research article

Quantitative aspects of diffusion-weighted magnetic resonance imaging in rectal cancer response to neoadjuvant therapy

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Background. The aim of the study was to evaluate the added value of the apparent diffusion coefficient (ADC) of diffusion-weighted magnetic resonance imaging (DW-MRI) in patients with rectal cancer who received neoadjuvant chemoradiotherapy (CRT). The use of DW-MRI for response evaluation in rectal cancer still remains a widely investigated issue, as the accurate detection of pathologic complete response (pCR) is critical in making therapeutic decisions.

Patients and methods. Thirty-three patients with locally advanced rectal cancer were evaluated retrospectively by MRI in addition to diffusion-weighted images (DWI) and its ADC pre- and post- neoadjuvant CRT. These patients subsequently underwent curative-intent surgery. Tumor staging by MRI and ADC value were compared with histopathological findings of the surgical specimen.

Results. MRI in addition to DWI had a sensitivity of 96.1%, specificity of 71.4%, positive predictive value of 92.5%, and negative predictive value of 83.3% in the detection of pCR. The pre-CRT ADC alone could not reliably predict the pCR group. Post-CRT ADC cutoff value of 1.49 x 10^{-3} mm^2/s had the highest accuracy and allowed a 16.7% increase in negative predictive value and 3.9% increase in sensitivity. Patients with pCR to neoadjuvant treatment differed from the other groups in their absolute values of post-CRT ADC ($p < 0.01$).

Conclusions. The use of post-CRT ADC increased the diagnostic performance of MRI in addition to DWI in predicting the final pathologic staging of rectal carcinoma.

Key words: rectal cancer; neoadjuvant therapy; diffusion MRI

Introduction

Restaging locally advanced rectal cancer after neoadjuvant chemoradiotherapy (CRT) is critical in making therapeutic decisions based on magnetic resonance imaging (MRI). The diagnostic performance of this radiological method is reduced in the restaging of patients undergoing neadjuvant therapy, because of the difficulty in differentiating residual tumour within radiotherapy induced fibrosis.[1-3]

Several publications of the last decade reported the potential use of diffusion-weighted magnetic resonance imaging (DW-MRI) through its apparent diffusion coefficient (ADC) as an additional way to clarify the radiological and biological behavior of these tumors.[4] This technique measures the characteristics of water diffusion in a tissue, which depends on the cell density, vascularization, extracellular viscosity, and integrity of the cell membrane. Any change in tissue components, including the ratio of protons of water molecules between the

extracellular and intracellular environment, may modify the diffusion coefficient of water.[5-7]

Previous studies of different tumor types have suggested that this quantitative interpretation of the ADC could be used as a reliable biomarker of response to neoadjuvant treatment.[5,7-9]

However, there is no consensus regarding the use of different ADC cutoff values or their eventual clinical use in daily practice in the evaluation of response to CRT in rectal cancer. Small-scale studies with varying methodologies and conflicting conclusions have contributed to the wide range of results.[1-10]

Given this knowledge gap, the objective of this study was to evaluate the diagnostic performance of MRI in addition to diffusion-weighted images (DWI) and measure the tumor's ADC, before and after CRT, through a pathological correlation with the surgical specimen.

Patients and methods

Patients

Forty-four patients were diagnosed and treated for rectal cancer in the State Public Servant Hospital of São Paulo (Brazil), from February 2010 to May 2014. This study was performed in accordance with the guidelines of the Helsinki Declaration, fulfilling all requirements for retrospective studies in humans. All the images were accessed in the hospital database, with the approval of the Ethics Committee of our institution (number 04989912.8.0000.5463). Informed consent was not obtained as patient records and information was anonymized and deidentified prior to all the analysis of this pure retrospective study.

The inclusion criteria were the following: patient with histological biopsy of rectal adenocarcinoma, completion of a full course of neoadjuvant CRT, and having undergone MRI and DW-MRI pre- and post-CRT. Thirty-eight patients met the above criteria. The exclusion criteria were the following: failure to obtain a specimen for pathological examination when the surgery was contraindicated during treatment, a history of previous pelvic irradiation, and subjects with missing data. Among 38 patients, 5 patients were excluded due to disease progression (n = 1), missing data (n = 1) and previous pelvic irradiation (n = 3). Thirty-three patients remained in the final study population, 18 males and 15 females. The median age was 59 (± 11.53) years with a range of 36–80 years. Surgery performed included low anterior resection (n = 15), abdominoperineal resection (n = 15), and pelvic exenteration (n = 3). The clinical characteristics are summarized in Table 1.

Neoadjuvant chemoradiation therapy

The neoadjuvant CRT regime used in all patients consisted of radiation to a total dose of 4500 cGy, divided into 5 days per week, a 28-day treatment period, and one boost of 540 cGy. This regimen was associated with the use of 5-fluorouracil at a dose of 350 mg/m^2/day and folinic acid at a dose of 20 mg/m^2/day, in bolus for 5 days in the first and fifth weeks of radiation therapy.

Histopathological examination of the surgical specimens

The histopathological analyzes were performed by expert colorectal pathologists subspecialized in gastro-intestinal pathology, who had no radiographic information. Hematoxylin and eosin (H&E)-stained slides were used for microscopic analysis in all 33 subjects. The standard of reference was based on pathological staging (TNM staging system).[11] The histopathological parameters used

TABLE 1. The patients' clinical characteristics and patohystologic characteristics of the tumor

	All	pCR	non-pCR
Average age, years	59.6 ±11.5	58.5 ±11.2	59.9 ±11.8
Gender*			
Male	18	5	13
Female	15	2	13
Clinical T stage pre-CRT (MRI classification)*			
T2	3	1	2
T3	23	5	18
T4	7	1	6
Average tumor distance to the anus (cm)*	5.1 (± 2.2)	6.1 (± 1.3)	4.8 (± 2.3)
Type of resection*			
Low anterior resection	15	3	12
Abdominoperineal resection	15	4	11
Pelvic exenteration	3	0	3
Histologic grade (biopsy)*			
Well differentiated	6	2	4
Moderately differentiated	23	4	19
Poorly differentiated	4	1	3

* = number of individuals; CRT = chemoradiotherapy; pCR = pathologic complete response

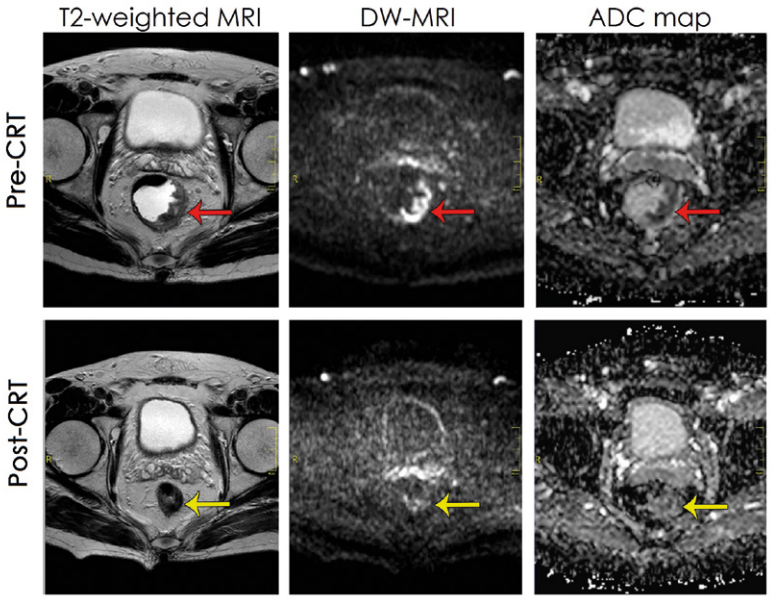

FIGURE 1. Sample of a T2-weighted MRI, DW-MRI (b-value 1000 s/mm^2), and ADC map from a locally advanced rectal tumor. The *red arrows* point to different aspects of the left lateral pre-CRT tumor area. The *yellow arrows* point to the cancer shrinkage in the post-CRT. Pre- and post-CRT ADC values were 0.92 x 10^{-3} mm^2/s and 1.50 x 10^{-3} mm^2/s, with pCR in the surgical specimen.

in this study were the maximum degree of tumor penetration in the rectal wall, the circumferential and longitudinal resection margin, and the presence or absence of intramural mucin. A pathologic complete response (pCR) was defined as no viable cells present on pathological examination of the surgical specimens.[11]

Imaging technique

The mean interval between pre-CRT MRI and the start of the neoadjuvant treatment was 20 ± 3 days. The mean interval between the completion of CRT and post-CRT MRI for response evaluation was 58 ± 8.8 days.

The MRI equipment used in the study was a 1.5 Tesla whole-body system (Achieva®/Philips Medical Systems, Best, Netherlands), with a 16-channel phased-array coil. The sequences used and their specifications were sagittal T2-weighted (T2W) MRI fast spin echo (repetition time/echo time [TR/TE]: 5030/100 ms; field of view [FOV]: 20 cm; gap: 0.5 mm; section thickness: 3 mm; matrix size: 268 x 210; axial T2W MRI fast spin echo; TR/TE: 4681/90 ms; FOV: 20 cm; gap: 0.3 mm; section thickness: 3 mm; and matrix size: 212 x 168). Axial DW-MRI were obtained using the single-shot echo planar imaging technique with the following parameters: TR/TE: 2800/70 ms; gap: 1 mm; slice thickness: 3 mm; matrix size: 104 x 100; and field of view: 20 cm. The axial sequences were obtained in the perpendicular plane to the longitudinal axis of rectal cancer. All sequences (including DW-MRI) were used for conventional MRI reading. In all MRIs the standard of reference was based on previous radiologic staging protocols and T2W images were used to help correctly identify the tumor, if that was the case.[10,21]

The diffusion-weighted images were acquired using four different b-values (b = 0, 50, 500 and 1000 s/mm^2). Patients did not receive antispasmodic medication or bowel preparation before MRI examinations. Two experienced researchers in pelvic MRI and DW-MRI (JFF and TB), in consensus, blinded to patients' data and surgical or pathological results, reviewed the anonymized DICOM files, using computer software (iQ-View, version 2.7, IMAGE Information Systems, London, UK).

Image analysis

The diffusion-restricted area was characterized on one single slice, as the region with the most prominent restrictive diffusion (hyperintense signal) on DW-MRI (b = 1000 s/mm^2). This same region of interest (ROI) was identified and superimposed on the ADC map as a low signal area, which was reconstructed automatically by the computer software on a pixel-by-pixel basis, avoiding T2 shine-through effect. The tumors' ADC value was obtained through the calculation of the ROI, manually designed, in which the whole tumor area was depicted and delineated, excluding visible necrotic or cystic portions and distortion artifacts. For criteria of magnetic resonance complete response, the residual tumor was absent in all sequences, and the ROI included the areas of fibrosis, which was characterized by the hypointense area on T2W and no residual hyperintense signal on high b-value DW-MRI (Figure 1).

Statistical analysis

The statistical analysis investigated the following aspects: calculation of diagnostic performance of conventional MRI and combined set of conventional MRI in addition to DWI (sensitivity, specificity, positive predictive value and negative predictive value); Hypothesis test - two-way ANOVA (Analysis of Variance) using two factors: staging (ranging from ypT0 to ypT4) and treatment status (pre- or post-CRT) with Bonferroni test post-

hoc; Student t-test for comparison after normality test; Correlation between post-CRT ADC values and final T staging with Spearman correlation; Gaussianity tests and the estimation of a Gaussian distribution of post-CRT ADC.

Statistical analyzes were performed using the t and ANOVA tests, conducted with Epi Info software (version 3.3.2, Control Diseases Center, Atlanta, GA, USA). The receiver operating characteristics (ROC) curves were used to analyze the different cutoff values, aiming at the point of highest sensitivity and specificity to the differentiation between pCR and non-pCR. The analyzes of ROC curves and the gaussianity tests were performed using SPSS for Windows (version 10, IBM SPSS, Chicago, IL, USA). Estimates of power analysis were calculated for each sample using Stata software version 8.2 (Stata, College Station, TX, USA). The study had a 95% confidence level ($\alpha = 0.05$), and the value of $p \leq 0.05$ determined the significance in all tests.

Results

Treatment characteristics

All patients were operated on with the total mesorectal excision technique.[12] The mean interval between the end of neoadjuvant CRT and surgery was 77 ± 9.1 days. The longitudinal and circumferential resection margins of the specimen were free of cancer in all 33 patients. pCR occurred in 21.2% (7/33); ypT1 in 3.0% (1/33), ypT2 in 30.3% (10/33), ypT3 in 27.3% (9/33) and ypT4 in 18.2% (6/33) patients. Small amount of intramural mucin occurred in 8 (24.2%) patients, and half of these had pCR. Mesorectal fascia involvement occurred in 8 (24.2%) cases. The mean time interval between the restaging MRI and surgery was 21 ± 13.7 days.

Diagnostic performance of conventional MRI and combined set of conventional MRI in addition to DWI

For detecting the pCR group, conventional post-CRT T2W MRI had a sensitivity of 86.9% (20/23; 95% CI: 0.65 to 0.96), specificity of 50% (5/10; 95% CI: 0.20 to 0.79), positive predictive value of 80% (20/25; 95% CI: 0.58 to 0.92), and negative predictive value of 62.5% (5/8; 95% CI: 0.25 to 0.89). Post-CRT MRI in addition to DWI had a sensitivity of 96.1% (25/26; 95% CI: 0.78 to 0.99), specificity of 71.4% (5/7; 95% CI: 0.30 to 0.94), positive predictive value of 92.6% (25/27; 95% CI: 0.74 to 0.98), and negative predictive value of 83.3% (5/6; 95% CI: 0.36 to 0.99). MRI in addition to DWI also increased the overall accuracy of conventional MRI from 75.7% to 81.8%. These aspects are summarized in Table 2.

TABLE 2. Calculation of diagnostic performance of conventional T2W MRI and combined set of conventional T2W MRI in addition to DWI for the diagnosis of complete rectal cancer response to neoadjuvant therapy

	T2W	95% CI	T2W + DWI	95% CI
Sensitivity%	86.9	(0.65–0.96)	96.1	(0.78–0.99)
Specificity%	50	(0.20–0.79)	71.4	(0.30–0.94)
PPV%	80	(0.58–0.92)	92.6	(0.74–0.98)
NPV%	62.5	(0.25–0.89)	83.3	(0.36–0.99)
Accuracy%	75.7	(0.57–0.88)	81.8	(0.63–0.92)

95% CI = 95% confidence interval; DWI = diffusion-weighted imaging; T2W = T2-weighted; NPV = negative predictive value; PPV = positive predictive value

Pre-CRT ADC value

The average pre-CRT ADC value was 1.01 ± 0.05x10^{-3} mm^2/s and did not vary as a function of tumor staging found in the surgical specimen ($p > 0.05$).

Post-CRT ADC value

Post-CRT ADC values differed in each T stage group ($p < 0.01$). Due to the small sample of ypT1, this comparison was impaired, and there was no statistical difference ($p > 0.05$).

Analyzing the distribution of the post-CRT ADC values and its correlation with the result of the pathological examination, we found a significant statistical correlation between them (Spearman's Rho = -0.54 which indicate a moderate negative correlation; 95% confidence interval -0.75 to -0.24). The pCR ADC-median value (1.53 x 10^{-3} mm^2/s) is far away from the lower (1.04 x 10^{-3} mm^2/s) and upper (1.31 x 10^{-3} mm^2/s) quartiles - 25th and 75th percentiles, respectively - of the non-pCR box (unpaired t test, $p < 0.01$).

These quantitative aspects of the ADC and the rectal cancer pathological findings are shown in Figure 2 A, B, C.

Using the post-CRT ADC values, the ROC curve was constructed. The cutoff value of 1.32 x 10^{-3} mm^2/s obtained a specificity of 100.0% (95% CI: 0.56 to 1.00) and sensitivity of 80.8% (95% CI: 0.60 to 0.92), with 84.8% accuracy. All patients who had pCR were allocated above this value. The cutoff value with highest accuracy (93.9%) was 1.49 x 10^{-}

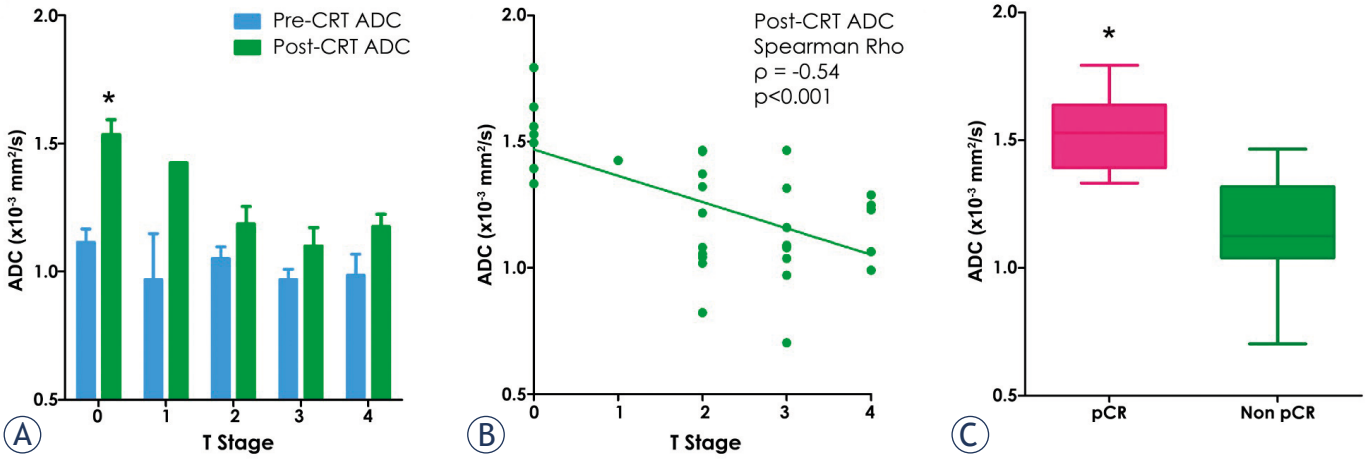

FIGURE 2. Correlation between ADC values and final T staging. **(A)** The pre-CRT ADC values were similar in the different groups (*blue bars*, ($p > 0.05$), although post-CRT ADC values differed in each group (*green bars*, $p < 0.01$); statistical significance (*). **(B)** Post-CRT ADC values with a moderate negative correlation and slope different from zero degrees (Spearman's Rho = -0.54; 95% confidence interval -0.75 to -0.24). **(C)** Box plot analysis between post-CRT ADC values and final T staging. The pCR ADC-median value (1.53 x 10^{-3} mm^2/s) is far away from the lower and upper boundaries of the non-pCR box ($p < 0.01$).

^{3} mm^2/s, with a sensitivity of 100% (95% CI: 0.83 to 1.00) and specificity of 71.4% (95% CI: 0.30 to 0.94) (Figure 3A). All patients with residual tumor in the surgical specimen were allocated below this threshold.

A histogram was created to estimate the post-CRT ADC values distribution in a following Gaussian distribution population. Its coefficient of variation (which is the ratio of the standard deviation to the mean) was 10% and 16% respectively, for non-pCR and pCR groups, both values being considered sufficient for high forecastability. Figure 3B depicts the normal distribution based on the sample size of this study.

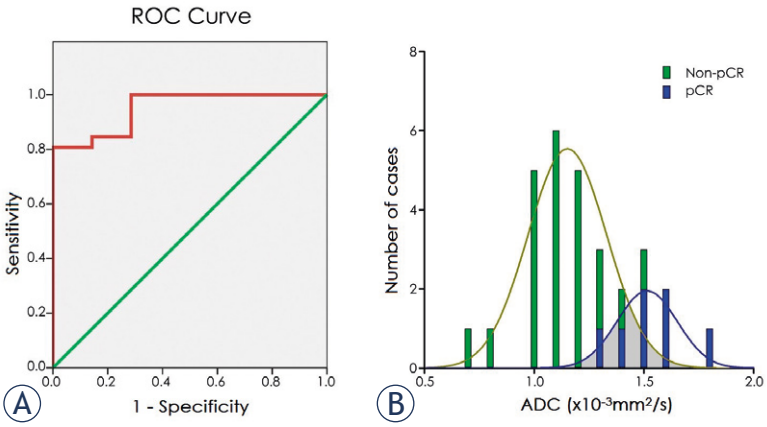

FIGURE 3. Receiver operating characteristic (ROC) curve and histogram in patients with rectal carcinoma with a normal distribution. **(A)** The optimal post-CRT ADC cutoff value 1.49x10^{-3} mm^2/s (area under the curve = 0.95). **(B)** Histogram. The mean post-CRT ADC values of patients with pCR was 1.53 (± 1.96 x0.15x10^{-3} mm^2/s) and of patients with non-pCR 1.16 (± 1.96x0.19x10^{-3} mm^2/s); the area in *gray* highlights the possible overlap in these values.

Discussion

The growing interest in using DW-MRI through its ADC to study tumor behavior is a reality. This method is sensitive to the motion of water molecules, which vary in function in cell membranes and intracellular elements, providing potential access to the cellular architecture on a millimetric scale. Promising results have been described for breast cancer, liver metastasis, sarcoma and brain tumor.[13-17]

The demand for an image that allows a reliable interpretation of tumor aggressiveness and the need for a safety reevaluation of the response to neoadjuvant CRT in rectal cancer have stimulated research.[1-10,18-23] DW-MRI has advantages, such as the absence of the use of exogenous contrast and irradiation, it does not induce pain or cause discomfort in the patient, besides the fact that DW-MRI can be obtained relatively quickly if incorporated into routine standard MRI.[24,25]

This study explored quantitative aspects of the ADC in patients with rectal cancer who received CRT and it is in line with the growing use of potentially powerful imaging biomarker. This kind of radiological approach may allow a better understanding of the biological tumors cells behavior, and enable a more personalized management, in an era focused at less extensive surgeries.[24]

However, many challenges still exist for widespread implementation of DW-MRI to reevaluate rectal cancer after CRT. Koh *et al*.[1], Lambregts *et al*.[2], and Engin *et al*.[3] warned that because the measurements and analyzes of this radiological method are not yet standardized, the validation and reproduction of several studies is difficult due to the lack of a uniform methodology among them, thus quality assurance is placed at risk. This plurality of results was the target of a recent systematic review in which we observed a wide range of conflicting results.[4]

In the present study, we first retrospectively evaluated the use of conventional MRI alone and in addition to DWI in patients undergoing neoadjuvant CRT and subsequently performed surgery for rectal adenocarcinoma. We observed that adding DWI can improve the diagnostic performance of conventional MRI, increasing its sensitivity, positive and negative predictive value, specificity and accuracy. Foti *et al*.[31] recently published and described the same positive impact of using DWI sequences in conventional MRI reading for radiological re-assessment of rectal cancer response to CRT.

Other important focus of this study was to evaluate the diagnostic performance of ADC values pre- and post- neoadjuvant CRT to assess the response to treatment, through the correlation with histopathological parameters.

No difference was found in the distribution of pre-CRT ADC values between pCR and non-pCR groups. The possible use of pre-CRT ADC value to predict tumor response to CRT was first published by Andrzej Dzik-Jurasz *et al*.[28] However, this correlation is controversial, and it was not reproduced later, in 6 of 9 published papers, compiled in a recent systematic review.[4] Our results also suggest lack of differences for pre-CRT ADC to predict the final response to therapy. These findings are in line with those of Engin *et al*.[3], Kim *et al*.[5], Curvo-Semedo *et al*.[6], as recently published by Blazic *et al*.[29]

Moreover, the analysis of post-CRT ADC values was significantly different between patients with pCR and those in which the tumor was identified in the specimen. The ypT0 group was statistically different from the other patients, corroborating the findings of Song *et al*.[7] Sun *et al*.[8] proposed that this ADC increase reflects the local necrosis and sensitivity of tumors to treatment and is greater in patients with ypT0 staging, which was also observed in this study.

The importance of post-CRT ADC values was evident by the increase in the specificity of MRI in addition to DWI in 28.6% of scans, increasing from 71.4% to 100%, considering the cutoff value of 1.32 x 10^{-3} mm^2/s. Thus, all ypT0 patients were above this threshold. This fact has already been described by other authors.[3,5,9] The maximum sensitivity and diagnostic performance of post-CRT ADC values was achieved with the cutoff of ADC 1.49 x 10^{-3} mm^2/s, below which all subjects who had viable tumor in the surgical specimen were allocated. Other cutoff values available in the literature ranged from 1.04 to 1.41 x 10^{-3} mm^2/s.[4]

The histogram obtained in this study characterized this previous phenomenon and allowed an inference from the behavior of the curves of post-CRT ADC values in a population with normal distribution. Based on the sample in this study, 95% of patients with non-pCR had post-CRT ADC values between 0.77 and 1.54 x 10^{-3} mm^2/s.

This study has some limitations. First, this was a single center, retrospective study that had an overall small population without a validation set, which may lead inevitable bias. Second, the ADC values were obtained in a single slice ROI containing the whole visible tumor area, which may not be fully representative of the overall profile of the tumor. Variations in ROI size and positioning can effect tumor ADC measurements. However in recent previous studies single slice ROI and whole-tumor volume methods had comparable diagnostic performance levels with similar AUCs. In this context, single slice ROI can be used as a less time consuming alternative and relatively efficient approach for clinical practice, in the assessment of tumor response to CRT.[29,30] Third, the presence of small amount of mucin in specimen, as tumor regresses, may have changed the post-CRT ADC value, as already observed by others authors.[10,26-27] Fourth, because of the retrospective nature of this study, all patients had already been operated on when we analyzed the MRIs, thus it was not possible to perform the dissection and histopathological evaluation of each of the suspicious lymph nodes.

Conclusions

This study provides quantitative aspects of the use of DW-MRI through the pre- and post-CRT ADC values. Our data support the fact that post-CRT ADC values increased the overall diagnostic performance of MRI in addition to DWI. In the future, larger studies may separate these populations with greater precision, revealing and making clear the area of interception between the pCR and non-pCR groups.

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