-MRI for biologic characterization in future cancer clinical trials.

2.2 Computed Tomography

2.2.1 Contrast-enhanced CT—CT is the most commonly used imaging modality in patients with advanced cancer that involves the neck, chest, abdomen or pelvis and is considered widely 1st-enhanced CT can be used to quantify additional size metrics and other metrics. In patients with advanced cancer with multiple sites of disease, tumor length and volume are highly correlated for most forms of advanced cancer, however years of exploration of tumor volume as a potentially superior biomarker have not moved the field away from tumor length as the primary imaging biomarker in advanced cancer. Tumor volume may have a more important role in evaluation of locoregional disease, though tumor length is still frequently the metric of choice. This is in part due to the fact that tumor volume is more difficult and time consuming to measure than tumor length.

The CT Liver Surface Nodularity (LSN) score is a length-based imaging biomarker that is used to assess the severity of chronic liver disease (CLD) and cirrhosis (Figure 2).[42, 43]

Hepatocellular carcinoma (HCC) is one of the late complications of CLD and treatment options are dependent on several prognostic criteria. Surgery is the most effective treatment for HCC[44]; however, the underlying liver pathology can hinder patients from undergoing surgery and is a risk factor for post-operative complications. In a recent study, the LSN score was predictive of post-operative complications including post hepatectomy liver failure, bile leakage and ascites.[45] Additionally, LSN score showed better preoperative risk stratification of HCC patients when compared to other biomarkers, including the model for end-stage liver disease (MELD) score.

The vascular tumor burden (VTB) is another example of a size metric that is designed to quantify the amount of vascularized tumor on CT images (Figure 3). VTB is the area of tumor in a 2D region of interest between 40 and 300 HU for contrast-enhanced CT image and between 20 and 300 HU for nonenhanced CT images.[46] These thresholds are designed to measure the amount of vascularized tumor rather than air, lung, fat, water, necrotic tumor, non-enhancing tumor, cortical bone, dense tumor calcification, hyperattenuating contrast in large vessels, or metal clips.[6] VTB had high inter-observer agreement and was a more accurate predictor of progression free survival (or drug efficacy) in patients with metastatic renal cell carcinoma undergoing anti-angiogenic therapy than other traditional response criteria and length and mean attenuation metrics.[46]

2.3 Positron Emission Tomography

2.3.1 FDG-PET— ^{18}F Fluorodeoxyglucose (FDG) -PET imaging performed with radiotracer, FDG, and integrated with CT is a powerful non-invasive imaging modality most commonly used for tumor diagnosis, staging of patients with newly diagnosed malignancy, and restaging of patients following radiation therapy and treatment surveillance [47–49]. ^{18}F FDG-PET/CT allows clinicians to combine the anatomical data provided by the CT with metabolic information provided by the ^{18}F FDG-PET scan to assess disease staging and metastasis. FDG is a glucose analogue that enters the cell via glucose transporters, notably Glut-1 and Glut-3 which are upregulated in cancer cell membranes, and remains trapped inside the cell after hexokinase phosphorylation [50, 51]. In its radiolabeled form, ^{18}F FDG can be used to assess glucose consumption in the body via PET imaging [52]. Assessment of glycolytic activity of tumors has proven important because upregulated glycolysis is associated with cancer aggressiveness, invasiveness, and poor prognosis [53]. Furthermore, ^{18}F FDG-PET/CT has also been used to evaluate proliferative activity and malignancy grades of tumors which are significant prognostic indicators [54]. However, while extremely useful in clinical practice and universally available, ^{18}F FDG-PET has high incidence of background signal and low specificity. Novel molecular PET radiopharmaceuticals have been developed showing higher sensitivity and specificity for biomarkers of therapeutic response.

2.3.2 FLT-PET—3'-deoxy-3'- ^{18}F -fluorothymidine, ^{18}F FLT, is a known marker for imaging of cell proliferation and has been used in multiple studies for early assessment of response to therapy. In a study investigating imaging of response in patients with acute myeloid leukemia, Han et al showed ^{18}F FLT showed good sensitivity and a negative predictive value in a small cohort of patients[55]. In a recent lung cancer study, Kairemo et

al reported that [^{18}F]FLT could be used to predict early response to certain therapies in as little as 9 days[56]. Figure 4 shows rapid changes in [^{18}F]FLT uptake over the course of MDM2 therapy. Similar studies in melanoma and breast cancer patients have shown that serial [^{18}F]FLT imaging can modestly predict response prior to anatomical changes as assessed by CT or other conventional imaging modalities [57, 58]. In another study in glioblastoma patients, baseline [^{18}F]FLT imaging was shown to be predictive of overall survival[59]. While these studies illustrate the potential of [^{18}F]FLT in certain cancer types, several groups have reported that [^{18}F]FLT alone is not suitable for early response assessment in metastatic colorectal cancer[60, 61].

[^{18}F]FLT signal interpretation in the context of early response assessment may be more difficult over the course of radiotherapy as higher cell proliferation may indicate a better response to this type of treatment. For example, Everitt et al recently reported on the use of [^{18}F]FLT to monitor response to therapy in patients with lung cancer. Interestingly, stable uptake of [^{18}F]FLT at week 2 was associated with better outcomes[62].

2.3.3 FMISO-PET—Tumors that rely on anaerobic metabolism may develop a state of tumor hypoxia [63]. [^{18}F]-fluoromisonidazole ([^{18}F]-FMISO) is a nitroimidazole radiolabeled with fluorine-18 [64]. In normoxic conditions, a reduced [^{18}F]FMISO will be oxidized and can perfuse out of cells; however, in hypoxic conditions, the reduced [^{18}F]FMISO cannot be oxidized and will accumulate in cells [65]. [^{18}F]FMISO PET imaging has been clinically used to noninvasively inform on molecular and prognostic factors associated with patient outcome[66]. In patients with glioblastoma multiforme, Kawai et al and Hirata et al observed that [^{18}F]FMISO PET imaging is correlative of VEGF expression and that [^{18}F]FMISO PET imaging may be used to distinguish tumor malignancy [67, 68]. While [^{18}F]FMISO-PET was initially evaluated in brain tumors, the benefits of quantifying hypoxia as an imaging biomarker have not been widely shown to help direct patient care. In patients with HNSCC, Norikane et al and Sato et al observed correlations between FMISO uptake and HIF-1 α expression [69, 70]. In patients with breast cancer, Cheng *et al.* found that FMISO uptake was significantly correlated with clinical outcomes following endocrine based therapy [71].

2.4 Multimodality and multiparametric approaches

2.4.1 PET/MRI approaches—The simultaneous use of PET and MRI combines the anatomical and functional data of MRI with the physiological and molecular throughput of PET [72]. Rakheji *et al.* noted that PET-MRI allows for increased imaging of soft tissue and comparison of radiotracer SUV and apparent diffusion coefficient (ADC) [73]. In patients with GBM, Spence *et al.* observes that the addition of PET imaging techniques to MRI can help improve diagnostic power by differentiating between healthy and necrotic cancerous tissue [74]. In patients with HNSCC, Surov *et al.* combines diffusion weighted MRI and FDG-PET to correlate glucose metabolism with tissue diffusion coefficient. It was observed that the analysis of FDG SUV and ADC values can be used to predict proliferative tumor potential [75].

In assessing breast cancer response to neoadjuvant therapy, both RECIST and PERCIST have been used for evaluation. In a retrospective review in Japan 2018, Kitajima et al. evaluated both methods of tumor assessment, comparing the performance of RECIST and PERCIST in terms of sensitivity, specificity, and accuracy for evaluation of pathologic complete response (PCR) prediction.[76] The overall sensitivity, specificity, and accuracy of the RECIST criteria was found to be 28.6%, 94.4%, and 65.6%, respectively. PERCIST, however, was found to have a sensitivity of 100%, specificity of 22.2%, and accuracy of 56.3%. This revealed that both the high level of specificity and negative predictive value of RECIST as well as the high sensitivity and positive predictive value of PERCIST make complementary in assessing response to therapy. PERCIST was more likely to overestimate PCR, while RECIST was more likely to underestimate response. They also noted that tumor subtypes influenced the accuracy of each method. For instance, triple negative tumors were more accurately assessed using PERCIST and luminal A and B tumors were better assessed by RECIST. Controversy remains as to the use of RECIST vs PERCIST in breast cancer with conflicting studies.[77–81] As simultaneous acquisition of PET/MRI becomes more universally available, there will be more imaging biomarkers that utilize multimodal approaches to assess response.

2.4.2 Multiparametric imaging and Radiomics—Radiomics focuses on the acquisition, extraction, quantification and analysis of medical imaging through image segmentation and feature extraction [82, 83]. The rationale behind radiomics is the concept that distinct phenotypes, or radiomic features, can be used to predict diagnosis and therapeutic response in oncology [84]. Moreover, radiomics has been demonstrated in retrospective studies to be used to predict tumor heterogeneity and eventual patient outcome. Zhang et al and Aerts et al. conducted a radiomic analysis of head and neck cancer and was able to sort patient phenotypes into categories such as tumor shape, texture or histogram features which were found to have an association with oncologic outcomes and can be used to predict tumor behavior or patient phenotype [85, 86]. In patients with breast cancer, radiomics is being used to inform on and increase the accuracy of MR imaging and prognostic potential of mammography [87]. Additionally, multiparametric approaches, such as those combining quantitative biological information from DW- and DCE-MRI have shown to have increased predictive capabilities when compared to individual metrics by themselves[88].

3. Novel and translational integrated imaging biomarkers focused on therapeutic response in oncology

3.1 AI and machine learning

In clinical trials, longitudinal evaluation of advanced cancer tumor response is typically done by adhering to the rules of one or more tumor response criteria.[89] At many institutions, the neck, chest, and abdomen/pelvis are separately evaluated by radiologists, and the tumor measurements are included in one or more text-based reports. Some study coordinators extract the tumor finding from these reports, which is highly prone to errors. Some academic medical centers have dedicated tumor metrics labs that provide patient-level reports that adhere to the specific tumor response criteria used in the study protocols. For either method,

target lesions are identified and tumor metrics (typically length measurements) are commonly gathered and recorded to manually calculate total tumor burden and percent changes in tumor burden relative to the baseline exam or lowest tumor burden (or nadir). In addition, non-target lesion response is tracked semi-objectively over time. The changes in tumor burden of target lesions, non-target lesion response, and presence or absence of new sites of disease are used to derive final objective tumor response. This entire process is highly manual, inefficient, and burdensome to perform. In addition, the use of multiple different local radiologists leads to errors, bias and inconsistencies.[90]

Computer assisted response evaluation (CARE) refers to the use of a computer guided workflows in the settings of cancer response evaluation to improve standardization and enhance efficiency.[91, 92] In a multi-institutional study where radiologists utilized evaluated advanced cancer, CARE eliminated common errors and markedly improved efficiency compared to manual methods, but CARE did not improve inter-observer agreement.[91]

More recently, artificial intelligence (AI) algorithms have been developed to assist with various tasks including tumor segmentation, labelling and tracking over time (Figure 5a). In a recently complete multi-institutional comparative effectiveness trial, AI-assisted tumor response reduced major errors by 99%, was twice as fast, and improve inter-observer agreement by 45% compared to the current manual-based standard of care method of tumor assessment using dictated reports.⁵ Further, the AI-assisted method generated a graphical report and table with relevant longitudinal data and key images displaying all tumor measurements (Figure 5b). AI-assisted tumor response methods are clearly the future of tumor response assessment in both clinical trials and clinical practice as they will reduce errors and improve accuracy, precision, and standardization and enhance communication. Interestingly, the AI-assisted segmentation could be used to develop and validate radiomic biomarkers.

3.2 Antibody-and peptide - based PET imaging

New imaging agents for therapeutic targets have expanded the field companion diagnostics. Imaging agents focused on the target density in the tumor or an understanding of the pharmacokinetics of the therapeutic drug have both contributed to a better understanding of patient response to therapy. In particular, ⁸⁹Zr antibody imaging has been shown to be an effective tool for the latter purpose[93]. ⁸⁹Zr Trastuzumab has been studied by several groups for imaging of HER2 in breast cancer[94, 95]. Importantly these studies have identified patients with metastasis with a HER2 expression different from the primary diagnosis (HER2 negative metastasis from a HER2 positive primary tumor and vice versa) which is likely to give rise to a mixed response to HER2 targeted therapy [95]. An example is shown in Figure 6. Additionally, ⁸⁹Zr antibody imaging may inform on therapeutic efficacy of compounds targeting a similar mechanism or pathway. For example, van Es *et al* reported on the successful use of [⁸⁹Zr]Bevacizumab to predict everolimus response in patients with renal cell carcinoma[96]. While studies in this field are still emerging, the early results illustrate the promising nature of this technique.

While ^{89}Zr labeled intact antibodies have advantages as they are typically based on an approved therapeutic drug, imaging with these agents can be logistically challenging as they typically require imaging at longer timepoints. Imaging with peptides or small molecules which bind to the therapeutic target can overcome some of these challenges. Additionally, these can be used for the development of theranostic strategies where similar (or identical) compounds are used for imaging and therapy. The enormous success of somatostatin imaging agent [^{68}Ga]DOTATATE is an example of this paradigm shifting concept. Currently, [^{68}Ga]DOTATATE imaging is used to select patients who are likely to respond to the therapeutic [^{177}Lu]DOTATATE[97]. In a similar fashion, ^{68}Ga and ^{18}F -labelled imaging agents targeting PSMA have been shown to predict patient response to PSMA targeted therapies (see additional information in section 3.3) [98].

3.3 Molecular imaging in prostate cancer

Significant advances in the molecular imaging of prostate cancer have occurred over the past decade, with approval of [^{18}F]fluciclovine in 2016 by the United States Food and Drug Administration (FDA) for use in PET imaging of patients with biochemically recurrent prostate cancer. However, despite its recent approval, little research has been performed evaluating the use of fluciclovine as an imaging biomarker in evaluation of treatment response. Concurrently, much work has been performed on a variety of prostate-specific membrane antigen (PSMA) compounds with FDA approval nearing for [^{68}Ga]PSMA-11. As PSMA radiotracers become increasingly utilized and more widely available, they are being integrated into clinical trials for prostate cancer as a response metric. RECIST 1.1 remains a key response metric for patients with nodal or visceral metastatic disease from prostate cancer, but is significantly limited for the evaluation of sclerotic osseous metastasis. Additionally, the use of [$^{99\text{m}}\text{Tc}$]-methylenediphosphate (MDP) bone scans can demonstrate a flare phenomenon after initiation of a new therapy and may mimic progression on the first bone scan. Utilization of PSMA-PET as a response metric and prognostic biomarker is optimal and overcomes many of the limitations of RECIST 1.1. In patients undergoing systemic therapy for metastatic castration-resistant prostate cancer (mCRPC), a recent study of PSMA-PET demonstrated that it provides reliable parameters for prediction of response to therapy and was significantly associated with response in serum prostate specific antigen (PSA).[99] Other studies have evaluated whole-body PSMA tumor volume and whole-body total lesion PSMA as a response metric on PSMA-PET and found that PSMA-PET-derived metabolic tumor parameters outperform SUVmax and CT-based response criteria for evaluation of treatment response.[100] These PSMA-PET-derived metabolic tumor parameters can provide a quantitative imaging biomarker that allows for standardization of quantitative changes in evaluation of treatment response.[101] Despite the advantages of utilizing PET-imaging biomarkers in clinical trial response a major challenge in patients with prostate cancer is to demonstrate added prognostic value of PET biomarkers over serum PSA monitoring, which is widely used in clinical practice. While it is clear that PET-based biomarkers offer significant advantages over RECIST 1.1 (namely the ability to evaluate sclerotic osseous lesions), further research is needed to justify the cost of these scans when serum PSA monitoring of response is often adequate.

3.4 Immuno-imaging in response to immunotherapy

Recent advances in immunotherapy have demonstrated that the immune system can be used to target and treat a variety of cancers. While checkpoint blockade has provided durable clinical responses for a minority of patients, most still derive no benefit [102]. This is one extremely important area for which the imaging community can currently offer very limited clinical support, is in assessing the response of tumors to immunotherapy. Early experiences made it quite clear that RECIST was inadequate for properly assessing the effects of immunotherapy, as the “response” to these drugs can frequently manifest as transient increases in tumor burden. Hence, several modified versions of RECIST, such as iRECIST and irRECIST, have been developed (reviewed in [103]) and are currently being evaluated. However, none of these more recent criteria report on the underlying physiological, cellular, or molecular responses caused by this class of drugs. There are, though, a number of promising PET-based probes in development (reviewed in [104, 105]) that may be sensitive to more specific effects induced by immunotherapy.

Molecular imaging techniques such as PET provide the ability to non-invasively visualize and quantify the interactions that occur between tumor cells and the immune system, which offer the potential for identifying patients who will benefit from immunotherapy prior to or shortly after initiation. A growing number of imaging agents can provide fundamental insights into tumor-immune cell interactions, and the molecules involved in these responses necessary to enhance the efficacy of immunotherapy. There are several targets available for understanding immune-oncology, including T cell surface lineage markers, membrane-bound functional markers, metabolic markers, and secreted functional markers. T Cell lineage markers that have been studied include cluster of differentiation 3 (CD3), used to identify the presence of all combined T cells, CD4, used to identify the presence of helper and regulatory T cells, and CD8, used to identify the presence of T effector cells [106–108]. T cell membrane bound functional markers seek to further define the phenotype of broad classes of immune cells, and imaging agents for programmed cell death receptor 1 (PD-1), programmed cell death receptor ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) have been reported [109, 110]. As targets of approved checkpoint inhibitors, these proteins could be utilized to improve patient selection and determine the correct application and timing of therapy. T Cell metabolism imaging, which aims to identify active immune cells through elevated uptake of anabolic metabolites, has been explored using glycolysis with [18F]-Fluorodeoxyglucose (FDG) and DNA synthesis with [18F]-fluorothymidine (FLT) and 2'-[18F]fluoro-9-b-D-arabinofuranosyl guanine [111, 112]. Although changes in metabolism have been widely used for diagnosing and assessing tumor response for decades, using metabolic markers presents a significant challenge since many metabolic pathways are shared between tumors and activated immune cells. A direct method of measuring current T cell activation through the detection of functional markers released by T cells have also been explored. T cell secreted functional molecules, including interferon gamma (IFN- γ) and Granzyme B (GZB) are only present in the event of activated cytotoxic T cells and have been shown to be capable of predicting response in tumor immunotherapy [113, 114]. In total, there is a significant demand for highly specific and quantitative imaging tools in order to enhance immunotherapy through a personalized approach to treatment. Whether a target is lineage-specific, metabolic or functional it can be

used to better understand the biology of the tumor immune microenvironment but may also present limitations as well. Thus, continued investigation into immune-oncology imaging is necessary, as it is likely that the future of immunotherapy will be influenced by the use of multiple imaging-based agents. These potential imaging strategies are described in Figure 7.

3.5 Theranostics

The term theranostics has come to be recognized as a molecule that has dual uses as either a therapy or as a diagnostic, and has been of recent excitement in the field of radiology to personalize oncology treatments based on radiology imaging biomarkers. The most successful example of a theranostic is the combination of $^{68}\text{Ga}/^{111}\text{In}$ - and ^{177}Lu -DOTATATE [115]. The NETTER-1 trial, which was designed an integral imaging biomarker to select eligible neuroendocrine cancer patients by ^{111}In -pentetreotide diagnostic imaging and then treat with ^{177}Lu -DOTATATE has fueled increased interest in using a similar strategy for other cancer antigens that are over expressed in a variety of different tumors. When designing a theranostic agent, the components can be simplified into two parts, the targeting vector and the payload. Targeting vectors should possess pharmacokinetics that include rapid blood clearance, low-off target accumulation, and minimal residualization in clearance organs. For this reason, small molecules, peptides and small biological proteins less than 20 kDa continue to be extensively explored. One of the most promising targets is PSMA, and a number of small peptide-like molecules are currently being explored clinically as theranostics [116, 117]. In patients undergoing systemic radioligand therapy with [^{177}Lu]PSMA, total tumor volume detected on PSMA PET was significantly associated with PSA response.[118] Changes in both total tumor volume on PSMA-PET and PSA were associated with overall survival benefit, while changes in measurements from RECIST evaluation were not.[118] Additionally, there are a number of other targets, including HER2, fibroblast activation protein, NY-ESO, CA-125, gastrin-releasing peptide receptor, and PARP that have been explored either pre-clinically or in small clinical trials [119].

In addition to the targeting vector, there are a number of choices for payload. For imaging, most theranostics utilize PET isotopes including ^{68}Ga , ^{18}F , ^{64}Cu , or ^{89}Zr , although SPECT agents such as ^{131}I , $^{99\text{m}}\text{Tc}$, and ^{111}In have also been used [116, 119–121]. PET isotopes are more frequently used, likely due to the higher sensitivity and quantitative measurements that can be used to help stratify patients into high and low target expression. Additional imaging modalities including magnetic resonance, fluorescence and ultrasound have also been reported [122]. The therapeutic payload of a theranostic agent is traditionally thought of as a paired radioisotope that emits a particle that is capable of inducing cell death. Beta-emitters such as ^{177}Lu or ^{90}Y have been used most extensively due to their longer range of therapeutic effect, however alpha emitters including ^{211}As , ^{225}Ac , ^{227}Th , ^{224}Ra , ^{212}Bi , and ^{212}Pb have also been employed [123]. Metals such as ^{212}Pb and ^{213}Bi can be chelated by the same chelators that bind ^{68}Ga and ^{64}Cu , whereas astatine must be bound using halogen specific chemistry. Other isotopes, such as ^{64}Cu and ^{111}In can be considered theranostic isotopes as they emit both imaging and therapeutic particles. While ^{64}Cu emits a beta particle, ^{111}In emits auger electrons, which if delivered to the nucleus, have been demonstrated to induce cell death [124]. While these represent the radioactive therapies that can be used for theranostics, the cell killing need not be delivered only through radioactivity.

Therapeutic antibodies such as the HER2 antibody Trastuzumab, can be radiolabeled with ^{89}Zr so that the same molecule used for therapy can also be non-invasively imaged to help stratify patients and understand drug pharmacokinetics [121]. As cell-based therapies continue to grow, including a reporter gene within the transfecting vector has also been used to track adoptively transferred T cells or even viral transfection strategies [125]. The reporter genes express targets for previously characterized imaging agents such as sodium iodide symporter, STSTR2, PSMA among others. These examples highlight a small number of the total theranostics being explored. Given the sheer number of choices for designing theranostic molecules, and the significant clinical impact being made by the first theranostic agents, this field is poised to expand significantly in the coming years.

4. Future directions in clinical imaging trials

Imaging has transformed the way clinical cancer care is performed as it is an integral component of oncology detection, staging, monitoring, treatment guidance and surgical resection. Imaging biomarkers have potential to further impact clinical patient care in the future through personalizing patient treatments based on identifying early anatomical, functional or molecular quantitative information related to the disease burden, tumor microenvironment and therapeutic response, thereby enabling improved clinical decision making for the treatment of disease. Timelines for development and integration of imaging biomarkers into clinical trials are shown in Figure 8. With continued advancement in novel combination therapies including targeted and immunotherapy, there is a need to sensitively and specifically identify response in a variety of solid tumors. While there are many challenges associated with the biological and technical validation of novel imaging biomarkers, a distinct roadmap has been created that is being implemented into many clinical trials to advance the development and implementation to push these novel imaging biomarkers of therapeutic response to continue to transform medicine.

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Figure 1:

Serial diffusion-weighted (DW) MRI demonstrating good response in a 54-year-old woman who underwent neoadjuvant treatment for grade III triple-negative cancer in the I-SPY 2/ACRIN 6698 Multicenter Trial. a) Imaging was performed on a 3.0-T MRI scanner; shown are axial postcontrast dynamic contrast-enhanced (DCE) MRI images (left), non-contrast DW MRI (b value = 800 sec/mm^2) images (center), and apparent diffusion coefficient (ADC) maps (right) for the pre-treatment and early-treatment (3 weeks after starting chemotherapy) time points. Tumor ADC was measured by defining a whole-tumor region of interest (ROI) across multiple slices (shown here for a representative slice, where the ROI was defined to avoid a central necrotic region) at each time point. b) Tumor ADC histograms demonstrate a substantial shift towards higher values with treatment, with mean tumor ADC increasing from 1.14 to $1.35 \times 10^{-3} \text{ mm}^2/\text{s}$ (change in ADC = 18%). This patient experienced a pathologic complete response. Figure adapted from Partridge et al. ACRIN 6698 Primary Aim results. Radiology 2018 with permission.

Figure 2.
The Liver Surface Nodularity (LSN) score adapted from CT is derived from 8 to 10 measurements of the anterior aspect of the left hepatic lobe where the liver is against visceral fat. This patient has advanced cirrhosis and hepatocellular carcinoma (white arrow). The high LSN score (4.3) suggest that patient is at high risk for post-operative complications.

Figure 3.

Contrast-enhanced portal-venous CT images depict a liver metastasis from renal cell carcinoma on pre-therapy (left) and initial post-therapy (right) images. A freeform region of interest is used to segment the liver metastasis at both time points and depicts the vascular tumor burden (VTB, shaded red) and tumor necrosis (shaded green). The graphical report on the right depicts the liver metastasis and two lymph node metastases along with quantification of total tumor length, VTB and necrosis. Note that length decreased by only 21%, but the VTB decreased by 81%. These changes are predictive of a favorable response to therapy, and the patient had progression-free survival >2 years.

Figure 4.

^{18}F -FLT PET/CT scans shows early response to MDM2-inhibitor targeted therapy whereas the conventional CT scan images do not show any responses in a patient with EGFR-negative lung adenocarcinoma comparing baseline (prior to treatment) to 9 days post therapy. Circles indicate location of the tumor. As seen in the FLT-PET image, the tumor has marked decreases in signal, indicating decreased proliferation, however in the CT alone image, the anatomical size of the tumor has remained unchanged. Adopted from Kairemo et al. *Diagnostics*, 2020.

Figure 5.

AI and machine learning algorithms are being developed to quantify therapeutic response in cancers and designed to implement into clinical workflow. Demonstration of (A) AI algorithms that assist with longitudinal tumor response assessment and (B) Demonstration of AI-assisted tumor reports are shown.

Figure 6.

A 47-year-old woman with primary ER-positive, HER2-negative invasive ductal breast carcinoma and known metastases in the liver, nodes, and pleura. A, Axial CT and PET images from a contrast-enhanced FDG PET/CT through the chest demonstrate FDG-avid right pleural masses (SUVmax, 6.0; arrows). B, Axial CT and PET images from a non-contrast-enhanced ⁸⁹Zr-trastuzumab PET/CT at the same level demonstrate ⁸⁹Zr-trastuzumab avidity in the pleural lesions (SUVmax, 6.9; arrows). The pleural lesion was selected for biopsy as the lesion with the lowest risk for sampling. Biopsy of the pleural lesion demonstrated HER2 IHC of 2+ and FISH of 2.4. As FISH was greater than 2.0, this was considered a true-positive ⁸⁹Zr-trastuzumab focus for a HER2-positive distant metastasis. Figure adapted from Ulaner, Lapi et al. Clinical Nuclear Medicine 2017 with permission.

Figure 7.

Novel imaging biomarkers of therapeutic response in immunotherapy are being developed to target the expression and activation of immune cells that may predict therapeutic response, as well as the involvement of the tumor microenvironment such as vascularity and cellularity.

Figure 8.

Workflow for development on new imaging biomarkers takes between 3–6 years from discovery to implementation into clinical trials. Novel radiopharmaceuticals for molecular imaging add additional time for toxicology studies prior to introduction into Phase 1 safety studies. Initial trials are typically introduced as integrated biomarkers to run parallel to therapeutic studies, prior to introduction of integrated metrics that guide treatment decision making.