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Functional Imaging Predictors of Response to Chemoradiation

Elaine Luterstein[1] · Ann Raldow[1] · Yingli Yang[1] · Percy Lee[1]

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Abstract

Purpose of Review Early prediction of response to chemoradiotherapy in locally advanced rectal cancer has the potential to minimize surgical intervention in patients with complete response, while allowing non-responding patients to explore more aggressive treatments. Functional imaging detection of tumoral microstructural and metabolic changes presents a valuable tool for preoperative chemoradiation response assessment.

Recent Findings Diffusion-weighted MRI has increasingly been incorporated into study protocols, with the apparent diffusion coefficient largely found to be the most robust global predictor of neoadjuvant therapy response. However, no definitive predictive biomarkers have been identified, with inconsistent results across all imaging modalities.

Summary We evaluated the pros and cons of PET/CT imaging; perfusion imaging; and diffusion-weighted, dynamic contrast-enhanced, multiparametric, and low-field functional MRI in the early prediction of response to chemoradiotherapy. Future directions of study include combinatorial imaging with both MRI and PET/CT modalities and further investigation of on-board low-field MRI imaging during radiotherapy treatment delivery.

Keywords Functional imaging · Rectal cancer · Diffusion-weighted MRI · Positron emission tomography imaging · Early-response predictive biomarkers

Introduction

In locally advanced rectal cancer (LARC), prediction of response to neoadjuvant chemoradiotherapy (NCRT) is essential to treatment plan optimization and efforts to create an individualized treatment approach. Current standard-of-care treatment for LARC is neoadjuvant chemoradiotherapy followed by total mesorectal excision (TME) [1, 2], but the uniform treatment of all patients with this tri-modal approach is ineffective in chemoradiotherapy non-responders and potentially introduces surgical morbidities [3, 4] to patients who have achieved a complete response after CRT.

Complete pathologic response to chemoradiotherapy has been correlated with durable response and favorable outcomes, with improved progression-free survival [5–7], and a wait-and-see protocol has been proposed and selectively implemented in patients with clinical complete response [8–10]. Sphincter-preserving local excision has also become a viable treatment option for good responders [11].

Despite these promising findings, however, only 15–27% of patients achieve pathological complete response (pCR), with 54–75% of patients achieving partial response and the rest exhibiting response resistance [7].

Ongoing investigations are focused on identifying imaging biomarkers in the pursuit of a comprehensive early-response prediction model. While anatomical imaging cannot distinguish between post-treatment fibrosis and persistent disease [12], functional imaging detects changes in tumoral microstructure and metabolic microenvironment that are indicative of NCRT response and can be identified earlier than anatomical and volumetric tumor changes.

Preoperative prediction of pathologic response may confer a dual benefit: predicted responders may avoid the complications of invasive surgical management and pursue

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✉ Percy Lee
percylee@mednet.ucla.edu

[1] Department of Radiation Oncology, David Geffen School of Medicine at UCLA, 200 UCLA Medical Plaza, Suite B265, Los Angeles, CA 90095, USA

surveillance-based organ-sparing protocols, while non-responders may opt for more aggressive treatment alternatives and undergo intensified treatment regimens [13–15].

Functional imaging NCRT response prediction presents a key opportunity to improve both the efficacy of treatment and the value of response assessment.

PET/CT

PET/CT has traditionally been employed to functionally assess and determine disease response, and 18F-Fluorodeoxyglucose (FDG) PET imaging was first utilized to assess therapy response in LARC in 1992, though no consensus was reached on the accuracy of NCRT response discrimination and optimal imaging timing [16]. The most studied parameter is maximum standardized uptake (SUV_{max}) [17, 18], which quantifies tumoral FDG uptake and reflects cell viability, and an investigation of 15 different 18F-FDG PET/CT qualitative/quantitative prediction parameters found that post-NCRT SUV_{max} is the best predictor of response [19].

The utility of 18F-FDG PET/CT was further demonstrated in a study of 103 patients, which found post-NCRT SUV_{max} and percent change SUV_{max} to be significant factors, with a sensitivity of 68.2% and specificity of 87.7%, and a sensitivity of 90.9% and specificity of 80.3%, respectively, in the prediction pCR [20]. Other studies have reported 81% sensitivity, 100% specificity, and 90% overall accuracy for a post-NCRT SUV_{max} threshold of 5.4 [21]; 79.5% sensitivity and 66.7% specificity for an SUV_{max} cutoff of 4.3 [22]; 73.7% sensitivity, 63.7% specificity, and 64.9% accuracy for a cutoff of 3.55 [23]; and 75% sensitivity and 100% specificity for a percent change in SUV_{max} of 32% [24].

A study of 41 LARC patients imaged with 18F-FDG PET/CT at three timepoints (baseline, delivered dose of 40 Gy, and end of neoadjuvant therapy) revealed significant differences in early SUV_{max} percent reduction ($p = .04$), with a cut off of 57% [25].

Simultaneously, however, trials have surmised that PET/CT imaging has little value [26], SUV_{max} reflects a single point and is not representative of the whole [27], and assessment accuracy declines rapidly with lesions smaller than 1 cm.

Other PET/CT techniques have been explored, among them 18F-fluoromisonidazole (18F-FMISO), which attempts to identify severe or prolonged tumor hypoxia that can lead to radio-resistance. Increased retention of 18F-FMISO in tumor cells pre-treatment is suggestive of hypoxia due to poor tumor microvasculature, increased diffusion distances, or reduction in blood oxygen transport capacity, but preliminary data does not support that reduced 18F-FMISO uptake is predictive of clinical response—and fundamental difficulties in interpretation arising from the spill-in from non-tumor activity in the rectum and bladder limit the clinical applicability [28].

The greatest shortcoming of PET/CT response prediction across all techniques remains the difficulty interpreting fibrotic scar tissue and inflammation [29], and the resulting necessity to delay imaging after treatment completion to account for post-radiation effects. This creates a window of time between treatment and response assessment during which progression may be undetected and further treatment strategies may be formulated on a flawed basis.

DW-MRI

Diffusion-weighted MRI (DW-MRI) is one of the most widely studied functional imaging techniques, and has been adopted in many protocols for both preoperative therapeutic response prediction and post-chemoradiotherapy restaging. DW-MRI differentiates between tumor and normal tissue on the basis of the diffusion properties of water arising from the microscopic Brownian motion of water molecules in intracellular and extracellular space, and quantifies intratumoral changes throughout the course of NCRT with the apparent diffusion coefficient (ADC) [30, 31]. The diffusion of water is contingent upon the density of cellular structures, and DW-MRI is uniquely sensitive to modulations in intratumoral cellularity and cell membrane integrity resulting from NCRT.

Low ADC is indicative of greater cellular density, while higher ADC is histologically correlated with areas of necrotic tissue and reduced cell density with a variable degree of edema, fibrosis, and inflammation [31–33]. Greater initial ADC is therefore prognostic of necrotic tumor tissue and compromised membrane structure, characterized by poor tissue perfusion, low oxygen concentration, and an acidic-hypoxic microenvironment responsible for greater therapy resistance [31, 34, 35].

NCRT treatment induces an initial rise in ADC—a reflection of acute vascular and cell membrane disruption, and tumor necrosis [36, 37]—which is followed by re-equilibration as a result of interstitial fibrosis with reabsorption of extracellular fluid [31, 32, 38].

A study of 31 rectal cancer patients revealed the relative strength of the percent change in ADC (sensitivity 100%, specificity 70.37%) [39], which was a stronger diagnostic marker for pCR than both pre-and post-treatment ADC. Further evidence was presented in a meta-analysis of 11 studies with 615 cumulative patients [40], which corroborated that the percent change in ADC was the preferred global parameter of response prediction, with a sensitivity of 90% and specificity of 86%.

An associated study of rectal adenocarcinoma patients treated with NCRT followed by TME examined 50 patients with pCR and 50 non-responders [41•] and found that pre-treatment ADC and percent change ADC were both moderate predictors of response, with percent change yielding a higher accuracy: pre-treatment ADC values were significantly lower in pCR patients ($p = .003$) and the percent change between

pre- and post-treatment ADC was 68% for patients achieving pCR compared to 48% for non-pCR patients ($p < .001$). Post-treatment ADC values were significantly higher in pCR patients, which supported related findings that post-NCRT ADC values obtained in a single-slice region of interest (ROI) containing the whole visible tumor area increased the diagnostic performance of MRI and achieved the highest accuracy, with a sensitivity of 96.1% and a specificity of 71.4% [42].

Importantly, this also matched with the results of a study of 34 patients evaluated for response to NCRT [43], which reported that both mean post-NCRT ADC and percent change in ADC in responders were significantly higher compared to non-responders ($p = .001$; $p = .01$).

Pre-NCRT ADC values alone were not reliable as a differentiator, and while post-NCRT ADC was stronger than change in ADC with respect to diagnostic performance, the challenges outlined in the previous study (namely limited imaging resolution and difficult ROI delineation for small regressed tumors) elucidated the limitations of post-treatment ADC as a global predictive factor.

The superiority of the percent change in ADC over both pre- and post-treatment ADC values was further highlighted in a study of 43 patients [44••] evaluated with 3.0 T DW-MRI before treatment, 2 weeks into NCRT, and 8 weeks post-treatment, which found that the percent change in ADC between pre-treatment and both the 2-week and post-treatment evaluation was significantly higher in complete responders (33.9 and 57% during and post, respectively, versus 13.5 and 2.2% in non-responders; $p = .006$ and $p < .001$). The change in ADC 2 weeks into NCRT resulted in a sensitivity of 75% and a specificity of 76.5%, and the change in ADC post-treatment showed a sensitivity of 95% and a specificity of 82.4%.

However, there was a discrepancy between the results reported for the 2-week evaluation and a parallel study, which purported that there were no significant differences in the percent ADC increase [44••]. This dichotomy likely resulted from differing numbers of *b* values for DW-MRI and ROI drawing techniques, whereby ADC was measured using consecutive ROIs throughout whole tumor instead of considering the level with the largest diameter.

Selection of ROI was a limitation in further trials, and resulted in inconclusive results in a study of 37 patients imaged with DW-MRI, where ADC values were insignificant as a predictive biomarker [45]. ADC values were ascribed little utility in a similar study of 45 patients, with no significant differences in pre-NCRT, post-NCRT, and percent change ADC between responders and non-responders [46], attributed to tumor heterogeneity. Relapsing tumor could not be differentiated from inflammation, which can simulate the presence of persistent tumor—both the absence of DW-MRI signal and residual hyperintensity on b800 DW-MRI (which is likely due to fibrotic scar tissue within the rectal wall simulating residual tumor) corresponded to complete response [38, 46].

A fundamental difficulty with DW-MRI is the lack of standardization of technique, with great variability in ADC measurements, which are influenced by imaging quality, spatial resolution, size, and ROI positioning [47]. ROI positioning in particular is an active area of research since it has thus far remained unclear whether the ROI for ADC should incorporate the entire tumor volume, a single tumor slice, or small tumor samples [47]. The impact of three different methods of ROI positioning for ADC measurements (three circular ROIs, single-section, and whole-tumor volume) was investigated in 62 patients [48••], and single-section and whole-tumor volume showed higher accuracy than three ROIs, but a definitively superior method was not identified. Each ROI produced different data, but the post-NCRT ADC values were comparable in all. While larger area measurements exhibited greater accuracy in response assessment and whole-tumor volume measurement of percent change provided the best results (with post-NCRT ADC and percent change in ADC both shown to accurately identify non-responders), the quickest method was single-section [48••], and it became a subjective trade-off. Furthermore, DW-MRI interpretation is operator-dependent, which is reflected by inter-observer differences in ADC measurements. In a report in which two independent non-expert readers scored the restaging DW-MRI in 100 patients for the likelihood of complete response versus residual tumor [49], the most common pitfalls were the interpretation of low signal on the ADC map (hypointense fibrosis), small susceptibility artifacts, T2 shine-through effects, suboptimal sequence angulation, and collapsed rectal wall.

Perfusion Imaging (Perfusion CT and DCE-MRI)

The motion of water molecules in viable tissues is influenced by both thermally driven motion (pure diffusion) and microcirculation blood perfusion, which cannot be captured by diffusion imaging alone. Dynamic contrast-enhanced MRI (DCE-MRI) provides information regarding the microcirculation perfusion of tissues and measures a volume transfer constant, K^{trans}, which is dependent on the perfusion and the permeability of the tumor vasculature [50]. However, it is limited in its clinical application due to the necessary administration of an exogenous gadolinium-containing contrast agent (which is costly and associated with medical risks) and the required derivation of model-based K^{trans} in comparison with straightforward visual assessment of signal intensity in DW-MRI [51]. DCE-MRI has been found to more accurately identify good responders than complete responders [52], and in a study of 37 patients who were imaged post-treatment with DCE-MRI [51], K^{trans} (volume transfer coefficient)

could not distinguish pCR, but was an indicator of at least 90% response. In the context of DW-MRI, DCE-MRI has inferior results, and a study combining functional and volumetric approaches determined that ADC was a superior surrogate of response regardless of volumetry—DCE-MRI did not add value for response assessment [53].

Perfusion, or dynamic contrast-enhanced, CT imaging similarly aims to determine blood flow patterns and changes, and has yielded promising early results as a method of NCRT response prediction. A study of 17 patients imaged with perfusion CT analyzed three perfusion parameters for both ROIs incorporating only hotspots of pronounced vascularity in a single axial plane and whole tumor measurements on multiple contiguous slices [54]. The findings revealed that peak hot spot blood volume 1–2 weeks into therapy and hot spot permeability decline 12 weeks after initiation were significant predictors of complete pathologic response outcome, thought to result from tumor vascularity increases in early stages due to inflammation and interaction between radiation-induced inflammation and cytotoxic/anti-angiogenic effects of chemo. Initially, a proposed advantage of perfusion CT was the ease of incorporation into routine diagnostic and serial CT scans, but as more advanced MRI imaging techniques were introduced with superior soft-tissue visualization and detail of evaluation of local disease, MRI became integrated into standard-of-care protocols. The results of early studies, while promising, have been attenuated by the complexity of perfusion CT protocols and subsequent variability, a dearth of inter-observer agreement and reproducibility, and complication of data acquisition by motion artifacts in colorectal tumor imaging [55].

Perfusion imaging as a whole is complicated by technical challenges, characterized by a lack of standardized post-processing techniques and cut-off values, signal variabilities, and planning difficulties [55, 56] that limit clinical application.

Multiparametric MRI

Multiparametric MRI (mMRI) combines anatomical and functional imaging and may overcome the inherent limitations

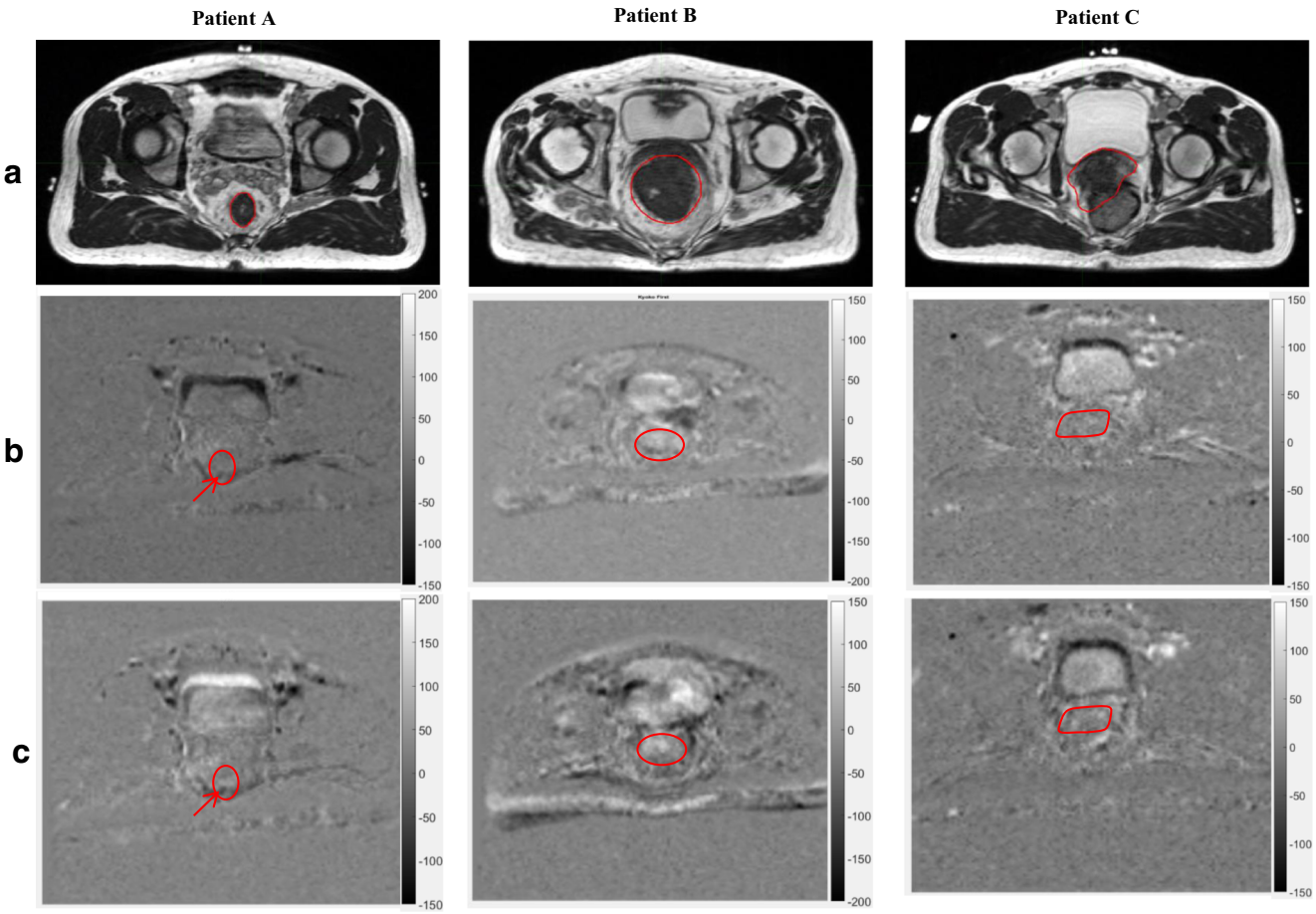


Fig. 1 Functional diffusion map (fDM) showing longitudinal pixel-wise evaluation of apparent diffusion coefficient (ADC) changes throughout neoadjuvant chemoradiation (NCRT). Darker regions represent a negative slope of ADC change throughout NCRT, reflecting a decrease in ADC. Brighter regions show a positive slope in ADC value changes, reflecting an increasing ADC. Analysis was performed for the first half of NCRT (**a**) and for the entire course of NCRT (**b**). Arrows point to discrete areas of darkness within the tumor ROI for Patient A during the first portion of NCRT

of singular imaging modalities. While DCE-MRI reveals perfusion and vascularity, DW-MRI quantifies cellularity, and combining the two imaging modalities might achieve a stronger predictive model.

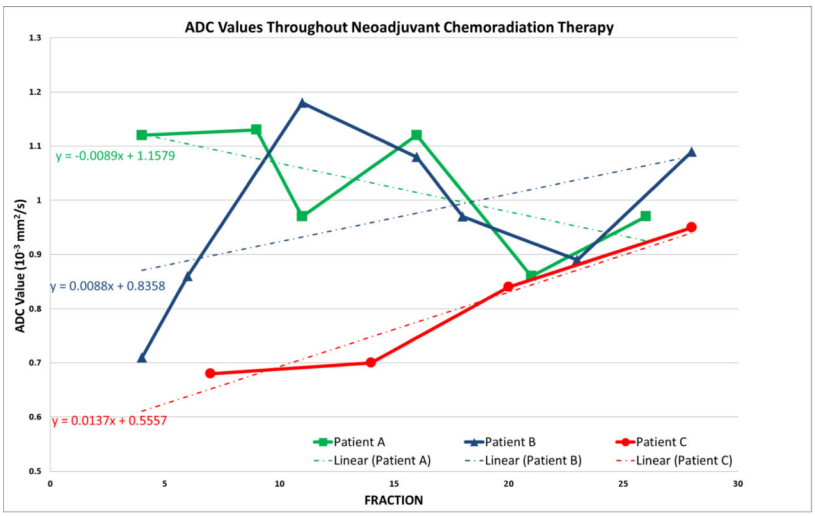
A study of 21 patients imaged with 3.0 T mMRI before and after NCRT determined that high initial ADC values could predict treatment response, but changes in DCE-MRI neovascularization markers did not reflect response [56]. An analogous study of 12 patients reported no significant difference in ADC between responders and non-responders, and no significant difference in perfusion MRI parameters except the volume of extravascular/extracellular space per unit volume of tissue, which was lower in the pCR group [57], but the results were compromised by insufficient statistical power from the small number of patients. Another study of LARC patients imaged with DCE-MRI and DW-MRI before and after NCRT ascertained that while tumor volumetry on both post-treatment DCE-MRI and DW-MRI correlated with tumor regression, no correlation existed with functional parameters [58]. This was further corroborated by a study of 67 patients, which concluded that mMRI is not sensitive enough to accurately predict complete response [59].

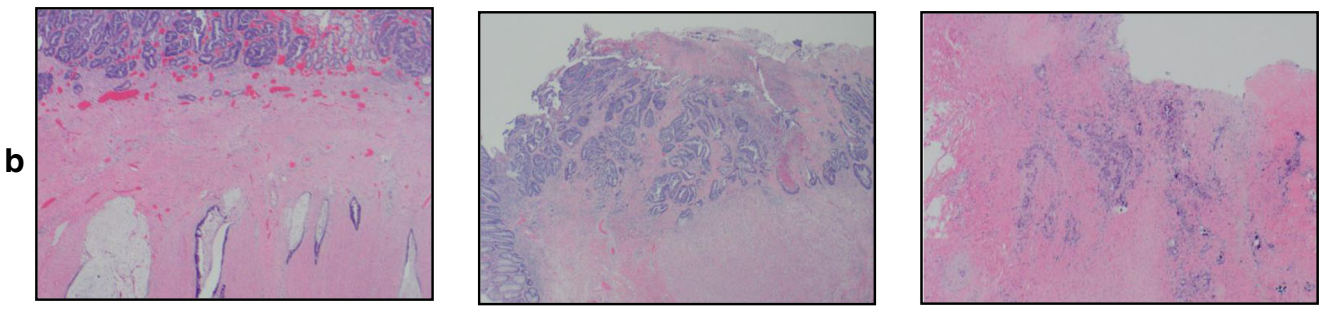
Overall, DCE-MRI was found to add little value to response assessment models, and mMRI was unable to reliably predict complete therapeutic response.

IVIM and Non-Gaussian Diffusion Models

Traditional diffusion imaging is based on the assumption that water diffusion follows Gaussian behavior and diffuses without restriction [60], and ADC is calculated using a mono-exponential model. In living tissue, however, diffusion is restricted by tissue microstructure, and random motion of thermally agitated water molecules within biologic tissues exhibits non-Gaussian phenomena [61].

Intravoxel incoherent motion (IVIM) DW-MRI can separately quantify pure diffusion motion and perfusion-related motion of water molecules without using an exogenous contrast agent as required in DCE-MRI [62]. Findings indicate pre-NCRT perfusion parametric values and post-NCRT





Patient A. Surgical pathology showing little necrosis and extensive residual cancer around mucous glands.

Patient B. Surgical pathology showing necrosis among groups of residual cancer cells.

Patient C. Surgical pathology showing abundant necrosis among single and rare groups of cancer cells.

Fig. 2 Longitudinal evaluation of apparent diffusion coefficient (ADC) values from the region of interest (ROI) throughout neoadjuvant chemoradiation for patients A, B, and C (**a**). Normalized ADC values of the ROI with respect to the initial measurement during neoadjuvant chemoradiation (**b**). Representative pathological slides from surgical resection after neoadjuvant chemoradiation for patients A, B, and C (**c**)

diffusion parametric values play an important and reliable role in noninvasively identifying pCR response, with higher microcirculatory perfusion, vascularization, and oxygenation levels at baseline leading to a better therapeutic response and IVIM-based diffusion values showing superior differentiation performance to purely DW-MRI-based ADC [63•].

However, these results were contradicted by a study of 98 patients evaluated at three timepoints (before, during, and after NCRT), which indicated that single-slice ROI IVIM parameters were inadequate for NCRT response prediction due to low reproducibility [64]. A retrospective comparison between single-section and whole-tumor volume ROI analysis addressed this issue, and the study of 31 patients evidenced the superior reproducibility of volumetric analysis and reported that both ADC- and IVIM-derived slow diffusion coefficient (D) were correlated with tumor response [65•]. This was corroborated by the phase II trial, LARC—radiation response prediction [66], which assessed 27 patients prior to neoadjuvant chemotherapy initiation and after the first three delivered radiation fractions, and found that a high baseline perfusion fraction (estimated from a simplified approach to the IVIM model) reflected tumor response with a sensitivity of 69% and specificity of 100%, and baseline perfusion fraction and tumor volume together predicted response with a sensitivity of 88% and specificity of 91% ($p < .001$).

A further study of 19 patients with rectal adenocarcinoma imaged with 1.5 T MRI with 7-*b* value diffusion sequences compared four diffusion models—mono- and bi-exponential Gaussian and non-Gaussian—and concluded that all candidate models exhibited good fitting performance, but no single diffusion model accurately described tumors [67•]. This was explained by increased tumor heterogeneity, whereby areas with high vascularity fit better with bi-exponential models and areas with necrosis mostly follow mono-exponential behavior. The two most complex models, bi-exponential Gaussian (14/19 patients best fitting) and bi-exponential non-Gaussian (best fitted tumor areas from all patients), exhibited the best fitting performance, but mono-exponential Gaussian remained the most reliable fitting algorithm [67•].

Low-Field 0.35 T fMRI

Across all imaging modalities, the timing of imaging in relation to chemoradiotherapy remains a point of contention, with imaging most often performed only before and after the treatment course, and some studies adding a 1 to 2-week early evaluation. A study of patients evaluated with on-board diffusion-weighted imaging with an integrated low-field .There is 35 T MRI radiotherapy system [68••] allowed for longitudinal, seamless DW-MRI imaging integration and enabled the creation of functional diffusion maps showing ADC changes in tumor subregions identifying potentially resistant regions (Fig. 1).

The study successfully demonstrated the utility of low-field MRI (in contrast to earlier studies, which used 1.5 T or higher fields) and the ability to serially image patients with DW-MRI. The study was also able to identify the slope of change in tumor ADC both over the entire treatment course and different segments of NCRT as early surrogates of response (Fig. 2).

Importantly, the study yielded promising results in a new direction of research and warrants further analysis of the integration of simultaneous radiotherapy and response evaluation imaging.

Conclusions

Response assessment timing is a key issue that must be further investigated, and on-board MRI response assessment during radiotherapy is a promising new avenue of research. Other studies are already underway to determine the predictive power of combining MRI and PET functional imaging. The study protocol: multiparametric magnetic resonance imaging for therapeutic response prediction in rectal cancer (Australia, New Zealand ACTRN12616001690448) plans to combine DW-MRI and DCE-MRI with PET, and a similar single-arm study: Predicting radiotherapy response of rectal cancer with MRI and PET (PRISM; Royal North Shore Hospital NCT02233374) expects to enroll 44 patients who will undergo 18F-FDG PET/CT and DW-MRI scans 2 weeks into NCRT treatment and 6 weeks after. Further trials are necessary to evaluate prediction models and emerging imaging technique applications in colorectal response assessment, including low-field MRI and non-Gaussian diffusion models.

Compliance with Ethical Standards

Conflict of Interest Elaine Luterstein declares that she has no conflict of interest.

Ann Raldow declares that she has no conflict of interest.

Yingli Yang has received a speaking honorarium from ViewRay.

Percy Lee has received a speaking honorarium from ViewRay.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major Importance

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