Dynamic Contrast-Enhanced Magnetic Resonance Imaging in Prostate Cancer Clinical Trials: Potential Roles and Possible Pitfalls

Abstract
Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) evaluates the tissue microvasculature and may have a role in assessing and predicting therapeutic response in prostate cancer (PCa). In this review, we review principles of DCE-MRI and present the potential quantitative information that can be obtained. We discuss how it may be used as a biomarker for treatment with antiangiogenic and antivascular agents and potentially identify patients with PCa who may benefit from this form of therapy. Likewise, DCE-MRI may play a role in assessing response to combined androgen deprivation therapy and radiation therapy and theoretically could be a prognostic biomarker in evaluating second-generation hormone therapies. We also address the challenges of using DCE-MRI in PCa clinical trials and discuss the difficulties with standardization of this methodology to allow for biomarker validation, with particular reference to PCa.

Introduction
Prostate cancer (PCa) is the most common cancer in men in North America and Europe, after nonmelanoma skin cancer, with 238,590 new cases estimated for 2013, and it is the second leading cause of cancer-related deaths in males after lung cancer [1]. As the US population of male “baby boomers” age, there will be an increase in PCa diagnosis and numbers of men presenting for therapy. Incidence is estimated to exceed 450,000 cases per year by 2015. Androgen deprivation therapy (ADT) is often first line for those who relapse after treatment of organ-confined disease or for advanced disease at the time of diagnosis. However, responses are not durable, and metastatic disease from castration-resistant prostate cancer (CRPC) is fatal. Angiogenesis has been shown to play a central role in the progression of CRPC [2], and microvessel density has been shown to correlate with Gleason score and predict disease progression [2–5]. However, unlike other solid tumors where inhibition of angiogenic pathways has been shown to be an effective treatment strategy [6–9], the role of antiangiogenic therapy in the management of PCa still remains to be defined [10]. In CRPC, the androgen receptor (AR) has been found to be the key regulator and driver of tumor growth, spread, and survival and the most promising therapeutic target [11]. As such, with the introduction of novel second-generation hormone therapies such as abiraterone and enzalutamide in the last few years, the treatment paradigms for CRPC appear to be rapidly changing.
Rationale for Antiangiogenic Therapy in PCa

Tumor vascularization is a complex process that involves interactions between the tumors and their surrounding stroma, in addition to proangiogenic and antiangiogenic regulating factors. A number of angiogenic agents have been implicated in PCa progression, such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and hepatocyte growth factor [18–21]. The expression of VEGF receptor 1 has been correlated with higher Gleason score [22]. In contrast to recent results with second-generation hormonal therapies [23–26], however, phase III studies of antiangiogenic agents in CRPC have failed to meet their primary end points [10,27,28]. Although the role for antiangiogenic agents remains controversial, the preclinical rationale for their use is strong. Development of predictive biomarkers to identify the appropriate subgroup of patients that may benefit from this form of targeted therapy is a current need, especially considering the added toxicity reported with some antiangiogenic studies [28].

Recent Developments in Treatment of CRPC

Androgens have been shown to stimulate key angiogenic events in male cells in vitro, sex-specific proangiogenic effects that are mediated through the AR [29]. Recently, clinical studies have confirmed that advanced PCa is driven by AR signaling. The androgen biosynthesis inhibitor abiraterone acetate was the first second-line hormonal agent to improve survival in metastatic CRPC [23,24]. It selectively inhibits cytochrome P450 17α-hydroxylase and cytochrome17,20-lyase, enzymes critical for androgen synthesis. The Food and Drug Administration (FDA) recently expanded its indication for use in the chemotherapy setting after abiraterone elicited significant delays in disease progression and a strong trend for increased overall survival in phase III studies [25]. The AR inhibitor enzalutamide has also demonstrated survival benefit in phase III studies in CRPC [26]. An international phase III trial (AFFIRM) was halted after an interim analysis revealed that patients given the drug lived for approximately 5 months longer than those taking placebo [26], and a subsequent trial (PREVAIL) demonstrated effectiveness of enzalutamide in patients who had not yet received chemotherapy [30]. Given that PCa is a very heterogeneous disease, an individualized approach may be required to maximize potential benefits from novel or combination therapies.

Rationale for Using DCE-MRI in PCa

Multiparametric MRI (mpMRI) of the prostate, the current clinical standard, refers to a set of sequences that include $T_2$-weighted imaging (T2WI), diffusion-weighted imaging (DWT), and DCE-MRI. mpMRI is known to play an important role in PCa detection and localization and PCa staging [31,32]. It also aids in tumor detection when there is a biochemical suspicion of residual or recurrent disease after treatment [33–35]. Compared to conventional prostate MR techniques from 5 to 10 years ago, which relied on morphology alone for tumor staging, localization, and characterization, standard-of-care prostate MR in 2013 provides a wealth of information regarding tumor functionality. Each of the individual sequences provides unique and complementary data. DWI is reflective of the random motion of water molecules at a cellular level and is thus sensitive to cell membrane integrity, hypercellularity, enlargement of the nuclei, and hyperchromatism. DWI [and more specifically, apparent diffusion coefficient (ADC), a quantitative metric derived from DWI] has been demonstrated on multiple occasions to inversely correlate with Gleason score and serve as a biomarker for prostate tumor aggressiveness [36–41]. DWI as a physiological measure also has the added benefit of not requiring injection of gadolinium chelates.

Unique capabilities of DCE also hold much promise for better characterizing PCa. On DCE, focal areas of PCa show early strong enhancement when compared to surrounding normal prostate tissue [42], as the number of vessels in tumor foci increase, and these newly formed tumor vessels (neovascularity) have higher permeability and more heterogeneous architecture than do normal vessels [22]. Immunohistochemical determination of microvessel density, which provides a count of the number of vessels per area, is significantly higher in PCa compared with normal prostate tissue [43,44]. A poorer prognosis has also been found to correlate with increasing irregularity and decreasing size of the new vessels [4,45]. These histologic observations highlight the potential of DCE-MRI for noninvasively assessing the microvascularization and angiogenesis in PCa, and indeed, DCE-MRI parameters have been demonstrated to correlate with microvessel density [46,47]. A recent study has shown that DCE-MRI quantitative parameters have the potential to assess PCa aggressiveness (low grade from intermediate and high grade) in the prostate peripheral zone [48]. DCE-MRI can be measured repeatedly and noninvasively, and because of the intrinsic soft-tissue contrast provided by MRI, it is an appealing biomarker to assess properties of the microcirculation that may capture the heterogeneity of tumor and its response to treatment. As a reflection of the value of DCE-MRI in the routine prostate clinical care, its use is recommended to be included in the standard prostate staging and assessment protocol [49].

Prostate DCE-MRI: Principles and Technique

DCE-MRI of the prostate is performed by rapid imaging after IV administration of a gadolinium chelate. MR contrast agents are specialized compounds that alter the magnetic properties of tissues and their neighboring protons. By observing the MR signal change caused by the shortening of the $T_1$ relaxation time, the concentration of the contrast agent at a given voxel can be measured, allowing the study of the distribution of the contrast agent over time. Molecules of the contrast agent can pass through the blood vessel walls and enter the extracellular extravascular space but cannot penetrate the cellular membrane and are gradually washed out and excreted by the kidneys.

In the prostate, the passage of the contrast agent through the gland is typically captured by specialized fast-imaging sequences, initiated before the contrast agent is injected to enable assessment of the baseline pre-enhancement properties of the tissue (Figure 1). The DCE-MRI protocol is optimized to find a balance between the spatial (important for localization of the lesion and assessment of disease extent) and

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temporal (important to accurately capture the peak concentration of the contrast uptake curve) resolutions of the image. Commonly used protocols used in clinic often allow for 5- to 10-second resolution in the prostate at 3 Tesla (3T) [32]. The acquisition should also be sufficiently long to capture the entire circulation of contrast agent through to venous washout (about 5 minutes) [49].

MR signal enhancement identified on DCE-MRI can be assessed in two ways, namely, semiquantitative analysis of signal intensity changes over time or by quantifying the amount of contrast agent concentration change using pharmacokinetic (PK) modeling techniques. Semiquantitative parameters include curve shape, maximum signal intensity, and washout gradient. The initial area under the signal intensity curve or contrast medium concentration (IAUGC) curve has also been studied. Quantitative techniques require PK models that are applied to changes in tissue contrast agent concentrations to estimate contrast agent concentration in vivo. Volume transfer constant of the contrast agent \( K_{\text{trans}} \) and the rate constant \( k_{\text{ep}} \) are commonly used parameters derived from quantitative techniques. In-depth discussion of PK modeling techniques is outside the scope of this paper but can be found in many detailed reviews [50–52].

**Prostate mpMRI as a Biomarker in Evaluating Response to PCa Therapy**

The broader oncology and cancer imaging community in the United States is attempting to address the need for, and standardization and requirements of, qualified biomarkers through collaborative efforts between the FDA, the National Cancer Institute (NCI), and other regulatory bodies, with the formulation of consortia such as the Oncology Biomarkers Qualification Initiative and the American Association for Cancer Research (AACR)-FDA-NCI Cancer Biomarkers Collaborative [53]. The NCI has also formed the Quantitative Imaging Network specifically to promote research and development of quantitative imaging methods for the measurement of tumor response to therapies in clinical trial settings.

In the prostate, a role for mpMRI in evaluating response to specific PCa therapies, such as antiangiogenic therapies, and external-beam radiation therapy and ADT are current areas of investigation. A role for mpMRI in evaluating response to second-line hormonal therapies remains to be determined.

**Systemic Therapy**

A recent review by O’Connor et al. [54] reported nearly 100 clinical studies of antivascular agents that have incorporated DCE-MRI and have yielded substantial data. They, however, point out that, although DCE-MRI can detect and monitor changes in vascular function and structure, such a change is necessary but not sufficient for proof of concept for antivascular drugs, as a significant change in DCE-MRI parameters is not sufficient evidence of clinically significant efficacy of antivascular therapy. However, the amount of change in parameters can help determine the biologically active dose (especially if there is a linear dose-dependent correlation between therapy and DCE-MRI parameter), optimal treatment schedule, and therapeutic window for the drug.

There has been significant evaluation of a role for DCE-MRI in assessing response to antivascular therapy in other tumors such as breast, lung [55], renal [15], and colon cancers [17]. In the prostate, many preclinical studies have validated the use of DCE-MRI for...
monitoring the effect of antiangiogenic agents on PCa. For example, in an experimental study evaluating the effect of sorafenib on experimental PCa, significant correlations were found between tumor perfusion indices and immunohistochemical tumor cell apoptosis and tumor vascularity [56]. Sampath et al. have found that, in a prostate xenograft model, DCE-MRI functions well as a pharmacodynamic assay to quantitatively measure the activity of phosphatidylinositol 3-kinase and dual phosphatidylinositol 3-kinase/mammalian target of rapamycin inhibitors [57].

A recent clinical study in men with CRPC demonstrated the use of DCE-MRI in predicting clinical outcomes associated with the antiangiogenic agent cediranib [58]. They found that baseline $K^{\text{trans}}$ was significantly associated with progression-free survival, thus indicating that DCE-MRI variables may prove effective as pharmacodynamic predictive biomarkers of clinical outcome for cediranib. This is similar to results previously shown for sorafenib in metastatic renal cell carcinoma [15] and non–small cell lung cancer [55].

Considering that androgens have been shown to stimulate key angiogenic events in male cells in vitro, mediated through the AR [29], a role for DCE-MRI in assessing response to the newer second-generation hormonal therapies is a strong possibility. On an individual basis, quantitative changes in mpMRI, including DCE-MRI, can be seen in patients with CRPC treated with enzalutamide (Figure 2). However, a role for DCE-MRI as a predictive or prognostic biomarker for CRPC remains to be determined.

**External-Beam Radiation Therapy and ADT**

In preclinical studies, androgen ablation has been shown to suppress glandular epithelial production of VEGF and induce apoptosis of endothelial cells [59,60]. There have been promising results from studies evaluating a role for mpMRI to assess response to ADT [61,62] and radiotherapy [63,64]. A DCE-MRI study found that ADT induces profound vascular collapse within 1 month of starting treatment [62], with significant decreases in tumor blood volume and blood flow, which decreased by 83% and 79%, respectively, and 74% of patients showing significant changes. After ADT, prostate gland shrinkage and fibrosis make tumor difficult to detect on routine T2WIs, as this sequence depends heavily on tissue proton content for contrast. A feasibility study [61] evaluated the use of mpMRI in monitoring response to ADT and suggested that DCE as a marker of

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**Figure 2.** Top two rows: Changes in mpMRI (T2WI, ADC maps, and the PK parameter $K^{\text{trans}}$) observed pretreatment (top row) and 180 days posttreatment (bottom row) with enzalutamide. $K^{\text{trans}}$ values in the tumor area decrease from 0.82 (pretreatment) to 0.35 (posttreatment). Graphs: Treatment-induced change is also reflected in the shapes of the contrast uptake curves. Pretreatment there is a faster uptake and washout of contrast in the tumor, compared to normal peripheral zone. Although the degree of uptake remains higher in the tumor tissue posttreatment, its overall shape begins to resemble that of normal peripheral zone. (Tumor in prostate peripheral zone, red slope; normal prostate peripheral zone, green slope.)
angiogenesis may help demonstrate ADT resistance, as ADT reduces prostatic blood flow and oxygenation.

As changes in serum prostate specific antigen (PSA) concentrations are not necessarily an accurate surrogate for tissue response post-ADT [65]—PSA reduction post-ADT may be secondary to androgen suppression rather than tumor cell death—it is possible that DCE may act as a stronger surrogate for angiogenesis, rather than PSA.

A Potential Role for Prostate DCE-MRI in PCa Drug Development

Trials of antivascular agents using DCE-MRI as an end point were first reported in 2002 [66,67], and more recent developments have advanced the accuracy of information that can be obtained from DCE-MRI for early-stage clinical trials, as reported by the Imaging Committee of the Experimental Cancer Medicine Centers [68]. In almost all DCE-MRI studies of phase I antivascular agents to date, DCE-MRI parameters are secondary end points, providing information on proof of concept or on the relationship between DCE-MRI parameters and drug PK parameters [54].

Specific to PCa, the Prostate Cancer Clinical Trials Working Group (PCWG2) [69] has recognized that cytotoxic agents typically result in regression of target lesions and a decrease in PSA, whereas noncytotoxic agents that slow tumor growth or prevent angiogenesis may not do so. Clinically meaningful responses in patients on targeted therapy may therefore be underestimated given that these agents often cause decreased tumor vascularity and necrosis without appreciable reductions in tumor size. PCWG2 has suggested that response assessment in phase II trials should focus on time-to-event time points.

Assessment in response to antiangiogenic therapy in PCa is challenging, as progression-free survival is difficult to define on bone scan for distant metastases or using Response Evaluation Criteria in Solid Tumors. Response Evaluation Criteria in Solid Tumors was primarily designed for use with cytotoxic agents, and it has limitations when applied to targeted therapy, which may provide clinical benefit for patients without causing marked tumor shrinkage. As an early validated surrogate end point could help with timing of regulatory approval, many radiotracers with positron emission tomography [70] and number of circulating tumor cells [71] are being investigated. The PCWG3 is currently being drafted and will include recommendation for imaging biomarker development in PCa trials. Identifying a role for DCE-MRI as a predictive biomarker may allow further insight into induced changes in microvascular structure and function in PCa by the drug under investigation.

A Role for DCE-MRI in Helping Define the Biologically Effective Dose

A key rationale for using DCE-MRI in early-phase trials has been to define the biologically active dose of drugs in phase I trials and also to inform drug scheduling and assist in dose selection for phase II studies [72]. As reviewed by O’Connor et al. [54], reductions in $K_{\text{trans}}$ and IAUGC have shown a linear dose-dependent relationship with cediranib, sorafenib, and vatalanib in other tumors, and maximum drug concentration in the plasma has also correlated with changes in $K_{\text{trans}}$ and IAUGC following treatment. Parameter relationship to drug exposure studies remains to be investigated in the prostate.

Selection of DCE-MRI Biomarker Parameter in PCa Drug Development

In general, $K_{\text{trans}}$ and IAUGC have been used as the preferred DCE-MRI end points in clinical trials [51,73]. $K_{\text{trans}}$ was chosen as the primary end point because it reflects contrast agent delivery (perfusion) and transport across the vascular endothelium (permeability). IAUGC was chosen as an alternative semiquantitative end point because it does not require model fitting and is therefore relatively robust and comparable across sites. It is calculated from the area under the contrast agent concentration curve up to a specified cutoff time (usually 60 seconds). However, IAUGC does not have a simple relation to tissue perfusion and permeability. As VEGF is considered to reduce vascular permeability [74], it therefore should reduce tumor $K_{\text{trans}}$ and would be a sensible choice if an anti-VEGF compound is being investigated. If, however, treatment effect is being achieved through blockade of FGF, alternate functional biomarkers other than $K_{\text{trans}}$ and IAUGC should also be looked at, as the imaging-related effects achieved through blocking FGF are not yet understood. Likewise, as vascular targeting agents cause reduction in blood flow and tumor necrosis [75] and can therefore alter measures of perfusion (including $K_{\text{trans}}$ and IAUGC), vessel permeability may not be altered. As such, other functional DCE-MRI biomarkers such as blood plasma volume ($v_p$) within tumor voxels or alternative biophysical measurements such as enhancing tumor volume could be measured. Ideally, the biologic end points being sought with DCE-MRI should relate to the proposed mechanism of action of the drug.

Challenges with Prostate DCE-MRI as a Biomarker in Clinical Trials

As with quantitative imaging in any cancer clinical trials, there are pitfalls and challenges that need to be addressed. These include, but are not limited to, patient and referring physician reluctance and fear of quantitative...
imaging components in clinical trials, institutional limitation for quantitative imaging, costs involved with including imaging, and concerns that clinical trials may be underpowered for quantitative imaging [76]. DCE-MRI, however, presents its own unique additional challenges for its use as a biomarker in clinical trials, addressed below.

**DCE-MRI Methodology**

DCE-MRI is able to distinguish malignant from benign and normal tissues by exploiting differences in contrast behavior in their microcirculations. Currently, the DCE-MRI protocol is not standardized, with multiple methodological choices at many levels, making cross-institutional comparisons challenging. Accurate PK modeling of DCE-MRI requires knowledge of precontrast native tissue $T_1$ values [77], which may be based on literature values [78] or explicitly measured for each patient. It also requires knowledge of the concentration of the contrast agent in the feeding vasculature, the so-called arterial input function (AIF), which can be estimated manually [79,80], through automatic determination of individual AIFs [81–83], or a popular option is

Figure 4. mpMRI demonstrating tumor in the left peripheral zone of the prostate (outlined in blue). Top row: Left: ADC ($b = 0, 500$), Middle: T$_2$WI, and Right: subtraction DCE-MRI (early arterial phase − precontrast phase) demonstrate tumor in the left peripheral zone. Bottom row: Left: $K^{\text{trans}}$ map from DCE-MRI also demonstrates tumor in left peripheral zone which is confirmed on (Right) whole-mount (outlined in red ink) to be Gleason 3 + 4.

Figure 5. Left and middle MR imaging panels: Preprocedural planning mpMRI of the prostate showing anterior area consistent with suspected tumor cancer presence on the basis of appearance on mpMRI images, particularly subtraction DCE-MRI, $K^{\text{trans}}$ map, and ADC map (outlined in blue). Right panel: At the time of biopsy, preprocedural T$_2$WI diagnostic images are registered to the intraprocedural T$_2$WI image, and targets (arrow) based on diagnostic preprocedure MRI are placed on intraprocedural T$_2$WI images. Photograph on bottom: Transperineal prostate biopsy sample is then obtained, which confirmed a 3 + 4 Gleason grade adenocarcinoma in this case.
to use a model-based population-averaged AIF, which assumes an \emph{a priori}
known AIF obtained from population studies [84,85]. Once AIF choice and
prostate \( T_1 \) have been decided on, quantitative \( T_1 \) changes can be
measured during a high temporal resolution enhancement acquisition
to estimate contrast agent concentration \emph{in vivo}. The concentration
time curves are mathematically fitted using one of a number of recog-
nized PK models [51] to derive the quantitative parameters. It should
be noted, however, that \( K^{\text{trans}} \) is vulnerable to model-fitting failures
in cases of motion, in poorly perfused areas, or in highly vascular
areas. IAUGC, conversely, does not require any physiological model,
as it is based on the early part of the gadolinium uptake curve. It is also
difficult to be certain how accurately model-based PK estimates com-
pare with each other and with the physiological parameter that they
supposedly measure, as there is no reliable clinical gold standard.
Nevertheless, quantitative kinetic parameters can provide insights into
underlying pathophysiological processes within the tumor that may
influence drug development.

**Optimal Time of Prostate DCE-MRI Measurement**

Deciding on the optimal time points for DCE-MRI follow-up is
a challenge, as the exact onset and duration of action of many anti-
angiogenic agents and vascular targeting agents are not well understood.
If imaging is obtained at suboptimal time points, the drug effect win-
dow may be missed. For example, DCE-MRI parameters can change
rapidly (1 day) in glioblastoma multiforme in response to the VEGF
inhibitor cediritinib, and this change can persist for some time (28 days
for glioblastoma multiforme) [7], but this may not be so in other
tumors or with other VEGF inhibitors. In addition, there are limita-
tions to the number and timing of follow-up MRIs that can be ob-
tained for economical, practical, and physiological perspectives. Two
posttherapy MRIs cannot be carried out within 24 hours, until the
effect of gadolinium-induced \( T_1 \) relaxation from the first study has
subsided. To minimize patient inconvenience, follow-up MRIs are
usually coincided with follow-up clinical visits. When functional
imaging is to be incorporated into prostate clinical trials, all preclinical
and clinical PK data for that specific drug should help define the
optimal follow-up imaging schedules.

**Biomarker Standardization and Validation**

Standardization of imaging biomarkers is difficult, as they are
biophysical signals. This is particularly true for DCE-MRI where
PK values obtained may depend on the temporal resolution of the
DCE-MRI study, the reproducibility of the DCE-MRI acquisition
parameters, the measured or assumed \( T_1 \) value of the tissue being
measured, the AIF choice, the kinetic model choice, and finally,
whether the data are analyzed on the basis of tumor region of interest
(ROI) or pixel-based data analysis. In addition, it is important to
remember the biophysical dependence of \( K^{\text{trans}} \) and IAUGC on
blood flow and vessel permeability. The variability and repeatability
of DCE-MRI in the prostate have been evaluated in both in areas of
tumor and normal tissues [86], and the within-subject coefficient of
variation for prostate tumor \( K^{\text{trans}} \) is reported at 20.1%, similar to
findings in other tumors [87]. Spatial correlation of the pretherapy/
posttherapy changes in the prostate requires additional processing to
align (register) the imaging data collected at the different time
points. To compensate for the changes in the prostate volume, posi-
tion of the patient, and imaging coil, nonrigid registration may be
required (Figure 3).

To support the use of DCE-MRI in PCa clinical trials, it is also
expected that there be a correlation between the biologic effect and
the DCE-MRI PK parameter. Correlation of DCE-MRI parameters
with pathologic measurements is an initial step necessary in PK
parameter validation. mpMRI may be validated using whole-mount
pathologic validation of the prostatectomy specimen after radical
prostatectomy (Figure 4) or by using mpMRI-targeted biopsy of sus-
picious prostate lesions (Figure 5).

Awareness of the intrinsic variability of any biomarker on a par-
ticular MR system with a specific protocol is vital for accurate study
pretherapy/posttherapy study design. Standardized protocols and cen-
tralized image analysis may be required for individual clinical studies
if future approval of DCE-MRI as a standard and validated pharma-
codynamic biomarker is to be realized. Uniform quantification across
multiple sites may of course be difficult to achieve, through the use of
different MRI platforms and software packages. Follow-up studies
should obviously be performed using the same equipment and MRI
acquisition methods.

**Summary**

DCE-MRI in the prostate is a promising biomarker for assessing
response to therapy. Incorporation of functional information from
DCE-MRI into PCa clinical trials will strengthen clinical investiga-
tions. DCE-MRI–derived parameters may provide information about
the action of therapeutics and potentially help in discriminating re-
sponders from nonresponders. Its use, however, requires committed
multidisciplinary teams and very careful quality assurance and stan-
dardization within PCa clinical trials, considering the many potential
variables in arriving at DCE-MRI PK parameters.

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