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APPLICATION OF DIFFUSION KURTOSIS IMAGING BASED ON MULTIMODAL MRI IN MICROSATELLITE INSTABILITY OF ENDOMETRIAL CANCER

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Abstract: Background: Microsatellite instability (MSI) based on multimodal MRI is a critical molecular marker in endometrial cancer (EC), associated with distinct biological behaviors and therapeutic responses. Diffusion kurtosis imaging (DKI), an advanced diffusion-weighted imaging technique, offers insights into tissue microstructural complexity and has shown potential for non-invasive cancer characterization.
Objective: This study aims to evaluate the application and diagnostic performance of DKI in assessing MSI status in endometrial cancer.
Methods: A retrospective analysis was conducted on patients with confirmed endometrial cancer who underwent preoperative DKI and MSI testing. Quantitative DKI parameters, including mean kurtosis (MK), mean diffusion(MD), and ADC were extracted and compared between MSI-high (MSI-H) and microsatellite stable (MSS) groups. Statistical analyses were performed to assess the diagnostic accuracy.
Results: MSI-H tumors demonstrated significantly higher MK,MD and ADC values compared to MSS tumors ($p < 0.01$), reflecting increased tissue heterogeneity and microstructural disorganization. Receiver operating characteristic (ROC) analysis indicated that MK had the highest diagnostic performance, with an area under the curve (AUC) of 0.731, sensitivity of 52.2%, and specificity of 95.1%.
Conclusion: DKI provides a non-invasive, quantitative method for differentiating MSI-H from MSS endometrial cancers. Its excellent diagnostic accuracy highlight its potential as a biomarker for MSI status of endometrial cancer.
Keywords: Diffusion kurtosis imaging; Microsatellite instability; Endometrial cancer

1 INTRODUCTION

Endometrial cancer is one of the most common gynecologic malignancies worldwide, with increasing incidence rates, particularly in developed countries[1-2]. Microsatellite instability (MSI), a result of defective DNA mismatch repair, is a critical molecular marker in endometrial cancer. MSI is associated with distinct clinical and pathological features, including enhanced mutational burden, increased tumor heterogeneity, and heightened sensitivity to immune checkpoint inhibitors[3-9]. Accurate detection of MSI is essential for guiding personalized treatment strategies, particularly in identifying candidates for immunotherapy.

Traditional methods for MSI detection, such as polymerase chain reaction (PCR)-based assays and immunohistochemistry (IHC), require tissue samples obtained through invasive biopsy or surgery[4-5]. While these methods are highly reliable, they are limited by their inability to capture the dynamic tumor microenvironment or evaluate whole-tumor heterogeneity[4-5]. Non-invasive imaging biomarkers that correlate with MSI status could overcome these limitations, enabling preoperative stratification and comprehensive tumor assessment.

Diffusion kurtosis imaging (DKI), an advanced diffusion-weighted imaging (DWI) technique, has emerged as a promising tool for non-invasive tumor characterization. By capturing the non-Gaussian diffusion of water molecules in biological tissues, DKI provides detailed insights into tissue microstructural complexity, heterogeneity, and cellular density. These attributes DKI could be assessing the biological and morphological changes associated with MSI-positive tumors.

Diffusion kurtosis imaging (DKI) based on multimodal MRI has shown significant potential in the evaluation of endometrial cancer across multiple domains. Its applications include distinguishing between benign and malignant lesions, assessing myometrial invasion,detecting microsatellite instability (MSI) , aiding in preoperative evaluations, and analyzing histological characteristics. These advancements highlight the value of DKI as a non-invasive imaging technique in the diagnosis and management of endometrial cancer[10-19]. Preliminary studies suggest that DKI-derived parameters, such as mean kurtosis (MK) and mean diffusion(MD), may reflect the increased cellularity and structural disorganization characteristic of MSI-positive tumors. Research on the application of diffusion kurtosis imaging (DKI) in assessing microsatellite instability (MSI) in endometrial cancer is still in its early stages. While DKI has shown promise in various aspects of endometrial cancer evaluation, its role in detecting MSI remains an emerging area of investigation, warranting further exploration to fully understand its diagnostic potential and clinical utility.

This study aims to evaluate the potential of DKI as a non-invasive imaging technique for assessing MSI status in endometrial cancer, providing valuable insights into its role as a diagnostic tool for molecular characterization.

2 MATERIALS AND METHODS

2.1 Study Design and Patient Population

This retrospective study aimed to investigate the role of Diffusional Kurtosis Imaging (DKI) in detecting microsatellite instability (MSI) in endometrial cancer. We reviewed the medical records of patients diagnosed with endometrial cancer between August 2021 and October 2023 at Yuebei People's Hospital. Eligible patients were those who underwent both MRI imaging with DKI sequences and testing for MSI status, including immunohistochemistry (IHC) for mismatch repair (MMR) protein expression.This study was approved by the institutional review board (IRB) at our hospital.
Inclusion criteria included histologically confirmed endometrial cancer,Availability of preoperative MRI data with DKI sequences,Availability of molecular test results for MSI status (IHC),No prior treatment with chemotherapy or radiotherapy at the time of imaging.
Exclusion criteria included Presence of other malignancies,Inadequate MRI quality (motion artifacts, incomplete imaging protocols).
A total of 64 patients met the inclusion criteria and were included in the final analysis.

2.2 MRI and DKI Protocol

MRI imaging was performed on a 3.0 Tesla MRI scanner (MAGNETOM Vida,Siemens, Munich, Germany). The imaging protocol included routine sequences for endometrial cancer evaluation, such as T1-weighted images, T2-weighted images, DKI sequences,and post-contrast dynamic contrast-enhanced (DCE) MRI. The sequence parameters for MRI examination are detailed in Table 1.

Table 1 Main Scanning Sequence Parameters

Parameters	T1WI	T2WI	DKI	DCE-MRI
Orientation	Axial	Axial	Axial	Axial
Sequence	TSE	TSE	EPI	VIBE-Dixon
TR/TE（ms）	6000/95	4700/95	6800/74	552/245
FOV（mm×mm）	360×360	270×270	380×380	380×380
Matrix	358×448	326×384	112×164	310×352
Bandwidth (Hz/pixel)	286	868	1906	680
Slice thickness (mm)	4	4	4	4
No. of sections	24	24	24	24
NEX	1	1	2	1
B values	-	-	0，700，1400，2100	-

TSE=turbo spin echo ;EPI=echo planar imaging ;TR/TE=repetition time/echo time ;
FOV = field of view ;NEX = number of excitations

2.3 DKI Data Analysis and Quantification

DKI data were analyzed using commercially available post-processing software DiffusionLab(BoDiLab, Chengdu ZhongYing Medical Technology Co,Chengdu. China). Regions of interest (ROIs) were manually drawn on the corresponding DKI images to include the entire tumor volume.
For DWI parameters, the calculation formula is as follows:

$$S(b)/S0=\exp(-b\times ADC) \quad (1)$$

S represents signal intensity, b denotes the b value, and ADC is the apparent diffusion coefficien.
The following DKI parameters were calculated:

$$S(b)/S0=\exp(-b\times Dapp+b2\times Dapp2\times Kapp/6) \quad (2)$$

S is the signal intensity, b is the b value, Dapp(MD) represents the corrected apparent diffusion coefficient (10-3 mm2/s), and Kapp(MK) is the apparent kurtosis coefficient, representing the degree of deviation from a Gaussian distribution and is a dimensionless parameter.
Mean Kurtosis (MK): This parameter reflects the degree of non-Gaussian diffusion and provides information about tissue complexity and microstructural heterogeneity.
The mean diffusivity (MD) : This parameter reflects the average motion of water molecules within a voxel across all directions, reflecting changes in tissue microstructure and cellular density. The DKI parameters were compared between the MSI and MSS groups to identify potential correlations with MSI status.

2.4 Histopathological Analysis and MSI Testing

MSI status was determined by IHC testing. IHC for MMR proteins (MLH1, MSH2, MSH6, and PMS2) was performed using commercially available antibodies. Tumors with complete loss of one or more MMR proteins were classified as MMR-deficient (dMMR), indicative of MSI.

The histopathological diagnosis of endometrial cancer was confirmed in all cases, and tumor grades were classified according to the World Health Organization (WHO) classification system for endometrial carcinoma.

2.5 Statistical Analysis

Statistical analysis was performed using SPSS (version 27, IBM) . Continuous variables were compared between groups using t test or the Mann-Whitney U test for non-parametric data between DKI parameters (MK, MD,ADC) and MSI status.
Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of DKI parameters in differentiating MSI-H from MSS tumors, with the area under the curve (AUC) calculated to determine the optimal cutoff values for each parameter.A p-value of <0.05 was considered statistically significant for all tests.

3 RESULTS

3.1 Patient Characteristics

A total of 64 patients with histologically confirmed endometrial cancer were included in the study. The median age of the patients was 54 years (range: 38–71 years). The distribution of tumor stages according to the International Federation of Gynecology and Obstetrics (FIGO) classification was as follows: 44 patients (68.7%) had stage Ia, 7 (10.9%)had stage Ib,2 (3.1%) had stage II, 11 (17.1%) had stage III.
Based on IHC testing, 24 (35.9%) tumors were classified as microsatellite instability-high (MSI), 41 (64.1%) as microsatellite stable (MSS).The clinical and pathological characteristics of the patients primarily included age, pathological type, FIGO staging and grading, IHC testing (Table 2).

Table 2 Clinical and Pathological Characteristics of Endometrial Cancer Patients

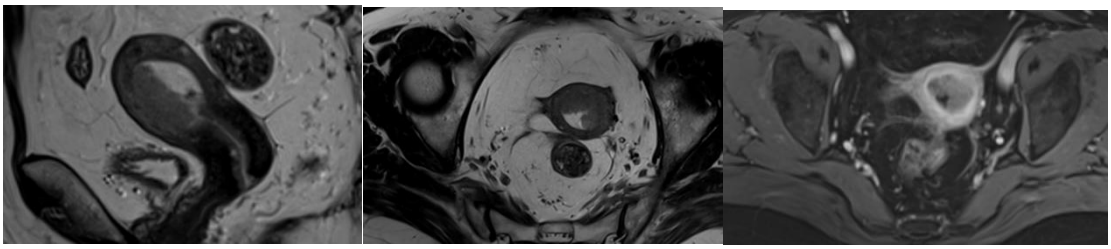
Variable	Data
Age，mean	54
FIGO stage（%）	
Ia	44 (68.7)
Ib	7 (10.9)
II	2 (3.1)
≥III	11 (17.1)
Pathological type（%）	
Endometrioid adenocarcinoma	63（98.4）
Non-endometrioid adenocarcinoma.	1（1.6）
FIGO Grade of Endometrioid adenocarcinoma（%）	
G1	34（53.1）
G2	25（39.1）
G3	5（7.8）
IHC testing（%）	
MSI	23（35.9）
MSS	41（64.1）

3.2 DKI Parameters and MSI Status

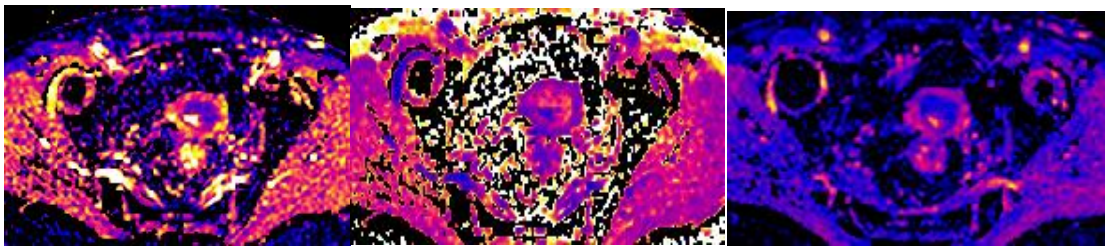
The Diffusional Kurtosis Imaging (DKI) parameters were successfully obtained for all 64 patients, with no significant motion artifacts or imaging quality issues.The intraclass correlation coefficients (ICC) for MD, MK, and ADC in the evaluation of microsatellite instability (MSI) in endometrial cancer were 0.826, 0.804, and 0.765, respectively. The diffusion kurtosis imaging (DKI) parameters, including MD, MK, and ADC, demonstrated statistically significant differences in the assessment of microsatellite instability (MSI) in endometrial cancer. The MD,MK and ADC for each group of MSI status are summarized in Table 3 and Figure 1.

Table 3 Comparison of DKI Parameters among MSI of Endometrial Cancer

Group	MD($\times10^{-3}$ mm^2/s)	MK	ADC($\times10^{-3}$ mm^2/s)
MSI Group (n=23)	1.08±0.14	1.108±0.16	0.66±0.07
MSS Group (n=41)	1.18±0.13	0.97±0.08	0.72±0.08
P-value	0.003	0.005	0.007



SAG-T2WI T2WI T1WI-FS



MD MK ADC

Figure 1 66-year-old Female with Endometrial Cancer. The Images Show DKI Parameters, MD, MK, and ADC with MSI[MLH-1(-),PMS-2(-),MSH-2(+), MSH-6(+)] of Endometrial Cancer.

3.3 Diagnostic Performance of DKI Parameters for Detecting MSI

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of DKI parameters in distinguishing MSI tumors from MSS tumors. The results are presented in Table 4 and Figure 2.

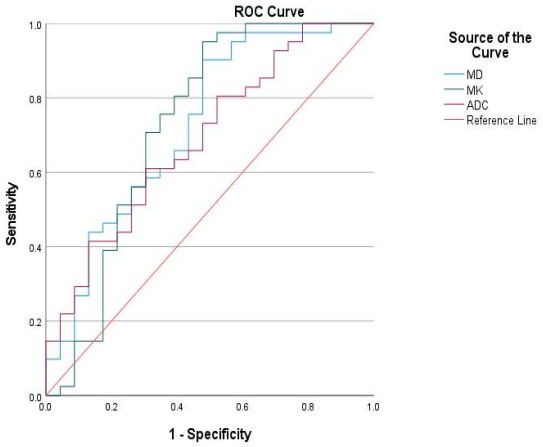


Figure 2 ROC Curve of DKI Parameters among MSI of Endometrial Cancer

Table 4 AUC, Sensitivity,Specificity of DKI Parameters among MSI of Endometrial Cancer

Variable	AUC(Asymptotic 95% Confidence Interval)	Sensitivity(%)	Specificity(%)
MD	0.725(0.59,0.861)	90.2	52.2

MK	0.731(0.582,0.879)	52.2	95.1
ADC	0.689(0.555,0.824)	61.0	69.6

Receiver operating characteristic (ROC) analysis indicated that MK had the highest diagnostic performance, with an area under the curve (AUC) of 0.731, sensitivity of 52.2%, and specificity of 95.1%.

4 DISCUSSION

This study explores the application of diffusion kurtosis imaging (DKI) in assessing microsatellite instability (MSI) in endometrial cancer (EC). Our findings demonstrate that DKI parameters can serve as potential imaging biomarkers to non-invasively detect MSI status, which is critical for personalized cancer treatment strategies.

4.1 Significance of DKI in MSI Characterization

DKI provides advanced diffusion-weighted imaging metrics, including mean kurtosis (MK), mean diffusivity (MD), ADC, which are sensitive to tissue microstructural complexity. MSI tumors displayed significantly altered DKI parameters compared to MSS tumors. These changes reflect the distinct biological characteristics of MSI endometrial cancer, including increased genomic instability, immune infiltration, and tumor microenvironment heterogeneity. The observed differences align with prior histological studies showing that MSI tumors exhibit denser and more disorganized cellular structures, which are effectively captured by non-Gaussian diffusion metrics.

4.2 Advantages of DKI Over Conventional Techniques

Conventional imaging techniques, such as T2-weighted MRI and standard diffusion-weighted imaging (DWI), primarily provide anatomical or Gaussian diffusion-related information. DKI extends these capabilities by quantifying deviations from Gaussian diffusion, thereby offering more detailed insights into tumor heterogeneity. This DKI particularly valuable in identifying subtle microstructural differences between MSI and MSS endometrial cancers that might be overlooked with traditional imaging.

4.3 Implications for Clinical Practice

MSI status has emerged as a crucial biomarker for guiding treatment decisions in endometrial cancer. MSI tumors are associated with favorable responses to immune checkpoint inhibitors and distinct prognostic outcomes. The ability of DKI to non-invasively predict MSI status could reduce the reliance on tissue biopsy, especially in patients with inaccessible or low-quality biopsy samples. Furthermore, incorporating DKI into routine imaging protocols could enhance preoperative planning and treatment stratification, ensuring that patients receive tailored therapeutic interventions.

4.5 Challenges and Limitations

Despite the promising potential of DKI, several limitations must be addressed. First, the relatively small sample size in this study may restrict the generalizability of the findings. Further studies with larger, multicenter cohorts are required to validate the diagnostic performance of DKI in diverse populations. Second, factors such as tumor grade, stage, and coexisting genetic alterations were not fully accounted for in this study. These factors may influence DKI parameters and should be considered in future research to refine the diagnostic accuracy of the method.

5 CONCLUSION

In conclusion, this study highlights the potential of diffusion kurtosis imaging as a non-invasive and quantitative tool for identifying microsatellite instability in endometrial cancer.

CONFLICT OF INTEREST

The authors have no relevant financial or non-financial interests to disclose.

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