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Is quantitative DCE-MRI useful in differentiation of indolent and significant prostate cancers?

Sessiz ve anlamlı prostat kanseri ayrımında kantitatif DCE-MRG faydalı mıdır?

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Abstract

Aim: Direct visual assessment is recommended in prostate magnetic resonance imaging (MRI) for dynamic contrast enhancement (DCE), however, being a qualitative approach, it may cause inter-reader variability. The purpose of this study was to compare quantitative DCE parameters in the differentiation of clinically significant prostate cancer from indolent cancer using whole-mount histopathology.

Methods: Seventy-six patients who underwent multiparametric MRI with suspicion of prostate cancer and subsequent radical prostatectomy were included. Index tumor location was determined with pathology reports. MRI findings of this location were evaluated by a different radiologist using prostate imaging-reporting and data system version 2.1 (PI-RADSv2.1) guideline. Gleason 3+3 tumors were considered indolent, and Gleason ≥ 3+4 tumors were considered significant cancers. Region-of-interests (ROI) were placed in the lesion and the normal peripheral zone. Lesion values and lesion/normal ratios of Ktrans, Kep, Ve, area under curve (iAUC) were calculated. T test was used in statistical analysis.

Results: The numbers of cases with PI-RADSv2.1 scores of 2, 3, 4 and 5 were 5, 4, 24, and 43, respectively. There were 13 indolent cases and 63 patients with significant prostate cancer. Lesion/normal ratios of Ktrans, Kep, Ve, iAUC were 1.6, 1.59, 12, 2.1, respectively, in indolent cancers, and 3.1, 4.04, 1.39, 2.8, respectively, in significant cancers. Lesion/normal ratio of Ktrans was higher in significant cancers while lesion/normal ratio of Ve was higher in indolent cancers. Kep and iAUC were similar (P>0.05 for each).

Conclusion: Quantitative DCE assessment may demonstrate more reproducible results. Lesion/normal tissue ratios of Ktrans and Ve were helpful in differentiation between indolent and significant prostate cancers.

Keywords: Dynamic MRI, Gleason, Multiparametric prostate MRI, Perfusion MRI, Prostate cancer

Öz

Amaç: Prostat manyetik rezonans görüntülemede (MRG) dinamik kontrastlı inceleme (DKİ) için direk görsel değerlendirme önerilir. Kalitatif bir yaklaşım olarak bu okuyucular arası uyumsuzluğa neden olur. Bu çalışmada, tüm-spesimen histopatolojisini referans kabul ederek sessiz ve anlamlı prostat kanserlerinde kantitatif DKİ parametrelerinin karşılaştırılması amaçlanmıştır.

Yöntemler: Multiparametrik MRG ve ardından radikal prostatektomi yapılan 76 olgu çalışmaya dahil edildi. İndeks tümörün yeri patoloji raporu kullanılarak tespit edildi. Bu bölgenin MRG bulguları başka bir radyolog tarafından prostat görüntüleme-raporlama ve bilgi sistemi versiyon 2.1 (PI-RADSv2.1) kullanılarak incelendi. Gleason 3+3 tümörler sessiz, Gleason ≥ 3+4 tümörler anlamlı kanser kabul edildi. İlgi alanı (ROI), lezyona ve normal periferal zona yerleştirildi. Ktrans, Kep, Ve, başlangıç eğrisinin altındaki alan (EAA) için lezyon değeri ve lezyon/normal oranı hesaplandı. Bu parametreler T testi kullanılarak sessiz ve anlamlı kanserlerde karşılaştırıldı.

Bulgular: Olguların PI-RADSv2.1 skoru 2'den 5'e olgu sayısı sırasıyla 5, 4, 24 ve 43'tü. Sessiz kanserli olgu sayısı 13, anlamlı kanserli olgu sayısı 63 idi. Ktrans, Kep, Ve, EAA lezyon/normal oranları sessiz kanserler için sırasıyla 1.6, 1.59, 12, 2.1 iken, anlamlı kanserler için 3.1, 4.04, 1.39, 2.8 idi. Ktrans lezyon/normal oranı anlamlı kanserlerde yüksek iken, Ve lezyon/normal oranı sessiz kanserlerde yüksekti. Kep ve EAA için sessiz ve anlamlı kanserlerde anlamlı fark yoktu (P>0,05).

Sonuç: Kantitatif değerlendirme, dinamik MRG'de daha objektif-kopyalanabilir sonuçlar sunar. Ktrans ve Ve lezyon/normal doku oranları, sessiz ve anlamlı kanserin ayrımında yardımcıdır.

Anahtar kelimeler: Dinamik MRG, Gleason, Multiparametrik prostat MRG, Perfüzyon MRG, Prostat kanseri

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Introduction

Prostate cancer (PCa) has become an important health problem, especially in developed countries, with the increase in average life expectancy. The American cancer society estimates that prostate cancer will rank 5th in cancer-related deaths in 2020 [1]. PCa is screened with prostate-specific antigen (PSA), digital rectal examination (DRM) and systematic biopsy [2]. Magnetic resonance imaging (MRI), with high diagnostic performance, is utilized for cancer detection and risk stratification of PCa, as well [3].

Prostate MRI is evaluated with multiparametric (mp) approach including T2 weight imaging (WI), diffusion weighted imaging (DWI), and dynamic contrast enhancement (DCE) in prostate imaging-reporting and data system version 2.1 (PI-RADSv2.1). Category 3 peripheral zone (PZ) lesions were upgraded to category 4 when DCE was positive. DCE has a limited role in scoring, which revives biparametric (bp) approach without DCE-MRI [4]. BpMRI had comparable results in meta-analysis [5,6]. However, PI-RADS steering committee was concerned that frequency of missed significant cancer may increase with bpMRI. DCE is a "back-up" sequence and remains essential in assessment of prostate MRI [4].

PI-RADSv2.1 proposed direct visual assessment in DCE-MRI, and the criteria on DCE did not change: "Focal, and earlier than or contemporaneously with enhancement of adjacent normal prostatic tissues is positive for DCE-MRI" [4]. This qualitative definition has resulted in inter-reader variability [7]. The inter-reader agreement of DCE-MRI was lower than DWI-MRI [8]. Quantitative DCE assessment has a potential to overcome those limitations.

In this study, we aimed to compare quantitative DCE parameters in the differentiation of clinically significant prostate cancer from indolent cancer using whole-mount histopathology as the reference test.

Materials and methods

Study population

The principles of the Declaration of Helsinki were conformed with. Written informed consent was obtained from all participants. The patients who underwent mpMRI with suspicion of prostate cancer and subsequently, radical prostatectomy (RP), were included in this retrospective study between January 2019 and March 2020. The patients who underwent bpMRI due to contraindications for contrast media administration, those who had more than 6 months between mpMRI and RP, had severe artifacts or received hormonotherapy or radiotherapy before mpMRI were excluded.

Radiological evaluation

All MR scans were obtained on a 1.5T scanner (Aera, Siemens Healthineers, Erlangen, Germany) using a pelvic-surface coil with 18 channels. All technical parameters complied with PI-RADSv2.1 [4]. All three basic sequences including axial T2WI, DWI, and DCE were performed with a slice thickness of 3 mm without any gap. Slice locations of 3 sequences were the same. DCE was performed using ultra-fast gradient echo (GRE) in axial plane (repetition time, 2.48 msec; echo time, 1.52 msec; the field of view, 260×215 mm; acquisition matrix, 160×108). Temporal resolution was high, 7 seconds. T1 mapping was added to protocol in 2019 to make quantitative analysis. Gadobutrol (0.1ml/kg) was injected with automatic pump via antecubital vein using an injection rate of 3 ml/sec followed by a 15 ml saline flush.

One radiologist determined the location of the tumor with highest Gleason score using whole mount histopathology report. Other radiologist blinded to the pathology result evaluated only this part of mpMRI and assigned a PI-RADSv2.1 score. Gleason 3+3 tumors were considered indolent, and Gleason ≥ 3+4 tumors were considered significant cancers.

Quantitative evaluation was performed in the workstation (Syngo.via, Siemens Healthineers, Erlangen, Germany) with tissue 4D analysis (Tofts model) [9]. Free handed region-of-interests (ROI) were placed to the lesion, and normal PZ, and Ktrans, Kep, Ve, initial under the curve (iAUC) were calculated (Ktrans: Transfer constant, Kep: Efflux rate constant, Ve: Extracellular-extravascular volume fraction).

Prostate volume was calculated from axial and sagittal T2WI using ellipsoid formula. Patients' age and serum PSA level before mpMRI were recorded. PSA density (PSAd) was calculated using the formula of serum PSA/prostate volume.

Statistical analysis

Statistical analyses were conducted using SPSS version 20 (IBM®, Armonk, NY, USA). Perfusion parameters including lesion k-trans, Kep, Ve, iAUC and lesion/normal ratios of k-trans, Kep, Ve, iAUC were compared between indolent and significant cancer using student's T test. A *P*-value < 0.05 was considered statistically significant.

Results

Median age of 76 patients included in this study was 69 (6.6) years. Mean serum PSA and PSAd values were 12.03 (12.13) ng/ml, and 0.306 (0.371) ng/ml/cm^3, respectively. Mean lesion diameter was 17.6 (8.6) mm with a range of 5-51 mm (Table 1).

There was no case with PI-RADSv2.1 score 1. The numbers of cases with PI-RADSv2.1 scores of 2, 3, 4 and 5 were 5, 4, 24, and 43, respectively. Pathology results were as follows: 13 patients had Gleason 3+3, 29 patients, Gleason 3+4, 22 patients, Gleason 4+3, 8 patients, Gleason 4+4, 3 patients, Gleason 4+5 and 1 patient had Gleason 5+4. Finally, there were 13 indolent and 63 significant prostate cancers (Table 2).

Table 1: Demographic results of this cohort

Parameters	Mean (SD)	Minimum	Maximum
Age (years)	67.31 (6.6)	47	80
PSA (n/ml)	12.03 (12.13)	3.16	75.66
PSAd (ng/ml/cm3)	0.306 (0.371)	0.060	2.680
Dimension (mm)	17.6 (8.6)	5	51

SD: standard deviation

Table 2: PI-RADSv2.1 score vs Gleason grade

PI-RADSv2.1	Gleason grade						
	3+3	3+4	4+3	4+4	4+5	5+4	Total
Score 2	3	2	0	0	0	0	5
Score 3	2	2	0	0	0	0	4
Score 4	5	13	4	2	0	0	24
Score 5	3	12	18	6	3	1	43
Total	13	29	22	8	3	1	76

Lesion values of Ktrans, Kep, Ve, iAUC were 0.11, 0.57, 0.24, 0.12 in indolent cancers, and 0.13, 0.94, 0.21, 0.13 in significant cancers, respectively. Lesion/normal ratios of Ktrans, Kep, Ve, iAUC were 1.6, 1.59, 12, 2.1 in indolent cancers, 3.1, 4.04, 1.39, 2.8 in significant cancers, respectively (Figure 1).

Lesion/normal ratio of Ktrans was higher in significant cancers (p = 0.04) while lesion/normal ratio of Ve was higher in indolent cancers (*P*<0.001). Other parameters were similar between indolent and significant cancer groups (Table 3).

Table 3: Comparison of quantitative DCE parameters in indolent and significant cancer groups

Quantitative DCE Parameters		Indolent cancer with Gleason 3+3 Mean (SD)	Significant cancer with Gleason ≥ 3+4 Mean (SD)	*P*-value
Lesion	Ktrans	0.11 (0.65)	0.13 (0.11)	0.398
	Kep	0.57 (0.29)	0.94 (2)	0.357
	Ve	0.24 (0.2)	0.21 (0.14)	0.504
	iAUC	0.12 (0.075)	0.13 (0.085)	0.682
Lesion / Normal tissue	Ktrans	1.6 (0.72)	3.1 (2.6)	0.04
	Kep	1.59 (0.95)	4.04 (7.7)	0.094
	Ve	12 (39)	1.39 (1.2)	< 0.001
	iAUC	2.1 (1.3)	2.8 (2.4)	0.255

DCE: dynamic contrast enhancement, SD: standard deviation, iAUC: area under curve

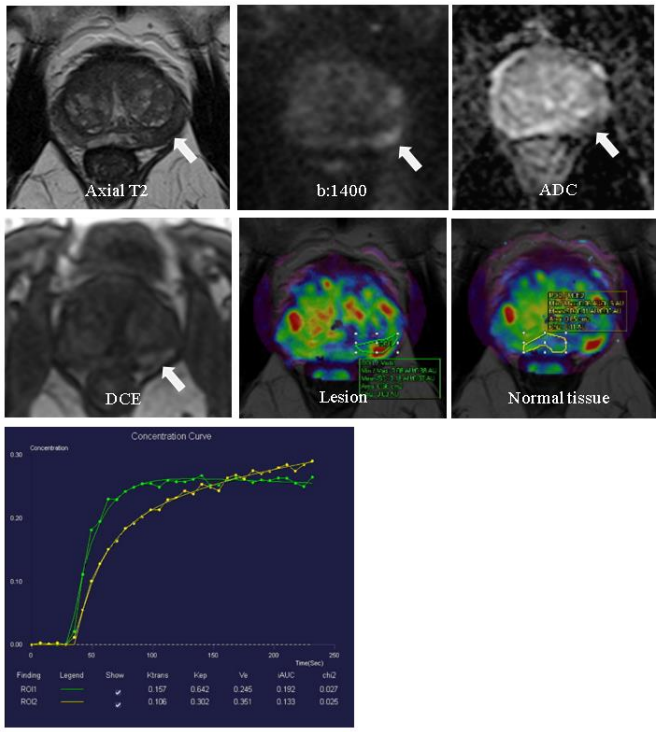

Figure 1: Multiparametric MRI and quantitative DCE-MRI results of a 73-year-old male with a PSA of 4.77 ng/ml and PSAd of 0.08 ng/ml/cm3. Arrows are showing a PI-RADS category 5 lesion placed on left mid-peripheral zone. Green curve is representing the lesion whereas yellow curve is showing normal prostate. Lesion Ktrans, Kep, Ve, and iAUC values are 0.157, 0.642, 0.245 and 0.192, respectively. Lesion/normal ratios of Ktrans, Kep, Ve, and iAUC are 1.49, 2.13, 0.70 and 1.44, respectively. The lesion was Gleason 4+3 tumor in whole-mount report.

Discussion

Qualitative and visual evaluation was suggested for DCE-MRI in PI-RADSv2.1. DCE-MRI had a limited role in scoring and was used only when positive to elevate a finding in the PZ with score 3 [4]. In this study, we evaluated quantitative DCE parameters and found that lesion/normal ratio of Ktrans was significantly higher in clinically significant prostate cancer. Conversely, lesion/normal ratio of Ve was negatively correlated with increasing tumor grade from Gleason 3+3 to Gleason ≥ 3+4.

Cancer tissue includes increased number of vessels. These vessels are also more permeable, disorganized, and chaotic than normal vessels. More aggressive tumors have more ability of angiogenesis using factors such as vascular endothelial growth factor [10]. DCE-MRI contains information about tissue perfusion and vascular permeability. A contrast agent mimics the blood and T1 signal changes of the tissue recorded repeatedly, dynamically [11]. Pharmacokinetic model of Tofts, one of the most popular quantitative modeling methods in practice, is based on determination of contrast exchange rate between intravascular (plasma) and extravascular space using transfer rate constant, such as Ktrans, Kep, Ve, iAUC. Ktrans is forward volume transfer constant and closely related with vascular permeability. It demonstrates flux from intravascular to extravascular space. Kep is reverse reflux rate constant between extravascular space and plasma and demonstrates efflux of contrast from extracellular space back to plasma. Ve is the extracellular extravascular volume fraction and can be calculated with the formula of Kep = Ktrans/Ve [9,11,12]. iAUC represents area under the concentration curve in time [13]. High values of Ktrans, Kep, and iAUC were positively correlated with poor prognosis in some other cancers such as invasive ductal carcinoma, and glioblastoma [13-16].

Ktrans and Kep were elevated in prostate cancer [17-19]. Vos et al. [20] reported that there was a significant correlation between tumor aggressiveness and Ktrans and Kep. Wei et al. [21] found significant Ktrans and Kep differences between benign and Gleason 3+3 tumor. Ktrans was significantly different between Gleason 3+3 and Gleason ≥ 3+4, as well. The sensitivity of MRI increased from 56.6% to 92.1% with addition of Ktrans assessment. On the other hand, there were some challenging factors in quantitative method. The measurements can be affected by changing cardiac output, and the T1 time of the tissue [11]. In our study, no lesion perfusion parameters reached a significant level. However, lesion/normal ratio of Ktrans was positively correlated with increasing tumor grade from Gleason 3+3 to Gleason ≥ 3+4. Lesion/normal ratio of Ve was significantly lower in patients with Gleason ≥ 3+4 tumors. We believe that lesion/normal ratio is more appropriate than measurement from the lesion alone. The proportion may not be affected from challenging factors and may yield more reliable and reproducible results.

One of the most critical factors affecting the diagnostic performance of quantitative MRI is shorter acquisition time. PI-RADSv2 proposed a temporal resolution of ≤ 10 sec (<7 sec is preferred) [22]. This criterion was softened in PI-RADSv2.1 as ≤ 15 sec not to compromise image quality [4]. Benign-malign differentiation was better with higher temporal resolution. Ultra-fast T1 weighted gradient echo is performed for rapid imaging. The advantage of GRE sequence is fast acquisition [23]. However, it is sensitive to metal implants, such as hip prosthesis. Considering that prostate cancer risk increases with aging, adequate imaging may be challenging. In our study, DCE-MRI was performed with a high temporal resolution of 7 sec. Rapid imaging provided more detailed information on tissue perfusion. We excluded the cases (n=4) with hip prostheses not to contaminate the results of quantitative DCE-MRI.

Limitations

This study had several limitations. First, this was a retrospective study had a potential of selection bias. Second, it was conducted in a single center with a small sample size. The results should be supported with prospective, large, and multicenter studies. Third, considering complexity of post-processing, the result should be replicated with different software and workstations. Fourth, we used radical prostatectomy specimens as the reference test. There might be some selection bias because the patients with low risk, and those with aggressive

tumors with pelvic or rectal invasion could not undergo RP. Fifth, the locations of the tumors were marked by one radiologist using pathology reports. Then, another radiologist assigned a PI-RADSv2.1 score to this marked lesion. Score assignment was performed while blinded to pathological outcome. This method provided a perfect overlap between mpMRI and pathological results with a bias risk for assignment of higher PI-RADSv2.1 score. The reader of MRIs was blinded to pathological outcomes to minimize the bias risk. Interreader agreement may be tested with multireader and multicenter studies in future.

Conclusion

Quantitative DCE-MRI may demonstrate more objective and reproducible results. Lesion/normal ratios of Ktrans and Ve were helpful in differentiation between indolent and significant prostate cancers.

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