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Improving Bladder Cancer Imaging Using 3T Functional Dynamic Contrast-Enhanced MRI

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Abstract

Objectives—To assess the capability of T2-weighted MRI (T2W-MRI) and the additional diagnostic value of Dynamic Contrast-Enhanced MRI (DCE-MRI) using multi-transmit 3T in the localization of bladder cancer.

Materials and Methods—This prospective study was approved by the local Institutional Review Board. Thirty-six patients were included in the study and provided informed consent. MRI scans were performed with T2W-MRI and DCE-MRI on a 3T multi-transmit system. Two observers (with 12 and 25 years of experience) independently interpreted T2W-MRI prior to DCE-MRI data (maps of pharmacokinetic parameters) to localize bladder tumors. The pathological examination of cystectomy bladder specimens was used as a reference gold standard. The McNemar test was performed to evaluate the differences in sensitivity, specificity, and accuracy. Kappa scores were calculated to assess interobserver agreement.

Results—The sensitivity, specificity, and accuracy of the localization with T2W-MRI alone were 81% (29/36), 63% (5/8) and 77% (34/44) for observer 1, and 72% (26/36), 63% (5/8), and 70% (31/44) for observer 2. With additional DCE-MRI available, these values were 92% (33/36), 75% (6/8), and 89% (39/44) for observer 1, and 92% (33/36), 63% (5/8), and 86% (38/44) for observer 2. DCE-MRI significantly ($P < 0.01$) improved the sensitivity and accuracy for observer 2. For the twenty-three patients treated with chemotherapy, DCE-MRI also significantly ($P < 0.02$) improved the sensitivity and accuracy of bladder cancer localization with T2W-MRI alone for observer 2. Kappa scores were 0.63 for T2W-MRI alone, and 0.78 for additional DCE-MRI. Out of seven sub-centimeter malignant tumors, four (57%) were identified on T2W images and six (86%) on DCE

maps. Out of eleven malignant tumors within the bladder wall thickening, six (55%) were found on T2W images and ten (91%) on DCE maps.

Conclusions—Compared to conventional T2W-MRI alone, the addition of DCE-MRI improved interobserver agreement as well as the localization of small malignant tumors and those within bladder wall thickening.

Keywords

3T MRI; DCE-MRI; bladder cancer localization; bladder wall thickening; sub-centimeter tumors

Introduction

Bladder cancer is the fourth most common cancer in men and the tenth most common cancer in women in the United States (1). It is estimated by the American Cancer Society that 72,570 (54,610 in men and 17,960 in women) newly diagnosed cases of bladder cancer and 15,210 (10,820 in men and 4,390 in women) related deaths will occur in the United States in 2013 (2). About 70-80% of the diagnosed cases are found with non-muscle-invasive bladder cancer (3). Cystoscopy is the standard for the diagnosis and local management of bladder cancer. However, it is invasive and limited in assessing the fat infiltration of bladder malignancies (4). Computed Tomography (CT) is the most commonly used imaging modality to initially assess bladder cancer. CT is limited by the risk of ionizing radiation, low accuracy and high interobserver variability in the staging of bladder cancer (5). Accurate diagnosis of bladder cancer, which is essential to patient management and treatment, is still an unmet clinical need not yet resolved by cystoscopy and CT. Without ionizing radiation and with the capabilities of tissue characterization and multi-planar functional imaging, Magnetic Resonance Imaging (MRI) has been shown to be useful in evaluating chemotherapeutic response in bladder cancer (6) and to be the most accurate technique for the tumor staging (7) to address this unmet clinical need.

Functional dynamic contrast-enhanced MRI (DCE-MRI) can assess the microcirculation and visualize the neoangiogenesis of malignant tissues via the dynamic signal enhancement of a contrast agent. DCEMRI has already demonstrated good interobserver agreement and high accuracy in the differentiation of muscle-invasive from non-muscle-invasive bladder cancer (8). High field 3T MRI has been shown to be superior to lower field strength MRI in the spatial resolution, signal-to-noise ratio, contrast-to-noise ratio, and the delineation of the depth of tumor invasion in different types of cancer (9-14). To date, there has only been one study that used 3T MRI (with conventional T1-weighted and T2-weighted Imaging) for the local staging of bladder cancer (15). No prior study to assess the capability of 3T MRI with functional imaging for the localization of bladder cancer has been reported. We conducted a multi-parametric MRI study to systematically evaluate the capabilities of conventional and functional MRI for the localization, staging, and assessment of therapeutic response of bladder cancer.

The impact of dielectric artifacts such as shaded areas on MR images increases with the field strength. It was reported that multi-transmit technology helps 3T MRI reduce dielectric effects at high field, improve the homogeneity of RF field, and decrease scan times (16).

The purpose of this study is to evaluate the ability of T2-weighted MRI (T2W-MRI) and the additional diagnostic value of functional DCE-MRI in the localization of bladder cancer using current technology of multi-transmit 3T imaging.

Materials and Methods

Patients

This study is part of our on-going study which is aimed at using 3T MRI in the localization, staging, and assessment of chemotherapeutic response of bladder cancer. The study was approved by the local Institutional Review Board. The pathological examination of cystectomy bladder specimens was used as a reference (gold) standard. Patient enrollment criteria are: (1) patient is 18 years or older; (2) diagnosed with bladder cancer; (3) scheduled for radical cystectomy; (4) able and willing to give valid written informed consent; (5) with no contraindications to MRI. From July 2009 to November 2011, fifty patients (forty-one males, nine females; age range: 38-86 years, median: 68 years) were enrolled in the study. All patients provided informed consent. Nine patients did not complete the study protocol due to their specific co-morbidity. Five patients had poorly distended bladder volume via the visual inspection by two radiologists who were blinded to both clinical and pathological findings. These fourteen patients were excluded from the study.

Of thirty-six included patients, thirteen (seven who had aggressive bladder tumors and required immediate cystectomy, and six who had non-muscle-invasive tumors and did not receive chemotherapy) were directed to cystectomy after baseline MRI (Figure 1). The other twenty-three patients were treated with two cycles (21 days per cycles) of chemotherapy prior to mid-cycle MRI. Three patients were subsequently sent to surgery due to tumor progression during chemotherapy. The remaining twenty patients completed the other two cycles of chemotherapy and had post-chemotherapy MRI, followed by cystectomy. All cystectomy bladder specimens were examined by pathology. The study flow chart is described in Figure 1.

MR Imaging Protocol

All patients were scanned on a 3T MRI system (Achieva; Philips Healthcare, Cleveland, Ohio, USA) using 2-channel RF transmit and 32-channel phased-array surface coils.

Axial T2W-MRI was performed with a Turbo Spin Echo sequence (repetition time/echo time, 4264/80 ms; matrix, 292×323; spatial resolution (RL/AP/FH), 1.0×1.1×3.0 mm; slice gap, 0.3 mm; number of slices, 40; acquisition time, 5 minutes; field of view (RL/AP/FH), 290×341×130 mm; sensitivity encoding factor, 2) prior to the contrast administration.

DCE-MRI was performed using a 3D-spoiled Gradient Echo sequence (repetition time/echo time, 5/2 ms; flip angle, 20°; matrix, 212×213; spatial resolution (RL/AP/FH), 1.7×1.7×5.0 mm; number of slices, 19; field of view (RL/AP/FH), 360×360×95 mm; number of signal average (NSA), 1; temporal resolution, 8.3 sec; acquisition time, 8.5 minutes; number of dynamic scans, 60) in the axial orientation. A single dose (0.2 mmol per kilogram body weight) of Gd-based contrast agent (Magnevist, Bayer Healthcare) was intravenously injected at a constant flow rate of 0.5 mL/s after the fifth dynamic scan, followed by a flush

of 25 mL saline at a flow rate of 2mL/s. Depending on the patient's weight, injection time ranged from 21 to 50 s, with a median of 30 s.

Image Processing

DCE-MRI data were processed in an IDL (Exelis VIS)-based software environment by applying a modified Brix's linear two-compartment pharmacokinetic model (17, 18) to quantify the perfusion and microcirculation in body tissues via the dynamic signal enhancement of the contrast agent. An arterial input function (AIF) was manually selected for each dataset by placing an arterial region of interest (ROI) on the right common femoral artery. Pharmacokinetic parameters amplitude (Amp) and the AIF-adjusted exchange rate of the contrast agent between the extravascular extracellular space (EES) and the plasma space (k_{ep}) were quantified with the method proposed by Yang et al (18). The generation of combined Amp and k_{ep} maps were fully automated. The pharmacokinetic maps of Amp and k_{ep} were coded with the same color table and on the same parameter scale (see Color Table on Figure 2) for all cases. The display of color maps followed the standard display method for Brix's model (19). A threshold value of 1.0 (a.u.) was chosen for Amp. The color pharmacokinetic maps were overlaid on original DCE (T1-weighted) MR images.

MRI Data Interpretation

A Philips Extended Brilliance Workspace (EBW) workstation was used for data review. Two radiologists (with 12 and 25 years of experience) blinded to clinical as well as pathological findings independently reviewed MRI data. Each radiologist identified malignant bladder tumors on T2W MR images alone, and subsequently with additional pharmacokinetic maps (DCE-MRI maps) available. On color DCE-MRI maps, malignant lesions were identified with continuous color pixels on the bladder wall, indicating the neoangiogenic characteristics of tumor tissues via signal enhancement (Figure 2).

The location of bladder cancer was identified as right lateral, left lateral, anterior, posterior, dome, and trigone/apex of the bladder wall in both the radiological read of the pre-surgical MRI and the pathological examination of the cystectomy bladder specimen. An independent assessor was tasked to match the radiological read with the pathological examination of the same patient. A true positive finding of the radiological read was achieved when the bladder malignancy location was matched between the radiological read and the pathological examination. A true negative finding of the radiological read was confirmed when there was no malignant tumor found in the bladder by both radiology and pathology.

Statistical Analysis

Descriptive statistics (mean and standard deviation or median and range for continuous variables; frequency and proportion with 95% confidence interval for categorical variables) was used to summarize the data. The exact binominal method was used to calculate the 95% confidence interval of proportion. Kappa values were calculated to evaluate the interobserver agreement for the interpretation with T2W-MRI alone and with the addition of DCE-MRI. Agreement was considered to be moderate, good, and very good for kappa values of 0.41-0.60, 0.61-0.80, and greater than 0.80, respectively (5). For each observer, diagnostic sensitivity, specificity, and accuracy were calculated for the localization based on

T2W-MRI alone and combined with additional DCE-MRI maps. The McNemar test was performed on a commercial statistical package (SAS 9.2; SAS Institute Inc., Cary, NC, USA) to evaluate the differences in these diagnostic values. $P < 0.05$ was considered statistically significant.

Results

Tumor characteristics

Pathological examination confirmed malignant bladder tumors in twenty-eight patients and no malignancy in the other eight patients at the time of cystectomy. Of the eight negative patients, two did not have chemotherapy (transurethral resection of bladder tumor (TURBT) before baseline MRI may have removed all tumors from the patients), and six completed all four cycles of chemotherapy. Of the twenty-eight positive patients, eleven did not have chemotherapy, and seventeen had chemotherapy. A total of thirty-six malignant tumors were found by pathology. Four positive patients had two or more malignant lesions. The T stage was reported only for the most invasive lesion in multi-lesion patients. All malignant tumors were found to be of high grade by pathology except three tumors whose grades were not reported. The longest measurable tumor diameter ranged from 1 mm to 100 mm with a median of 26 mm. Tumor characteristics were summarized in Table 1.

Localization of malignant tumors in the whole patient cohort

On T2W MR Images, twenty-nine of thirty-six malignant lesions were identified by observer 1 and twenty-six by observer 2 (Figures 2 and 3). Both observers confirmed five of eight negative cases. In the three false positive cases, the benign bladder wall thickening was misdiagnosed as a malignant tumor. The sensitivity, specificity, and accuracy of bladder cancer localization using T2W-MRI alone were 81% (29/36), 63% (5/8) and 77% (34/44) for observer 1, and 72% (26/36), 63% (5/8), and 70% (31/44) for observer 2. The kappa score for the evaluation of interobserver agreement was 0.63 (95% CI: 0.38-0.88).

With the addition of color-coded DCE-MRI maps, thirty-three malignant tumors were identified by both observers (Figures 2, 3 and 4). Six negative cases were confirmed by observer 1 and five by observer 2. The sensitivity, specificity, and accuracy were 92% (33/36), 75% (6/8), and 89% (39/44) for observer 1, and 92% (33/36), 63% (5/8), and 86% (38/44) for observer 2. The kappa score increased to 0.78 (95% CI: 0.55-1.00) with additional DCE-MRI maps.

Compared to T2W-MRI alone, the addition of DCE-MRI maps significantly ($P < 0.01$) improved the sensitivity and accuracy of bladder cancer localization by observer 2. Additional DCE-MRI also increased the sensitivity and accuracy of the localization by observer 1, however, not significantly ($P=0.1$ for sensitivity and $P=0.06$ for accuracy).

Localization of malignant tumors in patients treated with chemotherapy

Twenty-three patients were treated with neoadjuvant chemotherapy. Seventeen were positive for malignancy with a total of twenty malignant tumors confirmed by pathology. Six were negative for malignancy. For the population of chemotherapy-treated patients, the

sensitivity, specificity, and accuracy of bladder cancer localization with T2W-MRI alone were 70% (14/20), 50% (3/6) and 65% (17/26) for observer 1, and 55% (11/20), 50% (3/6), and 54% (14/26) for observer 2. Adding DCE-MRI data produced a sensitivity, specificity, and accuracy of 90% (18/20), 67% (4/6), and 85% (22/26) for observer 1, and 85% (17/20), 50% (3/6), and 77% (20/26) for observer 2. The addition of DCE-MRI maps significantly ($P < 0.02$) improved the sensitivity and accuracy for observer 2 as compared to T2WMRI alone. For observer 1, the differences were not found to be significant ($P=0.1$ for sensitivity, and $P=0.06$ for accuracy).

Localization of sub-centimeter tumors

Seven (19%) out of thirty-six malignant lesions were sub-centimeter (less than 1 cm in the longest measurable diameter). The two radiologists localized four (57%, 95% CI: 18%-90%) sub-centimeter tumors on T2W images alone. With additional pharmacokinetic DCE-MRI maps, there were six (86%, 95% CI: 42%-100%) sub-centimeter lesions identified by the two observers (Figure 4). Using additional DCE-MRI maps increased the number of identified sub-centimeter tumors by 50%.

Delineation of malignant tumors within the bladder wall thickening

Eleven (28%) of thirty-six malignant tumors were found within bladder wall thickening. These eleven tumors were found in seven patients (six treated with chemotherapy). On T2W images, six (55%, 95% CI: 23%-83%) malignant tumors with an irregular margin and different signal intensity were differentiated from the bladder wall thickening (Figure 3). The other five tumors had smooth margins and were isointense within the bladder wall, thus, not identified on T2W images. When DCE-MRI maps were added, a total of ten (91%, 95% CI: 59%-100%) malignant tumors, including four of the five T2W-missed tumors, were differentiated from the benign bladder wall thickening (Figures 3 and 4). Adding DCE-MRI data significantly improved the delineation of malignant tumors within the benign bladder wall thickening ($P<0.05$).

Of eleven malignant tumors within bladder wall thickening, three were sub-centimeter and not identified on T2W images. These three tumors were all identified with pharmacokinetic parameter maps available.

Discussion

Accurate diagnosis of bladder cancer remains a challenge in bladder cancer imaging (4, 5, 20-22). In bladder cancer localization, a previous study of multidetector CT with multiplanar reformatted imaging and virtual cystoscopy had a high sensitivity of 94% in comparison with conventional cystoscopy (4). However, this study revealed that conventional cystoscopy had discrepancies with histopathology (4). Catheter-assisted ^{18}F -FDG-PET/CT imaging using standardized bladder flushing and filling presented with a sensitivity of 63% (23). ^{11}C -acetate PET/CT had a sensitivity of 80% (8 out of 10 malignant tumors) (24). Ultrasound was limited in identifying bladder tumors on the bladder floor and fundus (20, 21), with a reported sensitivity of 66% using micro-bubble contrast enhancement vs. 61% without contrast (21). Our MRI study used histopathological findings as a reference standard

and found a sensitivity of 81% (observer 1) and 72% (observer 2) with T2W-MRI alone and an improved sensitivity of 92% (both observers) with the additional use of DCE-MRI maps for the localization of bladder cancer.

High field 3T MRI has been shown to be better than 1.5T MRI in the spatial and temporal resolution (9), signal-to-noise ratio (11), contrast-to-noise ratio (12), and the differentiation of cancer from normal tissues (13). 3D T1-Weighted DCE-MRI at 3T has been shown to produce higher signal contrast between tumor and normal brain tissues than 1.5T (14), and aid in quantitative assessment of cerebral blood flow, cerebral blood volume, and permeability in MS lesions (25). Our study evaluated the capability of 3T MRI with DCE mapping in the localization of bladder cancer and demonstrated that 3T high-resolution T2W-MRI enabled the identification of sub-centimeter malignant tumors and the tumors within the bladder wall thickening. The addition of functional DCE-MRI maps provided further delineation of sub-centimeter tumors (86%) as well as the tumors within the bladder wall thickening (91%) to improve the sensitivity and accuracy of bladder cancer localization.

Contrast-enhanced MRI has been shown to have good interobserver agreement and high accuracy in the diagnosis of bladder cancer (8). Our study reported a similar result in the interobserver agreement of bladder cancer diagnosis using DCE-MRI. Adding DCE-MRI increased the Kappa score from 0.63 to 0.78, suggesting that a combined reading further improves the robustness of the radiological interpretation.

Pelvic imaging at 3T has traditionally been limited due to field inhomogeneity (16) which was overcome in this study by using an advanced 32-channel coil and utilizing multi-transmit acquisition to achieve consistently good diagnostic image quality. Our prior pilot work (unpublished) had already demonstrated that the application of multi-transmit acquisition obtained after less-than-one-minute B1 mapping enables a consistent substantial improvement of image quality. Thus, in this prospective study, we have used the multi-transmit acquisition approach which also has become our standard clinical procedure for 3T imaging.

The presence of bladder wall thickening including inflammatory and fibrous changes after chemotherapy has been reported to lower the accuracy of bladder cancer diagnosis with cystoscopy (26, 27), CT (22), ultrasonography (28) and 1.5T MRI (8, 29, 30). The patient cohort in our study included patients with TURBT only and patients with both TURBT and chemotherapy. Using T2W-MRI alone, the sensitivity, specificity, accuracy of bladder cancer localization for chemotherapy-treated patients were substantially smaller than those for the whole patient cohort (70%/50%/65% vs. 81%/63%/77% for observer 1, and 55%/50%/54% vs. 72%/63%/70% for observer 2). This has also demonstrated the negative impact of chemotherapy-induced bladder wall thickening on the localization of bladder cancer. The addition of DCE-MRI significantly improved the differentiation of malignant tumors from the bladder wall thickening to alleviate the negative impact of neoadjuvant chemotherapy on the localization of bladder cancer. Accompanied by good interobserver agreement, the localization of bladder cancer in the whole patient cohort had a sensitivity of 92% for both observers with the additional use of DCEMRI maps.

The most common pharmacokinetic models used to assess DCE-MRI are the linear two-compartment model proposed by Tofts (31) and the one by Brix (17). Due to its limitation (18), Brix's model has recently been less often applied to process DCE-MRI than Tofts's model. The modification to Brix's model proposed by Yang (18) solved the limitation in order to acquire pharmacokinetic parameters that have comparative tissue specificity to those derived with the Tofts's model. Compared to fast injection of the contrast agent, the slow injection used in our study allows a better delineation of wash-in phase which is characterized by the pharmacokinetic parameter k_{ep} . Using the modified Brix's model to process DCE-MRI data, our study has demonstrated the reliability of the model for the characterization and assessment of bladder cancer.

Our study had several limitations: First, the number of negative cases (N=8) was small. This small number may have been the factor that did not allow the demonstration of the significant improvement of specificity with additional DCE-MRI maps. A larger number of cases will be needed in subsequent studies to both solidify our findings and further demonstrate the diagnostic value of DCE-MRI. Second, the correlation between the radiological read and the pathological examination was in some cases challenging due to the lack of the 3D matching between pathological and radiological localization. This limitation can be resolved with an approach to 3D matching and specimen MR imaging. Third, not all patient's bladders were fully distended at the time of imaging. The research protocol which was composed of conventional imaging and different functional imaging techniques required a long scan time (1 hour). Therefore, a fully distended bladder, in some cases, caused the interruption of MRI exams. The future study will be performed with a more refined protocol to reduce the scan time, which allows maintaining a fully-distended bladder.

In conclusion, multi-transmit 3T DCE-MRI improves the interobserver agreement and the characterization of malignant bladder tumors, especially small tumors and those within bladder wall thickening. 3T MRI with DCE mapping appears to be a promising approach to substantially improve bladder cancer imaging beyond the current limitations of cystoscopy and CT.

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Figure 1. Study flow chart. Thirty-six patients were included in the study. All patients had cystectomy after their last MRI. All surgical bladder specimens were examined by pathology.

Figure 2. MR images of a 64 year-old male patient. Image A, axial T2W image; Image B, Amp+k_{ep} map. The patient was treated with chemotherapy. Tumor location (indicated by orange arrows and enclosed in white contours) was at the anterior and dome aspect of the bladder wall. Tumor stage: T3b; size: 38 mm. The malignant tumor was visualized on both T2W image and pharmacokinetic map. The malignancy was identified with continuous color pixels on the color DCE map.

Figure 3. MR images of a 63 year-old female patient. Image A, axial T2W image; image B, Amp+ k_{ep} map. The patient was treated with chemotherapy. Tumor location (indicated by orange arrows and enclosed in white contours) is at the right aspect of the bladder wall. Tumor stage: T2; size: 24 mm. The malignant tumor was differentiated from the bladder wall thickening with an irregular margin and different signal intensity on the T2W image. The continuous color pixels on the color Amp and k_{ep} map further confirmed the tumor location.

Figure 4. MR images of a 68 year-old male patient. Image A, axial T2W image; image B, Amp+k_{ep} map. The patient was treated with chemotherapy. Tumor location (indicated by an orange arrow and enclosed in a white contour) is located at the left and posterior aspect of the bladder wall. Tumor stage: T2; size: 9 mm. The malignant tumor with a smooth margin was not visualized on the T2W image. The malignancy was identified with continuous color pixels on the DCE-MRI map. This malignancy was both sub-centimeter and within the bladder wall thickening.

Table 1

Tumor Characteristics

Stage	Number of cases
Tis/Ta	2 (7%)
T1	3 (11%)
T2	11 (39%)
T3	8 (29%)
T4	4 (14%)
Number of malignant tumors per case	Number of cases
1	24 (86%)
2	1 (3.5%)
3	2 (7%)
4	1 (3.5%)
Size	Number of malignant tumors
1cm	7 (19%)
> 1cm	20 (56%)
NA *	9 (25%)
Configuration	Number of malignant tumors
Solid	19 (53%)
Papillary	8 (22%)
Lobulated	1 (3%)
NA *	8 (22%)

* Not reported