Value of intravoxel incoherent motion magnetic resonance imaging for differentiating metastatic from nonmetastatic mesorectal lymph nodes with different short-axis diameters in rectal cancer

ABSTRACT

Background: Conventional magnetic resonance imaging (MRI) does not accurately evaluate lymph node (LN) status, which is essential for the treatment and prognosis assessment in patients with rectal cancer.

Objective: The aim of this study is to evaluate the diagnostic value of intravoxel incoherent motion (IVIM) MRI in differentiating metastatic and nonmetastatic mesorectal LNs with different short-axis diameters in rectal cancer patients.

Materials and Methods: Forty patients (154 LNs) were divided into three groups based on short-axis diameter: 3 mm ≤ × ≤ 5 mm, 5 mm < × ≤ 7 mm, and × > 7 mm. MRI characteristics and IVIM parameters were compared between the metastatic and nonmetastatic LNs to determine the diagnostic value for discriminating them.

Results: In the 3 mm ≤ × ≤ 5 mm group, mean D values were significantly lower in metastatic than in the nonmetastatic LNs (P < 0.001). In the 5 mm < × ≤ 7 mm group, mean f values were significantly lower in metastatic than nonmetastatic LNs (P < 0.05). In the × > 7 mm group, only the short-axis diameter of metastatic LNs was significantly greater than that of nonmetastatic LNs (P < 0.05). The area under the curve, sensitivity, specificity, and cutoff values were used for differentiating the metastatic from the nonmetastatic LNs.

Conclusion: IVIM parameters can differentiate metastatic from nonmetastatic LNs with smaller short-axis diameters (× ≤ 7 mm) in rectal cancer, and the short-axis diameter is a significant factor in identifying metastatic and nonmetastatic LNs in larger short-axis diameter groups (× > 7 mm).

KEY WORDS: Intravoxel incoherent motion, magnetic resonance imaging, mesorectal lymph node, rectal cancer

INTRODUCTION

Rectal cancer is one of the predominant primary malignant neoplasms worldwide and has high morbidity and mortality rates.\(^{[1,2]}\) Accurate staging of tumor and the involvement of lymph nodes (LNs) is essential for clinical treatment planning and prognosis evaluation in patients with rectal cancer.\(^{[3,4]}\) Pelvic magnetic resonance imaging (MRI) is currently the preoperative standard for staging tumor invasion of rectal cancer. The diagnostic accuracy of conventional MRI in evaluating LN status remains insufficient.\(^{[5]}\) Moreover, a study of rectal cancer indicated that normal, reactive, and metastatic LNs had many overlapped in size.\(^{[6]}\) Therefore, more accurate quantitative parameters for evaluating LN status in patients with rectal cancer are needed.

MRI provides the possibility for a quantitative evaluation of tumors. Diffusion-weighted
imaging (DWI) allows for quantitative analysis of the dispersion of water molecules in human tissues through an apparent diffusion coefficient (ADC). The close correlation between ADC and cellularity in different tumors has been shown,\[^9\]\ with ADC significantly associated with T-stage, Ki-67 index, and CA19-9 levels of rectal cancer.\[^8\]-\[^10\] However, ADC value is also affected by tissue perfusion (pseudo-diffusion), and hence, it cannot reflect the tissue diffusion values accurately.\[^11\] Intravoxel incoherent motion (IVIM) is based on the bi-exponential model that can separate tissue diffusion and microcapillary perfusion, better, and more accurately reflecting signal attenuation than DWI.\[^12\] Values for the standard ADC, true diffusion coefficient (D), perfusion-related diffusion coefficient (D*), and perfusion fraction (f) are obtained by fitting with the Levenberg-Marquardt nonlinear least squares algorithm. Lu et al.\[^13\] found significant correlations between D and D* with histological type and f with differentiation degree in rectal cancer. In a study of neoadjuvant chemoradiotherapy for rectal cancer, D and f were correlated with vascular area fraction.\[^14\] Furthermore, several studies\[^15\]-\[^16\] have investigated the parameters of IVIM in the differential diagnosis of metastatic LNs in rectal cancer. Yu et al.\[^15\] considered that the mean D and D* values were significantly higher in benign than in metastatic LNs; conversely, Qiu et al.\[^16\] found that the mean D, f, and ADC values were lower in benign than in malignant LNs. These contradicting results indicate that many factors play a role in IVIM outcomes when evaluating the LN status of rectal cancer.

Several studies have reported different MRI cutoff values for determining malignant LNs in rectal cancer, which is necessary for selecting appropriate preneoadjuvant therapy.\[^17\]-\[^18\] However, limited studies have explored the relationship between IVIM parameters and nodal size in differentiating metastatic from nonmetastatic LNs in rectal cancer.

The purpose of this study was to investigate the diagnostic value of IVIM parameters and conventional MRI features in differentiating metastatic from nonmetastatic LNs with different short-axis diameters in patients with rectal cancer.

**MATERIALS AND METHODS**

**Ethics statement**

This study protocol was reviewed and approved by our Institutional Review Board and was also in accordance with the Helsinki Declaration of 1975, as revised in 2000. Written informed consent was obtained from all patients.

**Patient selection**

Patients with rectal cancer confirmed by colonoscopy plus biopsy were enrolled from January 2017 to July 2018. The inclusion criteria were as follows: (1) newly diagnosed rectal cancer; (2) anticipated surgical resection with total mesorectal excision; and (3) examination with MRI and an additional IVIM sequence. The exclusion criteria were as follows: (1) preoperative neoadjuvant therapy or chemoradiotherapy were conducted; (2) motion artifacts affecting the focus of the lesion in IVIM imaging; and (3) contraindications to anisodamine.

Sixty-seven patients with rectal cancer confirmed by colonoscopy plus biopsy were initially enrolled. Twenty-seven patients were excluded for the following reasons: no LNs were visible with MRI (n = 18), and neoadjuvant chemoradiotherapy was required before the scheduled surgery according to conventional MRI findings (n = 9).

**Patient preparation for magnetic resonance imaging**

The patients underwent rectal cleansing using a glycerine enema at a dose of 10 mL 24 h before the MRI examination. To reduce intestinal peristalsis, 20 mg of hyoscine butylbromide was injected subcutaneously (raceanisodamine, Hangzhou Minsheng Pharmaceutical Co, Ltd., China) 10 min before the examination, except in patients with contraindications.

**Magnetic resonance imaging protocol**

All the MRI examinations were performed on a 1.5T MRI scanner (HDXT2012, GE Medical Systems, Fairfield, CT, USA) using an eight-element phased array body coil. All patients underwent targeted scans of LNs after routine scanning of rectal tumors. The imaging protocols of targeted scans were as follows: (1) for the axial T₂-weighted cube sequence, a repetition time (TR) of 2000 ms, an echo time (TE) of 103 ms, a matrix size of 224 × 224, a slice thickness of 2 mm, an inter-slice gap of 0 mm, and a field of view (FOV) of 26 cm × 26 cm; (2) for the sagittal T₂-weighted imaging (T₂WI), a TR of 4500 ms, a TE of 102 ms, a matrix size of 320 × 192, a slice thickness of 3 mm, an interslice gap of 0 mm, and an FOV of 26 cm × 26 cm; (3) the axial IVIM protocol was performed using single-shot spin echo-planar imaging with free-breathing and fat suppression spectral pre-saturation with inversion recover, along three orthogonal diffusion-encoding directions using 12 b values (0, 25, 50, 75, 100, 150, 200, 400, 600, 800, 1000, and 1200 s/mm²). There was a TR of 4600 ms, a TE of 77 ms, a matrix size of 128 × 128, a slice thickness of 3 mm, an inter-slice gap of 0 mm, and a FOV of 26 cm × 26 cm. The total scan time for IVIM was 2 min and 41 s.

T₂WI cube sequences in the axial and T₂WI sagittal planes were applied to define the locations of the mesorectal LNs, and the definition principle was: (1) in the axial planes, LNs were marked in order from left to right and front (ventral) to back (dorsal); (2) in the sagittal planes, combined with the axial images, LNs were marked following the principle of upper (cranial) to lower (caudal) and then from front (ventral) to back (dorsal); and (3) if there was a conflict between the sagittal and the axial planes, LNs were marked from upper (cranial) to lower (caudal) by combining the sagittal and axial planes [Figure 1].
Magnetic resonance image analysis
Conventional magnetic resonance (MR) images were reviewed based on the consensus of two radiologists with <5 years of experience identifying rectal tumors and LNs. Next, the readers, who were blinded to clinical and pathologic information, qualitatively evaluated the morphologic parameters independently, including nodal location, border contour, and internal structure. Quantitative measurement of the nodal short-axis diameter was collaboratively performed in the axial T₂WI cube images by the readers and determined by reader 1.

Intravoxel incoherent motion postprocessing
The IVIM parameters measurements were conducted by another two independent radiologists with more than 5 years of experience in abdominal MRI diagnosis. The IVIM data were transferred to an Advantage Workstation with FuncTool software (AW 4.6, GE Healthcare, Milwaukee, WI, USA) for postprocessing. Then, standard ADC, D, D*, and f values were obtained using multiple ADC measurement tools. Axial T₂WI cube images were used as references to identify LNs on the corresponding IVIM parameters. To avoid measurement errors, all the matching LNs with a short-axis diameter <3 mm were excluded from the IVIM analysis. Regions of interests (ROIs)-containing LNs were delineated manually with polygonal ROIs of 15–256 mm², covering as much of the nodal parenchyma as possible while avoiding visually large necrotic, cystic, and hemorrhagic areas, and surrounding blood vessels. Mean value of three LN measurements was calculated.

Pathological examination
The mean time interval between MRI examination and total mesorectal excision was 7.3 days (range, 3–10 days). Each surgical specimen was fixed in formalin solution for 48 h. The LNs were traced by their size and position relative to the rectal tumor according to preoperative axial T₂WI cube MR and IVIM images. Subsequently, a radiologist and a pathologist dissected the specimens and harvested the marked LNs. Each specimen was sectioned transversely into 3-mm thick slices from the upper (cranial) to the lower (caudal) portion. A pathologist evaluated each LN tissue section, numbered sequentially. Any mismatches between the MR and IVIM images and the histological findings were excluded from the study. Only the LNs that were undoubtedly matched between the MR images and the surgical specimens were included in this study and categorized into metastatic and nonmetastatic groups. LNs were harvested, routinely stained with hematoxylin and eosin, and examined microscopically to observe tumor infiltration.

Statistical analysis
Interobserver agreement about the existence of the MRI features of LNs was evaluated by Cohen’s κ coefficient. Interobserver variability for the IVIM parametric measurement was evaluated by calculating the intraclass correlation coefficient.
The continuous values were expressed as the mean ± standard deviation (SD). The Kolmogorov–Smirnov test was first used to test the normal distribution of the IVIM parameters and conventional MRI features of the LNs. An independent sample t-test was used for normally distributed data, and the Mann–Whitney U-test was used to check for nonnormally distributed data. Categorical variables were analyzed using the Chi-squared test or Fisher’s exact test.

The parameters with significant differences were incorporated into the receiver operating characteristic (ROC) analysis to diagnose metastatic LNs. The area under the curve (AUC), sensitivity, and specificity of each IVIM parameter and MRI feature were calculated at cutoff points, maximizing the value of the Youden index.

Data were analyzed using the SPSS 21.0 software (IBM Corporation, Armonk, NY, USA). For all the statistical analyses, \( P < 0.05 \) denotes significance.

**RESULTS**

**Baseline characteristics of the patients**
Forty patients were included and analyzed in this study. The baseline characteristics of the patients are shown in Table 1.

| Characteristics          | Value (%) |
|--------------------------|-----------|
| Mean age (years)         | 63.43±9.9 |
| Gender*                  |           |
| Male                     | 26 (65.0) |
| Female                   | 14 (35.0) |
| Tumor location*          |           |
| Low rectum               | 18 (45.0) |
| Middle rectum            | 12 (30.0) |
| High rectum              | 10 (25.0) |
| Tumor differentiation*   |           |
| Moderately/well          | 31 (77.5) |
| Poorly                   | 7 (17.5)  |
| Mucinous                 | 2 (5.0)   |
| Pathologic T staging*    |           |
| T1                       | 1 (2.5)   |
| T2                       | 27 (67.5) |
| T3                       | 12 (30.0) |

*Except where indicated, data are numbers of patients, with percentages in parentheses.

**Conventional magnetic resonance imaging characteristics and intravoxel incoherent motion parameters of all lymph nodes**
Overall, 194 LNs were labeled on the MR images, and 217 LNs were harvested for histopathological analysis. Forty LNs on MR images were excluded due to the mismatching of locations and diameters between MR images and pathology, and 154 were successfully matched, including 75 metastatic and 79 nonmetastatic nodes. Each patient had 1–7 nodes (mean ± SD: 3.85 ± 1.46). Interobserver agreement for border contour and internal structure was very high (\( \kappa = 0.90 \) and 0.82, respectively), and the intraclass correlation coefficients for the standard ADC, D, \( D^* \), and f values were 0.930, 0.926, 0.942, and 0.913, respectively. The short-axis diameter of the metastatic LNs was significantly greater than that of the nonmetastatic LNs (\( P = 0.036 \)). There was no statistically significant difference in the IVIM parameters between the metastatic and the nonmetastatic LNs.

**Conventional magnetic resonance imaging characteristics of the lymph nodes for each subgroup**
The 154 LNs were divided into three groups, 86 in the 3 mm \( \times \leq 5 \text{ mm} \) group (metastatic/all, 29/86, 33.7%), 35 in the 5 mm \( \times < 7 \text{ mm} \) group (metastatic/all, 22/35, 62.9%), and 33 in the \( \times > 7 \text{ mm} \) group (metastatic/all, 24/33, 72.7%). The conventional MRI characteristics of the LNs in each group are shown in Table 2. Only the short-axis diameter of the metastatic LNs was significantly greater than that of the nonmetastatic LNs in the \( \times > 7 \text{ mm} \) group (\( P = 0.005 \)); there were no significant differences in MRI characteristics between metastatic and nonmetastatic LNs in the other two groups.

**Intravoxel incoherent motion parameters measurements of the metastatic and nonmetastatic lymph nodes for each subgroup**
The IVIM parameters for the LNs in each group are shown in Figure 2. In the 3 mm \( \times \leq 5 \text{ mm} \) group, the mean D values of the metastatic LNs were significantly lower than those of the nonmetastatic LNs (\( P < 0.001 \)). In the 5 mm \( \times < 7 \text{ mm} \) group, the mean f values of the metastatic LNs were significantly lower than those of the nonmetastatic LNs (\( P = 0.041 \)). In the \( \times > 7 \text{ mm} \) group, there was no statistically significant difference between IVIM parameters in the metastatic and the nonmetastatic LNs.

| Parameters | 3 mm \( \times \leq 5 \text{ mm} \) | 5 mm \( \times < 7 \text{ mm} \) | \( \times > 7 \text{ mm} \) |
|------------|-------------------------------|------------------------------|----------------------|
| Short-axis diameter (mm) | 3.73±0.54 | 3.89±0.66 | 0.418 |
| Border contour* | | | |
| Smooth | 27 (93.1) | 55 (96.5) | 0.870 |
| Irregular | 2 (6.9) | 2 (3.5) | | |
| Internal structure* | | | |
| Homogeneous | 27 (93.1) | 53 (93.0) | 1.000 |
| Heterogeneous | 2 (6.9) | 4 (7.0) | | |

*Except where indicated, data are numbers of patients, with percentages in parentheses.

*\( P < 0.05 \), †Except where indicated, data are numbers of patients, with percentages in parentheses.
Diagnostic performance of the intravoxel incoherent motion parameters and magnetic resonance imaging characteristics in differentiating metastatic from nonmetastatic lymph nodes  

The AUC, 95% confidence interval, sensitivity, specificity, cutoff, and P value of the statistically significant IVIM parameters and conventional MR characteristics between metastatic and nonmetastatic LNs in each group are summarized in Table 4. The ROCs of the IVIM parameters and short-axis diameter are shown in Figure 3.

**DISCUSSION**

The status of the LNs is one of the major factors associated with the preoperative decision and prognosis of rectal cancer patients. The number of LNs harvested was confirmed to be independently associated with local recurrence, treatment failure, and overall survival rate in patients with rectal cancer, and postoperative radiotherapy should be performed for pT3N0 rectal cancer patients who had <12 LNs harvested.[19] The size of LNs is considered a very important factor for rectal cancer staging and has been discussed in several studies.[18,20,21] Doyon *et al.*[22] revealed that a diameter of less than the 5 mm cutoff value for the short-axis diameter of benign nodes can improve the diagnostic accuracy and has the potential to reduce the risk of overstaging. A proposed cutoff at 7.2 mm resulted in the highest accuracy (68.3%), with a specificity of 94.3% and sensitivity of 32% in differentiating metastatic from benign LNs.[18] Taking into account these disagreements about
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the diameters of malignant LNs, we divided the LNs into three groups with short-axis diameters of $3 \text{ mm} \leq x \leq 5 \text{ mm}$, $5 \text{ mm} < x \leq 7 \text{ mm}$, and $x > 7 \text{ mm}$ to investigate the differential diagnosis value of IVIM parameters in LNs with different short-axis diameters.

The IVIM parameter $D$ represents the true diffusion of water molecules, which is closely related to histological type, vascular area fraction, cell count and Ki-67 index in rectal cancer. In our study, we found that the $D$ value of the metastatic LNs was significantly lower than that of the nonmetastatic LNs in the $3 \text{ mm} \leq x \leq 5 \text{ mm}$ group. Based on the anatomy and physiology of the lymphatic system, lymphatic fluid initially enters the LNs via afferent lymphatic vessels and travels into the subcapsular sinus, where the lymphatic fluid moves freely. When the tumor cells enter the LNs in a similar manner, the free movement of lymphatic fluid would be restricted by the invasive tumor cells, which may result in a decrease of the $D$ value. However, in the $5 \text{ mm} < x \leq 7 \text{ mm}$ and $x > 7 \text{ mm}$ groups, the $D$ value showed no significant difference between the metastatic and the nonmetastatic LNs. This discrepancy could be explained by the fact that the $D$ value depends mainly on cell density and extracellular space, and there are different internal structures between the LNs in the $3 \text{ mm} \leq x \leq 5 \text{ mm}$ group and the other two groups. In the $5 \text{ mm} < x \leq 7 \text{ mm}$ and $x > 7 \text{ mm}$ groups, the necrosis rates of the metastatic LNs were much higher than in the $3 \text{ mm} \leq x \leq 5 \text{ mm}$ group (22.7% and 37.5% vs. 6.9%, respectively). Although we drew the ROIs on the nodal parenchyma as much as possible, some invisible necrosis cannot be avoided. Moreover, the reactive hyperplastic LNs are also composed of abundant lymphocytes and plasmacytes with sparse cell arrangements. Therefore, the $D$ values may not be significantly different between the malignant and the benign nodes in the larger LN groups. According to the ROC analysis of parameter $D$, a cutoff value of $0.001605 \text{ mm}^2/\text{s}$ is required to differentiate malignant and benign LNs with a reliable AUC of 0.763. We speculated that the $D$ value would be a sensitive parameter for distinguishing the metastasis of small LNs in rectal cancer.

Parameters $f$ and $D^*$ are both considered perfusion-related parameters of IVIM; the parameter $f$ is the fractional volume (%) of capillary blood flowing in each voxel that correlated with differentiation degree, vascular area fraction, stained vessel area, total vessel area, and vessel count. In our study, the $f$ value of the metastatic LNs was significantly lower than that of the nonmetastatic LNs in the $5 \text{ mm} < x \leq 7 \text{ mm}$ group ($P = 0.041$) but was valueless in the other two groups. This might be explained by the neovascularization level in different tumor growth status. Folkman found that tumor cell proliferation is limited and may grow without neovascularization in the early phase of tumor growth. With the continuous proliferation of the tumor cell in LNs, angiogenesis may be greater than that

Table 4: Diagnostic performance of intravoxel incoherent motion parameters and magnetic resonance characteristic for metastatic and nonmetastatic lymph nodes in each group

| Parameters                  | AUC | 95% CI         | Sensitivity (%) | Specificity (%) | Cut off   | $P$     |
|-----------------------------|-----|----------------|-----------------|-----------------|-----------|---------|
| $3 \text{ mm} \leq x \leq 5 \text{ mm}$ | 0.763 | 0.651-0.876 | 94.7             | 49.3            | 0.001605 | <0.001** |
| $5 \text{ mm} < x \leq 7 \text{ mm}$ | 0.701 | 0.525-0.877 | 70.6             | 72.2            | 0.2385   | 0.041*  |
| $x > 7 \text{ mm}$         | 0.815 | 0.670-0.960  | 66.7             | 88.9            | 9.865    | 0.005*  |

*P<0.05, **P<0.001. AUC=Area under the curve, CI=Confidence interval, D=True diffusion coefficient, F=Perfusion fraction

Figure 3: Receiver operating characteristic curves of intravoxel incoherent motion parameters and magnetic resonance imaging characteristics. The receiver operating characteristic curves of $D$ value in $3 \text{ mm} \leq x \leq 5 \text{ mm}$ group (a), $f$ value in $5 \text{ mm} < x \leq 7 \text{ mm}$ group (b), and short-axis diameter in $x > 7 \text{ mm}$ group (c) for differentiation between metastatic and nonmetastatic lymph nodes.
of small LNs, but the neoplastic vessels are immature, with fragmented and incomplete basement membranes.\textsuperscript{[23]} Thus, we only found that the $f$ value had a moderate differential diagnosis value in the $5 \, \text{mm} < x \leq 7 \, \text{mm}$ group, but none in the other two groups. We did not find any significant differences of $D^*$ values between metastatic and nonmetastatic LNs in all three groups, which is consistent with the results of previous studies that also showed no differences in $D^*$ values between malignant and benign mediastinal LNs.\textsuperscript{[32,33]} $D^*$ is well known to reflect the dynamic flow rate in the microcirculation and correlates with mean vessel diameter.\textsuperscript{[23]} The parameter $fD^*$ was confirmed to be closely related to mean vessel diameter and showed a better correlation than conventional IVIM parameters in the correlation analysis of dynamic contrast-enhanced MRI quantitative parameters.\textsuperscript{[23,34]} However, the diagnostic efficacy of $f$, $D^*$ and $fD^*$ in differentiating malignant from benign LNs in rectal cancer needs to be further studied in standardized studies with larger samples.

Among all the MRI features, only the short-axis diameter showed the highest differential diagnostic power in the $x > 7 \, \text{mm}$ group and with the highest percentage of metastatic LNs in this group. These results indicated that the metastatic LNs are likely to have a larger size. Considering the overlapping of MRI features between metastatic LNs and nonmetastatic LNs in $3 \, \text{mm} \leq x \leq 5 \, \text{mm}$ and $5 \, \text{mm} < x \leq 7 \, \text{mm}$ groups, our results indicated that IVIM parameters are useful for identifying metastatic and nonmetastatic LNs, especially in smaller LNs, which is precisely where conventional MRI assessment is not useful.

Our study had several limitations. The patient cohort ($n = 40$) and the number of LNs included ($n = 154$) were relatively small. In addition, the study was conducted with a 1.5T MR scanner, which resulted in some LNs with short-axis diameters shorter than 3 mm not being evaluated due to the relatively poor resolution. Moreover, the analysis of IVIM parameters in our study was based on ROIs covering as much of the nodal parenchyma as possible to examine the mean parameter values; however, these do not reflect the histological heterogeneity of LNs with partial necrosis. Finally, considering that the stretched-exponential model works reasonably well only when $b$-values are sufficiently high, especially $>1200 \, \text{s/mm}^2$,\textsuperscript{[35]} this may result in decreased resolution of DWI imaging of LNs. Our study failed to include the parameters $\alpha$ value and distributed diffusion coefficient based on the stretched-exponential model, which showed better performance than IVIM parameters and ADC in predicting the pathological response and differential diagnosis of rectal cancer.\textsuperscript{[15,36]} The application of these parameters in differentiating metastatic from nonmetastatic LNs in rectal cancer remains to be further studied.

CONCLUSION

Our study revealed that different IVIM parameters are useful for differentiating malignant from benign LNs with different short-axis diameters in rectal cancer. The parameter $D$ is useful in $3 \, \text{mm} \leq x \leq 5 \, \text{mm}$ LNs, and it may have the potential to detect the small metastatic LNs. The $f$ value is more sensitive than the $D$ and $D^*$ values in $5 \, \text{mm} < x \leq 7 \, \text{mm}$ LNs, suggesting that perfusion changes occur at a later stage among LNs. Furthermore, in $x > 7 \, \text{mm}$ group, the size of LNs remains an important criterion for malignant LNs.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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