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Dynamic contrast-enhanced MRI for automatic detection of foci of residual or recurrent disease after prostatectomy

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Abstract

Purpose—This study aimed to develop an automated procedure for identifying suspicious foci of residual/recurrent disease in the prostate bed using dynamic contrast-enhanced-MRI (DCE-MRI) in prostate cancer patients after prostatectomy.

Materials and methods—Data of 22 patients presenting for salvage radiotherapy (RT) with an identified gross tumor volume (GTV) in the prostate bed were analyzed retrospectively. An unsupervised pattern recognition method was used to analyze DCE-MRI curves from the prostate bed. Data were represented as a product of a number of signal-vs.-time patterns and their weights. The temporal pattern, characterized by fast wash-in and gradual wash-out, was considered the “tumor” pattern. The corresponding weights were thresholded based on the number (1, 1.5, 2, 2.5) of standard deviations away from the mean, denoted as DCE1.0, ..., DCE2.5, and displayed on the T2-weighted MRI. The resultant four volumes were compared with the GTV and maximum pre-RT prostate-specific antigen (PSA) level. Pharmacokinetic modeling was also carried out.

Results—Principal component analysis determined 2–4 significant patterns in patients’ DCE-MRI. Analysis and display of the identified suspicious foci was performed in commercial software (MIM Corporation, Cleveland, OH, USA). In general, DCE1.0/DCE1.5 highlighted larger areas than GTV. DCE2.0 and GTV were significantly correlated ($r = 0.60$, $p < 0.05$). DCE2.0/DCA2.5 were also significantly correlated with PSA ($r = 0.52$, 0.67 , $p < 0.05$). K^{trans} for DCE2.5 was statistically higher than the GTV’s K^{trans} ($p < 0.05$), indicating that the automatic volume better captures areas of malignancy.

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Compliance with ethical guidelines

Conflict of interest N. A. Parra, A. Orman, K. Padgett, V. Casillas, S. Punnen, M. Abramowitz, A. Pollack, and R. Stoyanova state that they have no competing interests.

Ethical standards This article does not contain any studies with human participants or animals performed by any of the authors. Additional informed consent was obtained from all individual participants from whom identifying information is included in this article.

Conclusion—A software tool was developed for identification and visualization of the suspicious foci in DCE-MRI from post-prostatectomy patients and was integrated into the treatment planning system.

Keywords

Prostate cancer; Salvage radiotherapy; Prostate bed; Pattern recognition; automated; Dynamic contrast enhanced (DCE-)MRI

Radical prostatectomy (RP) is an effective treatment for prostate cancer [1, 2]. However, 20–30% of patients may experience a recurrence, which is typically first detected by a rise in serum prostate-specific antigen (PSA; >0.2 ng/mL) [3, 4]. The challenge is to distinguish between local versus distant disease, as these patients may benefit from local salvage therapy [5, 6]. Although PSA kinetics, along with clinical factors, may be helpful in overcoming this challenge [7, 8], imaging is often required to restage the patient and to assist with clinical decision making [9].

MRI offers superior contrast and spatial resolution over transrectal ultrasound and pelvic CT for identification of residual or recurrent disease foci [10, 11]. Endorectal coil T2-weighted MRI (e-MRI) has been shown to identify local recurrences in the prostate bed with sensitivity and specificity in the range of 80–100% in some studies [12–14], with improved accuracy seen with contrast administration [14–16]. Diffusion weighted imaging (DWI), however, is of limited incremental value for detection [16]. Recurrences present as lobulated masses with intermediate signal intensity on T2-weighted images, slightly higher than that of muscle or fibrosis, and they enhance early after intravenous injection of contrast medium [15].

One challenge involved in the use of dynamic contrast-enhanced MRI (DCE-MRI) to detect local recurrence is the variable interpretation of the scan [12]. Automated approaches using contrast wash-in and wash-out patterns may assist in image interpretation [17].

The authors describe herein an unsupervised pattern recognition method for the automatic identification of foci with a high probability of residual/recurrent disease. The approach is integrated into commercial medical image processing software (MIM Corporation, Cleveland, OH, USA). In addition, the foci are visualized in a manner that can guide salvage radiotherapy (RT) and other focal therapies. The developed tool may serve to draw attention to an area for physician review or as an automatic method for delineation of suspicious foci for biopsy or RT planning.

Methods

Patients and MRI acquisition

This is a retrospective study conducted under the approval of the Institutional Review Board at the University of Miami; informed consent was exempted. The study included 22 patients who were treated with salvage RT for rising PSA after RP between 2009 and 2013, and who had an MRI-identified gross tumor volume (GTV) contour (Table 1 and 2). Patients underwent prostatectomy between 2002 and 2012. The average interval between surgery and

MRI was 46 months. The median age at MRI examination was 61 years (range 47–79 years). All patients underwent salvage RT in the Department of Radiation Oncology, University of Miami. The median of the highest post-surgery and pre-RT PSA was 0.375 ng/mL (range 0.04–8.6 ng/mL).

Multiparametric MRI (mpMRI) data were acquired on 3T Trio Siemens (Siemens, Erlangen, Germany; $n = 20$) and 3T Discovery MR750 GE (GE, Waukesha, WI, USA; $n = 2$) systems. The mpMRI examination consisted of axial T2-weighted MRI of the pelvis: resolution: $1.25 \times 1.25 \times 2.5$ mm; field of view (FOV): 320×320 mm; slice thickness: 2.5 mm (no gap); 72 slices; and DCE-MRI: 12 series of T1-weighted with spatial resolution identical to T2 and temporal resolution at 30–34 s.

Automatic detection of suspicious foci in DCE-MRI

The mpMRI data were uploaded into MIM and all subsequent analyses performed using Java plugins. As part of RT treatment planning, the prostate bed and GTV were manually contoured by an attending radiation oncology physician who specialized in genitourinary malignancies (Fig. 1a). The signal-versus-time curves from the pixels within the prostate bed contour were analyzed with nonnegative matrix factorization (NMF) [18]. The application of the method to DCE-MRI data, together with the mathematical formulation, is described in detail in Stoyanova et al. [19]. Briefly, let $\mathbf{D}$ be the data matrix containing the individual pixel signal-versus-time curves in its rows. $\mathbf{D}$ can be represented as a product of k basic contrast signatures, $\mathbf{S}(t)$, and their weights, $\mathbf{W}(X)$, i.e., $\mathbf{D} \sim \mathbf{W} \times \mathbf{S}$, under the constraint that all elements of $\mathbf{W}$ and $\mathbf{S}$ are non-negative, such that

$$D_i \sim W_{1,i} \times S_1 + W_{2,i} \times S_2 + \dots + W_{k,i} \times S_k \quad (1)$$

for pixel i . Let $\mathbf{S}_T(t)$ denote the “pattern of interest”, i.e., the temporal pattern, related to well-perfused tissue and characterized by a quick wash-in and relatively fast washout of the contrast. Its corresponding weights in each pixel, likely to be associated with the foci of residual/recurrent tumor will be $\mathbf{W}_T(X)$. $\mathbf{W}_T(X)$ can be displayed in 3D and represent the a map of the foci. The pixels with the highest $\mathbf{W}_T(X)$ values have a higher probability of being related to tumor. The location of the tumor is mapped using four thresholds of $\mathbf{W}_T(X)$, based on the mean of $\mathbf{W}_T(X)$ plus 1.0, 1.5, 2.0 and 2.5 standard deviations (stdev) of $\mathbf{W}_T(X)$. Correspondingly, four concentric volumes are automatically generated in MIM. Here and in the remainder of the paper, these volumes will be labeled as DCE1.0 to DCE2.5. For instance, DCE2.0 will be the volume of $\mathbf{W}_T(X)$ with values larger than the threshold: $\text{mean}(\mathbf{W}_T(X)) + 2 \times \text{stdev}(\mathbf{W}_T(X))$.

Determining the number of enhancing tissues (k) a priori is challenging, because the prostate bed is a complicated mixture of various tissues, fibrosis, and biofluids. In this application, principal component analysis (PCA) is used to determine k —the number of significant principal components (PCs) in the data-matrix $\mathbf{D}$. k was defined as the smallest number of eigenvectors that explained 95% of the variance of the DCE-MRI data matrix $\mathbf{D}$.

Statistical methods and pharmacokinetic modelling

Manually contoured and automatically determined volumes were compared to maximum pre-RT PSA value using Pearson's correlation coefficient r and the Student's t -test.

Pharmacokinetic modeling was applied to characterize the dynamic curves in the (i) GTV, and (ii) DCE2.5, as well as volumes in (iii) the muscle, and (iv) an area in the prostate bed not suspicious for recurrence, termed nonspecific prostate bed tissue (NSPBT). The extended Tofts model [20, 21] was applied to the average signal-versus-time curves. Using the synthetic Parker fixed population average arterial input function (AIF) [22], valid compartmental modeling can be carried out even at the lower temporal resolution of the data [23]. The volume transfer constant between plasma and extracellular extravascular space (EES), K^{trans} (related to perfusion and permeability per unit volume of tissue), and the fractional volume, v_e , of the EES were quantified in the four volumes and compared with the Student's t -test.

Results

PCA of the variance of the DCE-MRI data matrix $\mathbf{D}(\mathbf{X}, t)$ determined the number of tissue types, k , used in NMF. In 17 subjects, two significant patterns were found. Three tissue types were identified in three subjects and four in two subjects.

The procedure is illustrated in Fig. 1 (patient #10 in Table 2). Axial and sagittal views together with contours of the prostate bed (yellow) and GTV (red) are displayed on T2-weighted images (Fig. 1a); the corresponding axial slice in DCE-MRI is shown in Fig. 1b. The first two sets are precontrast and the third shows an early enhancing lesion at the right side of the bladder, indicated by an arrow. This lesion fades throughout the series, indicating gradual washout of the contrast. At approximately 4 min post-contrast, the bladder lights up (also indicated with arrows), first posteriorly and then anteriorly. The timing is consistent with the expected clearance of contrast by the kidneys. NMF was run in MIM, seeking $k = 3$ solutions, as suggested by PCA. The resultant temporal patterns $S(t)$ and corresponding weights $\mathbf{W}(\mathbf{X})$ are displayed side-by-side in Fig. 1c. The top pattern shows fast early contrast wash-in while the temporal patterns below are associated with rapid contrast flow at a later time point. The smoothness of the first pattern in the wash-out phase is interrupted by the strong signals of rapid influx of the contrast into the in relatively large volume of the bladder. The maps of the weights $\mathbf{W}(\mathbf{X})$ show the suspicious lesion ($\mathbf{W}_T(\mathbf{X})$), related to the first pattern, and the second/third patterns are related to the bladder. The histogram of $\mathbf{W}_T(\mathbf{X})$ together with the four thresholds in different colors is presented on the left of Fig. 1d and the corresponding DCE1.0 to DCE2.5 in matching colors on the right of Fig. 1d.

Another example of an identified suspicious volume is shown in Fig. 2 (patient # 1 in Table 2). Here, Fig. 2a shows the prostate bed: clinical target volume (CTV) on T2. The loss in the signal intensity is due to the presence of metal surgical clips in the prostate bed. The four volumes, based on the different thresholds for $\mathbf{W}_T(\mathbf{X})$, are shown in Fig. 2b; Fig. 2c shows the DCE1.0, DCE2.5, and GTV volumes. Of note, the GTV volume was drawn prior to and independently of the DCE analysis.

In Fig. 3 (patient # 2 in Table 2), the relationship between the different thresholds for the automatic volumes and the physician-contoured GTV is shown in 3D. The DCE1.0 volume, based on a lowest threshold, is shown in green and is generally larger than the GTV. DCE1.0 performs mostly the task of providing the general area of the foci of interest. In contrast, the DCE2.5 volume (purple) is quite conservative and indicates volumes with the highest probability of malignancy; in this case, it follows the manual GTV quite closely. The suspicious foci in this case are around the urethra, and DCE1.0 additionally highlights the surrounding vasculature (note that the presence of urine in the urethra does not affect this pattern of rapid wash-in and wash-out, as the contrast appears in the urine at a later time point in the DCE series).

In Fig. 4a, the correlation between GTV and the automatic volumes is shown. The mean $\pm$ stdev of the volumes were: GTV: 2.0 ± 1.6 cc; DCE1.0: 8.46 ± 2.88 cc; DCE1.5: 4.43 ± 1.57 cc; DCE2.0: 2.17 ± 0.78 cc; and DCE2.5: 1.16 ± 0.44 cc. The Pearson's correlation coefficients between the manual and automatic volumes were DCE1.0: 0.26 ($p = 0.25$); DCE1.5: 0.40 ($p = 0.065$); DCE2.0: 0.60 ($p = 0.003$); and DCE2.5: 0.58 ($p = 0.005$). DCE2.0 and GTV were significantly correlated ($p < 0.05$). In addition, a paired t -test showed that only DCE2.0 volumes were not statistically different from GTV.

The correlation plots between maximum pre-RT PSA and manual (GTV) and automatic volumes are shown in Fig. 4b; $r = 0.42$ ($p = 0.052$); 0.36 ($p = 0.099$); 0.52 ($p = 0.01$); and 0.67 ($p < 0.001$), for DCE1–2.5, respectively, indicating that the DCE2.0/DCE2.5 are better correlated with PSA than the manual contours.

Pharmacokinetic modeling was carried out on signal-versus-time curves from several volumes in patient #8, as indicated in Fig. 5. The areas of NSPBT (yellow), muscle (magenta), GTV (red), and DCE2.5 (purple), and the corresponding signal-vs.-time curves are shown in Fig. 5a, b. Distributions of K^{trans} (min^{-1}) and v_e (%) are represented in Fig. 5c. K^{trans} for DCE2.5 was statistically higher ($p < 0.05$) than the constants for all other tissues, confirming that the volume better captures areas of malignancy. There was no statistical significance between v_e of GTV and DCE2.5.

Discussion

The authors describe herein an automated procedure for detection and delineation of suspicious foci in the prostate bed in men with rising PSA after RP. While there are previous reports with variable success in identifying recurrent tumors post-prostatectomy on MRI [12, 13, 17], this is the first application where the suspicious area is automatically localized and a target volume delineated. The software developments are carried out directly in MIM and the delineated volumes are seamlessly integrated into the RT planning workflow. In addition, the targets identified may be applied to MRI-guided prostate bed biopsies.

Patient management in cases of recurrent prostate cancer depends strongly on whether disease progression is confined to the prostatic fossa or distant spread has occurred. Positron emission tomography (PET)/CT is routinely used for evaluation of patients with rising PSA after RP. ^{18}F - and ^{11}C -labeled choline-labeled PET tracers [24, 25], and PET imaging using

the leucine analog ^{18}F -1-amino-3-fluorine 18-fluorocyclobutane-1-carboxylic acid (FACBC) with the prostate-specific membrane antigen (PSMA) antibody ^{111}In capromab [26] have been investigated in these patients. These studies report variable sensitivity in localized prostate cancer detection, requiring generally higher pre-treatment PSA. In direct comparisons of e-MRI and PET/CT, it was concluded that e-MRI is superior for the detection of local recurrence, while PET/CT imaging is superior for pelvic lymph node metastasis [27].

Previous applications for detection of suspicious foci on MRI in post-prostatectomy recurrence necessitated implementation of specific image acquisition sequences (e.g., high-temporal resolution) and application of endorectal coils, [10, 11, 14], which may be beyond the current standard clinical imaging protocols in many centers. In addition, MRI images obtained with an endorectal coil are not easily applied to RT planning, as they cause significant displacement of pelvic anatomy. A large FOV depicting the prostate bed and the surrounding tissues, and a small pixel size are required in RT for fusion with the CT scan and contouring.

The proposed unsupervised pattern recognition technique successfully identifies the suspicious foci in data of low temporal resolution relative to volumes drawn manually by experienced physicians. The sensitivity of the approach is improved by analyzing the entire dataset simultaneously, rather than on a pixel-by-pixel basis, as the signal-to-noise ratio is significantly increased. The large temporal signal from the contrast influx in the bladder, although challenging to disentangle in the later DCE series, is identified and removed from consideration. A possible alternative for handling this signal will be to contour the bladder and remove it from the prostate bed. This adds unnecessary burden to the physician and in this application, a typical contour of the prostate bed is utilized.

In this work, application of the procedure is limited to cases with previously identified and contoured suspicious foci, with the aim of confirming the approach. As a consequence, these patients may have a larger disease burden relative to the typical patients presenting for RT after failed surgery. However, the developed tool will also be valuable for this group of patients, as they have poorer outcomes with standard salvage radiation and would benefit from targeted focal dose escalation to the identified lesion. The investigated four thresholds illustrate the ability of smaller cutoffs (1/1.5 stdev) to highlight larger areas and thus be used as a guide to the treating physician for possible suspicious regions. The more conservative thresholds (2–2.5 stdev) are better correlated with the manual volumes. DCE2.0 and DCE2.5 are also better correlated with maximum pre-treatment PSA relative to the manually contoured lesions. The statistically significant correlations of these volumes with PSA (with the caveat of the limited number of patients) have not been found previously [12]. An additional confirmation that the automatic volumes indeed capture the areas of malignancy is that K^{trans} is significantly higher when compared to the fits from muscle, normal, and GTV volumes.

Conclusion

A software tool (available from the corresponding author upon request) was developed for visualization and analysis of DCE-MRI data in post-prostatectomy patients. The technique is straightforward and may be implemented in clinics without extensive physicist, engineering, and research support.

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Fig. 1.

a Axial and sagittal view of prostate bed on T2-weighted MRI of a patient presenting for salvage radiotherapy. The volumes of the prostate bed (*orange*) and gross tumor (GTV; *red*) were manually outlined by the treating physician. **b** Dynamic contrast-enhanced MRI (DCE-MRI) of the corresponding axial slice ($n = 12$). The *arrow* on the third image shows early enhancing foci with the contrast gradually washing out in the later DCE series. *Arrows* on images 8 and 9 indicate contrast flow in the bladder. **c** Results from negative matrix factorization application ($k = 3$) to DCE-MRI: *left* basic signal-vs.-time curves $S(t)$; *right* spatial distribution of the corresponding weights (W) in the selected axial slice. The first pattern identifies the suspicious lesion (W_T) and the second and third are related to the contrast entering the bladder. **d** *Left panel* histogram of W_T with indicated thresholds at 1.0, 1.5, 2.0 and 2.5 standard deviations from the mean; *right panel* volumes of DCE1.0 (*green*), DCE1.5 (*yellow*), DCE2.0 (*blue*) and DCE2.5 (*purple*), displayed on the T2 image

Fig. 2.

a Axial slice of prostate bed of a patient presenting for salvage radiotherapy on T2-weighted MRI. **b** The volumes of dynamic contrast-enhanced MRI threshold 1 – DCE1.0 (*green*), 1.5 – DCE1.5 (*yellow*), 2.0 – DCE2.0 (*blue*) and 2.5 – DCE2.5 (*purple*), displayed on the early enhancing DCE-MRI series. **c** Gross tumor volume (GTV; *red*), overlaid with DCE1.0(*green*) and DCE2.5 (*purple*)

Fig. 3.

Axial, sagittal, and coronal views in MIM (MIM Corporation, Cleveland, OH, USA) of a prostate bed of a patient presenting for salvage radiotherapy. Early contrast T1 image with gross tumor volume (GTV; *red*); dynamic contrast-enhanced MRI threshold 1.0 – DCE1.0 (*green*) and DCE2.5 (*purple*)

Fig. 4.

a Comparison between manual and automatic volumes. **b** Correlations between manual and automatic volumes and maximum pre-treatment prostate specific antigen (*PSA*) values. The linear trend line is displayed, together with Pearson's correlation coefficient *r*. *Denotes statistically significant correlations ($p < 0.05$). *GTV* gross tumor volume, *DCE1.0–2.5* dynamic contrast-enhanced MRI thresholds 1–2.5

Fig. 5.

a Illustration of volumes, analyzed with a pharmacokinetic model: muscle (*magenta*), gross tumor volume (*GTV*; *red*); dynamic contrast-enhanced MRI threshold 2.5 (*DCE2.5*; *purple*) and non-specific prostate bed tissue (*NSPBT*; *yellow*). **b** Signal-versus-time curves associated with the volumes in (**a**). **c** Distribution of the K^{trans} and v_e parameters in the volumes in (**a**)

Table 1

Summary of clinical post-prostatectomy patients

Characteristic	Patients (N = 22); n (%)
<i>Surgical Gleason score</i>	
6	5 (23 %)
7	11 (50 %)
8–9	7 (27 %)
<i>T stage</i>	
T2b/c	12 (55 %)
T3a/b	10 (45 %)
<i>ECE</i>	
Positive	8 (36 %)
Negative	14 (64 %)
<i>Surgical margin</i>	
Positive	13 (59 %)
Negative	9 (41 %)
<i>DRE</i>	
Positive ^a	2 (9 %)
Negative	20 (91 %)

ECE extracapsular extensions, *DRE* digital rectal examination^a A positive DRE corresponds to a palpable abnormality

Table 2

Characteristics of post-prostatectomy RT patients

Patient ID	Age at RT	Surgical GS (sum)	T stage	ECE	Surgical margin	Palpable DRE	Location	Max preRT PSA	GTV (cc)	DCE2.0 (cc)	Long axis DCE2.0 (cm)
1 ^a	47	7	T2c	Negative	Negative	No	Retrovesical	0.7	2.76	1.56	1.71
2 ^b	74	7	T2c	Negative	Negative	No	Bladder neck	0.3	1.25	1.5	2.12
3	73	7	T3a	Positive	Positive (focal)	No	Anastomosis	5.6	0.86	2.64	1.62
4	59	7	T3a	Negative	Positive (focal)	No	Anastomosis	0.1	1.44	2.16	1.34
5	73	7	T2c	Negative	Positive (focal)	Yes	Retrovesical	8.6	5.59	4.23	2.26
6	71	9	T3a	Positive	Positive (focal)	No	Anastomosis	0.35	2.32	1.64	1.82
7	61	6	T2c	Negative	Positive (focal)	No	Retrovesical	1.12	3.89	2.16	1.45
8 ^c	58	8	T3b	Negative	Negative	Yes	Bladder neck	3.1	5.2	2.27	2.26
9	64	7	T3b	Positive	Negative	No	Retrovesical	0.04	5.67	3.58	1.79
10 ^d	51	6	T2c	Negative	Negative	No	Retrovesical	1.3	1.11	2.02	1.3
11	56	7	T2b	Negative	Negative	No	Bladder neck	1.9	1.04	1.62	1.67
12	63	7	T2c	Negative	Positive (extensive)	No	Anastomosis	0.4	0.45	1.10	1.22
13	48	7	T2c	Negative	Positive (focal)	No	Anastomosis	0.2	0.9	2.27	1.46
14	51	8	T2c	Negative	Negative	No	Retrovesical	0.7	0.77	1.4	1.19
15	79	6	T2b	Negative	Negative	No	Anastomosis	0.63	0.92	2.57	1.9
16	64	6	T2c	Negative	Positive (extensive)	No	Bladder neck	0.34	2.58	3.04	2.08
17	61	9	T3a	Positive	Negative	No	Bladder neck	0.3	1.71	2.75	1.45
18	65	6	T2c	Negative	Positive (focal)	No	Anastomosis	0.35	1.1	1.27	1.61
19	61	9	T3b	Positive	Positive (focal)	No	Anastomosis	0.3	1.85	1.28	1.78
20	65	7	T3a	Positive	Positive (Extensive)	No	Retrovesical	0.4	1.21	1.87	1.43
21	56	7	T3a	Positive	Positive (focal)	No	Anastomosis	0.3	1.59	2.6	1.95
22	54	9	T3a	Positive	Positive (focal)	No	Bladder neck	0.2	0.38	2.27	1.2

RT: radiation therapy, GS: Gleason score, ECE: extracapsular extensions, PSA: prostate-specific antigen, GTV: gross tumor volume, DCE2.0: automatic tumor volume using 2.0 standard deviations as a threshold

^aData from this patient are reviewed in detail in Fig. 2

^bData from this patient are reviewed in detail in Fig. 3

Data from this patient are reviewed in detail in Fig. 5

Data from this patient are reviewed in detail in Fig. 5

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