ORIGINAL ARTICLE

Locoregional staging using magnetic resonance imaging in rectal cancer: Influence of diffusion-weighted imaging in the diagnostic accuracy

Estadificación locorregional por resonancia magnética del cáncer de recto: influencia de la imagen potenciada en difusión en la precisión diagnóstica

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Abstract

Objective: *The objective of the study was to assess whether the accuracy in locoregional staging using magnetic resonance imaging (MRI) in rectal cancer (primary or post-chemoradiotherapy) improves by adding diffusion-weighted imaging, according to the radiologist's degree of experience.* **Methods:** *Retrospective study on 100 MRI records (1.5 T, 2011-2016) from patients with rectal cancer (reference standard: histology of surgical specimens). Ten radiologists (three experienced in rectal cancer, three specialized in other areas and four residents) individually reviewed each case twice: first, evaluating just high-resolution T2-weighted sequences; second, evaluation of diffusion-weighted plus high-resolution ones. The analysis focused on the differentiation between early (0-I) and advanced (II-IV) stages. Accuracy, sensitivity/specificity and predictive values were calculated.* **Results:** *Experienced radiologists showed some worsening by adding diffusion-weighted imaging, mainly at primary staging (accuracy: 0.769-0.701). Inexperienced radiologists presented a post-chemoradiotherapy improvement (accuracy: 0.574-0.642; specificity of 19.1-29.8%), although with no other remarkable changes. Residents demonstrated a worsening at primary staging by adding diffusion (accuracy: 0.670-0.633; specificity: 45.8-39.6%), but post-chemoradiotherapy improvement (sensitivity: 80.6-87%). The differences between both reviews were not statistically significant.* **Conclusions:** *No significant differences were found in the distinction between early and advanced rectal tumors secondary to adding diffusion-weighted imaging to high-resolution T2-weighted sequences.*

Keywords: *Neoplasm invasiveness. Rectal neoplasms. Neoadjuvant chemotherapy. Magnetic resonance imaging. Diffusion-weighted imaging.*

Resumen

Objetivo: *Evaluar si la eficacia en la estadificación locorregional por resonancia magnética (RM) del cáncer de recto (primaria o posneoadyuvancia) mejora al añadir imágenes potenciadas en difusión, según la experiencia previa del radiólogo.* **Métodos:** *Estudio retrospectivo sobre 100 RM de 1.5 T (2011-2016) de pacientes con cáncer rectal (estándar de referencia: estadiaje histológico de pieza quirúrgica). Diez radiólogos (tres con experiencia en cáncer rectal, tres inexpertos y cuatro residentes) evaluaron individualmente cada caso dos veces: primero, solo secuencias T2 de alta resolución; segundo, valoración conjunta con difusión. Se analizó la diferenciación entre estadios precoces (0-I) y avanzados (II-IV), y se calcularon la precisión,*

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la sensibilidad y la especificidad, y los valores predictivos. **Resultados:** *Al agregar la difusión, los radiólogos experimentados presentaron peores resultados, sobre todo en estadiaje primario (precisión: 0.769 a 0.701). Los inexpertos mostraron mejoría posneoadyuvancia (precisión: 0.574 a 0.642; especificidad: 19.1 a 29.8%), sin otros cambios destacables. Los residentes manifestaron peores resultados en estadiaje primario (precisión: 0.670 a 0.633; especificidad: 45.8-39.6%), pero mejoría posneoadyuvancia (sensibilidad: 80.6 a 87%). Las diferencias entre ambas revisiones no fueron estadísticamente significativas.* **Conclusiones:** *No se encontraron diferencias significativas en la distinción entre tumores rectales precoces y avanzados al añadir secuencias de difusión al uso de secuencias T2 de alta resolución.*

Palabras clave: *Invasividad tumoral. Neoplasia rectal. Quimioterapia neoadyuvante. Resonancia magnética. Secuencias potenciadas en difusión.*

Introducción

The approach to rectal cancer has undergone marked changes in recent decades. Advances in less aggressive surgical techniques and neoadjuvant treatment with chemoradiotherapy (CRT) have achieved a significant increase in survival and a decrease in morbidity and local relapse[1-3]. For correct decision-making, the previous imaging staging as accurate as possible is essential, where magnetic resonance imaging (MRI) has demonstrated its value[4-6].

Today, some controversial points remain about MRI applied to rectal cancer, such as the usefulness of diffusion-weighted image (DWI) sequences[7,8]. Although there is agreement that high-resolution T2-weighted sequences (HRT2w) are essential for their assessment, the potential value of DWI for post-CRT evaluation or for complete response detection has been brought up[9-13]. Some debate persists on its use in primary or lymph node staging[14-16]; a recent consensus article does not recommend DWI in such cases, but previous meta-analyses highlight the scarcity and heterogeneity of available evidence[5,11,17].

There are only few studies on the influence of DWI on locoregional staging (TN), despite its common use in daily practice and its clinical relevance in decision-making[18]. Similarly, there are only few data on its performance when used by less experienced radiologists, for whom DWI would potentially be of greater interest by facilitating tumor visualization and delimitation and perirectal lymph nodes detection[12,15,19].

The purpose of our study was to evaluate whether adding DWI sequences improves the diagnostic efficacy of HRT2w sequences for differentiating early (0-I) from advanced stages (II-IV) in rectal cancer by MRI, as well as to assess whether there are differences between radiologists who are experts in rectal MRI and others with less experience.

Methods

Retrospective, cross-sectional, and MRI-based study of rectal cancer staging carried out in our center. The study was approved by the Hospital Research Ethics Committee; given its retrospective nature, no informed consent was requested.

Patients

MRIs were carried out between January 2011 and July 2016 and were consecutively included until reaching a final sample of 100 (Fig. 1). The study included patients with both surgery after primary staging and neoadjuvant treatment prior to surgery (post-CRT). The inclusion criteria were: (a) rectal cancer confirmed by colonoscopy and biopsy; (b) rectal MRI with a correct technique according to the established protocol, with all sequences available for review and without significant artifacts; (c) post-CRT follow-up MRI when neoadjuvant treatment was given; and (d) total mesorectal excision or abdominoperineal resection after MRI with complete surgical specimen. At primary staging, the maximum period admitted until surgery was 9 weeks (mean: 34.7 days). In post-CRT cases, those with surgery between 6 and 10 weeks after treatment completion (mean: 64.1 days) were included in the study. Post-CRT follow-up MRI was considered in the study when neoadjuvant treatment was provided; cases with a period of 5 weeks or less between CRT completion and follow-up MRI (mean: 40.7 days) were excluded from the study.

The need for CRT was assessed by the Hospital Committee for Colorectal Tumors. In general, Stages IIA with superficial infiltration on imaging, without factors of poor prognosis, were not considered an indication for CRT. Cases with tumors located at the upper third of the rectum or on the rectosigmoid junction were individually evaluated[3]. The neoadjuvant regimen

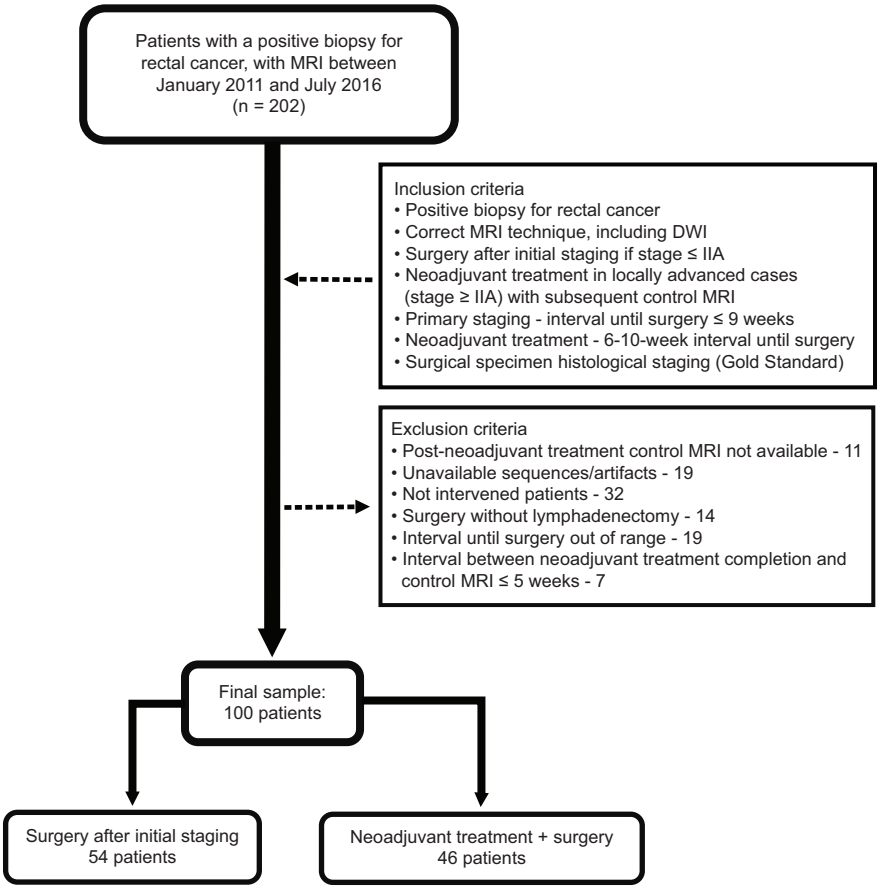

Figure 1. *Study workflow.*

consisted of oral capecitabine 825 mg/m^2 every 12 h, concomitant with a long cycle of radiotherapy (50.4 Gy in 25 sessions)[21].

For histopathological analysis, surgical specimens were fixed in formalin for 24 h. Representative sections of the tumor area and possible infiltration zones were taken; all detected lymph nodes were isolated from perirectal fat and entirely included. Two pathologists (with 7 and 10 years of experience in colorectal tumors) established the anatomopathological stage, which was the reference standard of the study.

MRI protocol

The scans were carried out on a 1.5-T MRI equipment (Magnetom Avanto; Siemens) with a 16-channel surface coil. All patients were previously rectally administered 50 mL of gel and 20 mg of butylscopolamine bromide by intramuscular route. The MRI protocol that was used is shown in table 1.

Image evaluation

The images were evaluated on high-resolution monitors with the Picture Archiving and Communication System (PACS; General Electric). Each case was evaluated by 10 radiologists with different degrees of experience in rectal cancer staging by MRI: three (ER) with previous experience of 6, 5, and 3 years (approximately 40 cases/year); three others (NER) with 7, 4, and 2 years of experience in MRI on areas other than gastrointestinal; and four radiology residents (RR) on their last specialization years, with general knowledge on abdominal MRI. At the beginning of the study, NERs and RRs received a basic training (2 hours) by an experienced radiologist, with review and discussion of several examples from the center itself.

All of them reviewed the cases individually and blindly, except for the history of positive biopsy for rectal neoplasm. The review of each case was carried out in two phases: the first one was based on analysis only with HRT2w sequences, and after a minimum

Table 1. Technical parameters of the magnetic resonance protocol used in the study

	T2w	HRT2w	DWI
Plane	Axial, coronal, sagittal	Axial, coronal, sagittal	Axial
Reference	Pelvis	Tumor axis	Pelvis
RT/ET	4700/95 ms	4000/95 ms	5000/70 ms
Section thickness	6 mm	3 mm	5 mm
Matrix	256 × 230	256 × 230	192 × 115
FOV	340	200	300
Duration	150 s	135 s	200 s

DWI: diffusion-weighted image sequences; FOV: field of view; HRT2w: high-resolution T2-weighted sequence; RT/ET: repetition time/echo time; T2w: T2-weighted sequence.

washout period of one month and randomization, the second phase consisted of a new assessment of each case, this time both with HRT2w and DWI sequences.

Main tumor assessment with HRT2w was based on the presence or persistence of foci of thickening or solid masses of intermediate intensity on the rectal wall, considering as a sign of infiltration a blurred margin with lobulations or extension to adjacent fat. The appearance of marked hypointensity on post-CRT follow-up MRI was considered indicative of fibrosis. With DWI, the criterion for suspected malignancy was the presence or persistence of high signal intensity at high b-values with hypointensity on ADC. To determine extramural involvement, the findings were correlated with their localization on HRT2w.

In regional lymph nodes assessment, the criteria for malignancy on HRT2w were morphological: presence of intranodal signal heterogeneity, irregular or round-shaped external margins[22]. Each lymph node was assessed using a confidence scale from 1 to 3 (1 = malignant; 2 = doubtful; and 3 = benign), with a count of the number of lymph nodes per grade in each patient; the presence of two or more criteria was considered suggestive of malignancy, while one alone was classified as doubtful. On DWI, the presence of lymph node hyperintensity at high b-values in comparison with a suppressed mesorectal fat background signal, associated with diffuse or focal hypointensity on ADC, was regarded as a criterion of suspicion. For joint evaluation with HRT2w and DWI, one grade of suspicion was given on the scale based on HRT2w and, if there was suspicion on DWI, the score was lowered by one grade (e.g., doubtful HRT2w + suspicion on DWI = malignant). Lymph node size was not included, given that during the design and data collection no clear limits or mixed criteria had been published[9,23]. Lateral lymph nodes were not evaluated, since the surgical technique did not always include systematic lymphadenectomy.

Based on these data, patient-to-patient locoregional stage at both phases was determined, in accordance with the American Joint Committee on Cancer (AJCC) guidelines[24]. For this purpose, only the lymph nodes described as grade 1 of the scale (malignant) were considered.

Statistical analysis

Statistical analysis was carried out with the IBM SPSS Statistics 24.0 (IBM Corp), Epidat 4.1 (SERGAS, Xunta de Galicia) and MedCalc 12.2.1 (Ostend) statistical packages. The results were grouped at the different phases according to the degree of experience, with group mean values being calculated.

Histological data were dichotomized in stages 0-I and stages II-IV, with the purpose to assess the performance in the detection of locally advanced tumors. The choice of the cutoff point was made taking into account the therapeutic changes that may derive from it: on primary staging, the need for CRT prior to surgery; on post-CRT control, prognostic factors variation and the possibility of less aggressive surgical techniques in case of tumor extent reduction[3].

Diagnostic accuracy was assessed by calculating the Receiver Operating Characteristic (ROC) curve area under the curve (AUC) for each review and observer. In addition, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), and negative likelihood ratio (NLR) were determined. Statistical significance was evaluated using Fisher's exact test ($p < 0.05$), and significance of differences between values with DeLong's method (in ROC curves) and McNemar's test (rest of parameters). Over-staging and under-staging rates were also calculated, as well as intra-group agreement between multiple observers for dichotomous categories defined by Fleiss' kappa statistic; this was assessed according to the scale proposed by Landis and Koch (0.00-0.20: poor; 0.21-0.40: slight; 0.41-0.60: moderate; 0.61-0.80: considerable; and 0.81-1.00: almost perfect)[25].

Results

The sample included 54 cases of primary staging with subsequent surgery and 46 post-CRT controls before surgery. Demographic and anatomopathological data are presented in table 2. Table 3 shows the accuracy, sensitivity, specificity, PPV, NPV, PLR and NLR results; all the presented results correspond to final locoregional staging (including T and N). The values were statistically significant ($p < 0.05$), except for those corresponding to post-CRT AUC and sensitivity/specificity without DWI by NERs, as well as post-CRT sensitivity/specificity by RRs, both without and with DWI. When the reviews without and with DWI were compared, no statistically significant differences were found.

ERs showed a moderate decrease in accuracy with the use of DWI in both primary and post-CRT staging (0.068 and 0.05, respectively). In the rest of the parameters, there were minimal changes with a tendency to worsen when DWI was added, with a drop of 8.3% for NPV and 6.7% for sensitivity at primary staging standing out, with a 3.7% increase in understaging (Table 4).

In contrast, NERs showed slight improvements when DWI was added, mainly in the post-CRT subgroup (increase of 0.068 in accuracy and 10.7% in specificity; and decrease of 0.12 in NLR and 4.5% in over-staging). RRs showed worse results for AUC (0.037), specificity (6.2%) and NPV (5.3%) at primary staging, with no other changes. Neither in the post-CRT subgroup were there major modifications, although an improvement in sensitivity (6.4%), NPV (6.1%), and NLR (0.15) stood out, with a decrease in under-staging (3.8%).

Agreements between observers of the same group were slight to moderate (kappa: 0.23 to 0.6) in all groups, without relevant changes being identified when DWI was added, except for an increase in NERs post-CRT agreement.

Table 2. Demographic data and data on post-surgical histological staging of the specimen

Demographic data	
Mean age	63 years (40-85)
Males (75)	65.5 years (42-85)
Females (25)	61.4 years (40-82)
Type of MRI examination and histology	
Primary Staging	54 cases
– Adenocarcinoma	50
– No malignancy	4
– No. of lymph nodes (median)	15 (5-46)
Post-neoadjuvant treatment staging	46 cases
– Adenocarcinoma	42
– No malignancy	4
– No. of lymph nodes (median)	12 (4-33)
Type of surgery (mesorectal excision)	80 cases
Anterior approach	20 cases
Abdominoperineal amputation	

Histological staging (surgical specimen)	**Primary study**	**Post-neoadjuvant treatment study**
Local staging		
0	9	7
I	15	12
IIA	10	9
IIB	1	1
IIIA	5	7
IIIB	9	10
IIIC	5	0
Tumor (T)		
T0	4	4
T1-2	25	24
T3	20	16
T4	5	2
Positive adenopathies (N)		
N0	35	28
N1	10	15
N2	9	3

Discussion

In our study, no significant differences were found in the distinction between early and advanced stages when DWI was added to HRT2w, in none of the radiologist groups or patient subgroups. However, a certain tendency towards obtaining poorer results when DWI was added in the ERs group stood out, mainly on primary staging.

Although there are numerous studies regarding MRI assessment of the degree of infiltration by the main tumor (T) and lymph node involvement (N), there is little information on the diagnostic efficacy of locoregional staging. However, this is clinically relevant for decision-making and provides a more representative approach to usual practice[18]. We have only found three published articles in this regard and only one evaluates the changes secondary to adding DWI, although with methodological differences that make comparisons difficult.

In a study on neoplasm changes secondary to CRT visualized only with HRT2w, Suppiah et al.[26] reported an accuracy of 43% for local stage. Based on the raw data provided in their article, for the determination of

Table 3. Statistical analysis results

	AUC	Sens.	Spec.	PPV	NPV	NLR	PLR	Kp
Global staging								
ER								
HRT2w	0.735	87.1%	50.4%	69.9%	74.7%	1.75	0.25	0.49
HRT2w+DWI	0.675	83%	48.1%	67.9%	68.1%	1.6	0.35	0.54
NER								
HRT2w	0.653	82.7%	40.5%	63.5%	65.2%	1.39	0.42	0.55
HRT2w+DWI	0.693	84.2%	45%	65.7%	69.4%	1.53	0.35	0.48
RR								
HRT2w	0.637	79.8%	37.2%	62.7%	58.1%	1.27	0.54	0.44
HRT2w+DWI	0.623	82%	32%	61.5%	57.2%	1.2	0.56	0.48
Primary staging								
ER								
HRT2w	0.769	86.7%	58.3%	72.2%	77.7%	2.08	0.22	0.5
HRT2w+DWI	0.701	80%	56.9%	69.9%	69.4%	1.85	0.35	0.54
NER								
HRT2w	0.703	76.3%	56.3%	67.4%	66.6%	1.74	0.42	0.6
HRT2w+DWI	0.725	80.3%	56.3%	68.5%	70.5%	1.83	0.35	0.53
RR								
HRT2w	0.67	79.2%	45.8%	64.6%	63.7%	1.46	0.45	0.46
HRT2w+DWI	0.633	77.5%	39.6%	61.5%	58.4%	1.28	0.56	0.49
Post-CRT staging								
ER								
HRT2w	0.693	87.7%	40.4%	67.6%	69.6%	1.47	0.3	0.48
HRT2w+DWI	0.643	86.4%	36.8%	66%	65.6%	1.36	0.37	0.5
NER								
HRT2w	0.574*	90.5%*	19.1%*	60%	60%	1.11	0.49	0.23
HRT2w+DWI	0.642	88.9%	29.8%	62.9%	66.6%	1.26	0.37	0.34
RR								
HRT2w	0.594	80.6%*	26.3%*	60.8%	48.7%	1.09	0.73	0.4
HRT2w+DWI	0.608	87%*	22.4%*	61.4%	54.8%	1.12	0.58	0.44

*Non-statistically significant results.

Diagnostic accuracy (AUC, area under the curve), sensitivity, specificity, positive and negative predictive values (PPV and NPV), positive and negative likelihood ratios (PLR and NLR) and intragroup agreement between several observers (Kp) for the entire MRI sample (global staging) and the primary or post-neoadjuvant treatment (post-CRT) staging subcategories. The results are grouped according to the degree of experience of radiologists, as well as according to the use only of high-resolution T2-weighted sequences (HRT2w) or with diffusion added (HRT2w + DWI) for evaluation.

ER: radiologists with previous experience in rectal cancer staging; NER: radiologists with no previous experience in staging; RR: radiology residents.

Table 4. Over-staging and under-staging rates

	Overall staging		Primary staging		Post-CRT staging	
	Over-st.	Under-st.	Over-st.	Under-st.	Over-st.	Under-st.
ER						
HRT2w	21.3%	7.3%	18.5%	7.4%	24.6%	7.2%
HRT2w + DWI	22.3%	9.6%	19.1%	11.1%	26%	8%
NER						
HRT2w	26.4%	9.6%	20%	12.8%	34.5%	5.4%
HRT2w + DWI	24.4%	8.8%	20%	10.7%	30%	6.3%
RR						
HRT2w	27%	11.5%	24%	11.5%	30.4%	11.4%
HRT2w + DWI	29.2%	10.2%	26.8%	12.5%	32%	7.6%

Over-staging and under-staging rates (%) for the entire MRI sample (global staging) and the primary or post-neoadjuvant treatment (post-CRT) staging subcategories. The results are grouped as in table 3.

DWI: diffusion-weighted image sequences; ER: radiologists with previous experience in rectal cancer staging; HRT2w: high-resolution T2-weighted sequences; NER: radiologists with no previous experience in staging; RR: radiology residents.

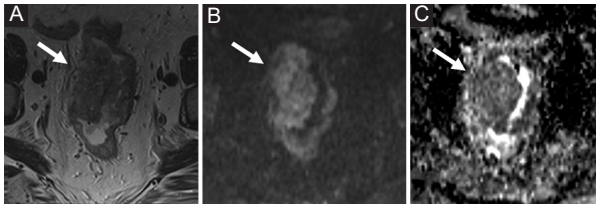

Figure 2. *Advantages of diffusion. Seventy-seven-year-old male patient with upper rectal cancer, primary staging. High-resolution T2-weighted TSE axial sequence.* **A:** *A mass dependent on the rectal wall (arrow) with prominence towards the lumen is observed; there are alterations of adjacent fat that sometimes could raise doubts when differentiating between desmoplastic reaction and infiltration.* **B:** *Diffusion shows hyperintensity of the mass with hypointensity on ADC.* **C:** *Consistent with restriction, with small tracts of similar behavior protruding toward the fat, suggesting infiltration. Stage IIA (T3N0) was confirmed in the surgical specimen.*

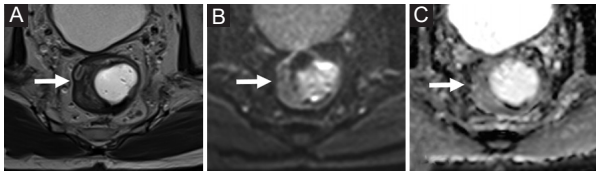

Figure 3. *Limitations of diffusion. 68-year-old male patient with middle rectal cancer and neoadjuvant chemoradiotherapy. Control MRI prior to surgery. High-resolution T2-weighted TSE axial sequence.* **A:** *Wall thickening (arrows) with moderate internal heterogeneity can be observed, which may raise doubts about the persistence of viable tumor, without signs of adjacent infiltration.* **B:** *Diffusion and ADC image.* **C:** *No foci suspicious of obvious restriction are observed, which could be interpreted as complete resolution. The surgical specimen showed Stage I (yT1N0), with isolated millimetric tumor foci, not detectable with the available technique.*

locally advanced stages (II-IV), a sensitivity of 82.8%, specificity of 35.7%, PPV of 76.3%, and NPV of 45.4% can be calculated, which are close to those in our study. For post-CRT assessment with HRT2w and DWI, van den Broek et al.[27] found a global accuracy of 28-47% (including all stages).

Most MRI studies in rectal cancer have been conducted at high-level centers with highly experienced radiologists. Although this would be the most desirable circumstance, this does not necessarily reflect the results of usual practice, generally at smaller centers and with less specialized professionals[10,18]. However, it is in these cases that DWI would potentially be of greater interest, since previous studies have shown that it can facilitate tumor visualization and delimitation (Fig. 2), as well as perirectal lymph nodes detection, which is why it could be of great help for radiologists in the learning process[12,15,19,20].

In the groups of inexperienced radiologists of our study, although the absence of significance limits the conclusions, the fact that a certain tendency towards better post-CRT assessment when DWI was added stands out. This is not surprising, since the sequelae of treatment and the foci of tumor persistence can be difficult to assess and differentiate (Fig. 3)[6,28,29]. DWI has been described to enable post-CRT viable tumor detection and delimitation[20,30,31]. It is reasonable thinking that this benefit of DWI becomes more evident with less experience[12,15,19,20], and thus its use might be advisable at the beginning of the learning curve. Only Sassen et al.[32] refer to the correlation of results with a radiologist with no previous experience in rectal cancer staging, but only referred to the determination of post-CRT complete response, and it is therefore not comparable with our results. This study showed worse AUC (0.74 to 0.7) and PPV (100% to 80%) when DWI was added, but better sensitivity (20 to 40%).

Our study has several limitations. First, its retrospective nature, and second, some learning bias was possible, mainly in less experienced radiologists, but this was avoided as much as possible by not providing information about their results throughout the study. Memory biases were avoided by randomization and separation between readings. Third, the criteria for lymph node malignancy in our study follow the recommendation of being based only on morphological aspects[8,9,33], without the latest consensus recommendations being applied, which were published coinciding with the final phase of data acquisition[5]. However, in our opinion, the results are still valuable: unlike the size (new added criterion), morphological criteria are subjective, which is why it is there where the addition of DWI could determine more significant changes[30,31].

Conclusions

The study results have not demonstrated significant differences in the distinction between early and more advanced rectal tumors when DWI is added to HRT2w, regardless of radiologists previous experience.

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Conflict of interests

The authors declare that there is no conflict of interests.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments have been performed on humans or animals for this research.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained informed consent from the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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