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Accuracy of High-Resolution MRI with Lumen Distention in Rectal Cancer Staging and Circumferential Margin Involvement Prediction

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Objective: To evaluate the accuracy of magnetic resonance imaging (MRI) with lumen distention for rectal cancer staging and circumferential resection margin (CRM) involvement prediction.

Materials and Methods: Seventy-three patients with primary rectal cancer underwent high-resolution MRI with a phased-array coil performed using 60-80 mL room air rectal distention, 1-3 weeks before surgery. MRI results were compared to postoperative histopathological findings. The overall MRI T staging accuracy was calculated. CRM involvement prediction and the N staging, the accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were assessed for each T stage. The agreement between MRI and histological results was assessed using weighted-kappa statistics.

Results: The overall MRI accuracy for T staging was 93.6% (k = 0.85). The accuracy, sensitivity, specificity, PPV and NPV for each T stage were as follows: 91.8%, 86.2%, 95.5%, 92.6% and 91.3% for the group ≤ T2; 90.4%, 94.6%, 86.1%, 87.5% and 94% for T3; 98,6%, 85.7%, 100%, 100% and 98.5% for T4, respectively. The predictive CRM accuracy was 94.5% (k = 0.86); the sensitivity, specificity, PPV and NPV were 89.5%, 96.3%, 89.5%, and 96.3% respectively. The N staging accuracy was 68.49% (k = 0.4).

Conclusion: MRI performed with rectal lumen distention has proved to be an effective technique both for rectal cancer staging and involved CRM predicting.

Index terms: *Rectum MR; Rectum NEOPLASM; Rectum staging*

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INTRODUCTION

Colorectal carcinoma is the third most common cancer worldwide (1). This neoplasm is associated with a high risk both for local recurrence and metastases. Traditional rectal cancer surgery is associated with high rates of local recurrence from 3% to 32% (2).

In recent years, two advances in therapy have proved to have a substantial effect on reducing the high local recurrence rate to less than 10%: total mesorectal excision surgery (TME) and the introduction of neoadjuvant chemoradiotherapy (3).

A multidisciplinary approach defining the optimal timing and a combination of surgery, chemotherapy and radiation therapy, is necessary to develop an effective individual strategy for therapy (4). Therefore the accurate preoperative staging of rectal cancer is mandatory and the challenge for imaging is to distinguish tumours with different risks for recurrence: early stage localized lesions, locally advanced cancers, advanced or metastatic disease (5).

In recent years a large amount of literature has focused attention on the importance of circumferential resection margin (CRM) as a strong predictor for local recurrence (6, 7). Today it is well-established that magnetic resonance imaging (MRI) with a phased array surface coil is the best way for staging rectal cancer and evaluating the involved CRM but there is no consensus among radiologists regarding the optimal study technique. Some authors prefer not to distend the rectal lumen (8-10), whereas others assess that distention improves rectal wall depiction with better estimation of the tumor extension (11-15).

The aim of our study was to evaluate the accuracy of this technique in the preoperative staging of rectal cancer and CRM detection in comparison with histological results.

MATERIALS AND METHODS

Our institutional review board approved the research proposal. All subjects provided informed consent after receiving a full explanation of the nature of the study. A prospective study was conducted between May 2006 and December 2011. 95 patients were studied with MRI using a phased array surface coil. All patients had an histological diagnosis of rectal cancer localized within 15 cm from the anal verge. Among them, 22 patients were excluded from the analysis for the following reasons: fifteen patients underwent preoperative long-course chemoradiotherapy, and seven patients for metastatic disease. Finally, 73 patients, 47 male and 26 female (mean age, 56 years; range, 33-73 years), were enrolled in the study. All patients underwent surgery within 1-3 weeks of the MR exam by total mesorectal excision either by means of anterior resection or abdominoperineal excision. Local transanal full-thickness resection was achieved in four patients with an early stage rectal cancer.

MR Technique

MR imaging was performed using a 1.5T unit (Sonata, Siemens, Erlangen, Germany) with a phased array surface coil. The patients performed routine rectal cleansing 3-4 hours before MR exam to limit misinterpretation due to stool. Rectal lumen distention, achieved with 60-80 mL room air insufflated through a rectal tube was routinely performed. Patients were placed comfortably in a prone position to allow for better luminal distention and a phased array surface coil was placed on the back. When the tumour was located on the anterior rectal wall, to avoid compression of the mesorectal fat, which is thinner in the anterior side, a supine position was preferred. Twenty milligrams of hyoscine butylbromide was administered intravenously before rectal insufflation, to reduce motion artifacts.

All sequences were acquired by non-breath-hold sequences as follows. Fast low-angle shot 2D T1-weighted sequences (repetition time [TR] 130 ms, echo time [TE] 4.32 ms, field of view [FOV] 370 mm, slice 5 mm, acquisition time 20 seconds) and Turbo Spin Echo (TSE) T2-weighted sequences (TR 4000 ms, TE 103 ms, FOV 350 mm, slice 5 mm, acquisition time 24 seconds) acquired on axial plane; high-resolution TSE (HR TSE) T2 sequences (TR 4200-5000 ms, TE 108 ms, FOV 180-240 mm, slice 3 mm, acquisition time 210-300 seconds) in at least two planes, sagittal and axial scan orthogonal to the long axis of the rectal tumour, were acquired. For low lying cancers an additional oblique coronal scan was performed along the long axis of the anal canal. A bolus of 0.2 mL/kg of gadolinium was intravenously administered. The MRI exam took about 25-30 minutes.

Image Analysis

The rectal cancer T staging at MR imaging is largely based on differences in T2 signal intensity between the tumour and the rectal wall layers. On T2-weighted images three different layers can be recognized: an inner hyperintense layer representing mucosa and submucosa, having no obtainable differentiation between them, a hypointense intermediate layer corresponding to the muscularis propria and an external hyperintense layer that represents perirectal fat tissue. A thin low-intensity layer enveloping the mesorectum corresponds to the mesorectal fascia that is clearly visible on the lateral and posterior views (15).

The tumor T stage was categorized according to TNM 6th edition (2002) (16) with the 7th edition since 2010 (17). Considering that differentiation between the T1 and T2 lesions is rather difficult, we combined both stages in the group of intramural lesions ≤ T2 characterized by a tumor signal intensity confined to the muscular layer with an intact interface between the muscularis propria and

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the perirectal fat (Figs. 1, 2). The T3 stage was defined when the muscular layer loses its homogeneous low signal intensity and appears disrupted with spiculations or nodular margins extending into the mesorectal fat (Fig. 3). Tumour invasion of the surrounding structures was assumed as T4 stage (16, 17). The CRM was accurately evaluated. An involved CRM was assumed if the shortest distance from either the extramural tumour extension, a suspected lymph node or a tumor deposit in the mesorectum, to the mesorectal fascia was less than 2 mm (Figs. 3C, 4). For the N staging, the presence of regional lymph nodes were evaluated based on their number and size. Nodes with a short axis of 5 mm or greater were considered metastatic, while those less than 5 mm were assumed to be uninvolved (Figs. 3A, C, 4). MR images were analyzed by consensus of two experienced abdominal radiologists.

Pathological Examination

Immediately after surgery rectal cancer resection specimens were carefully examined by an expert pathologist, the integrity of mesorectum was macroscopically evaluated and the segment not covered by peritoneum was inked. Specimens were then fixed in 10% formalin for 48 hours and afterward were sectioned along the coronal plane in order to obtain slices 0.5 cm thick to better assess the circumferential rectal margin. Samples of the tumour in relation to the CRM were taken (2). The distance between tumour, either represented by direct extension of the main mass or neural, venous invasion or metastatic lymph node, and the CRM was measured microscopically (18). A specimen

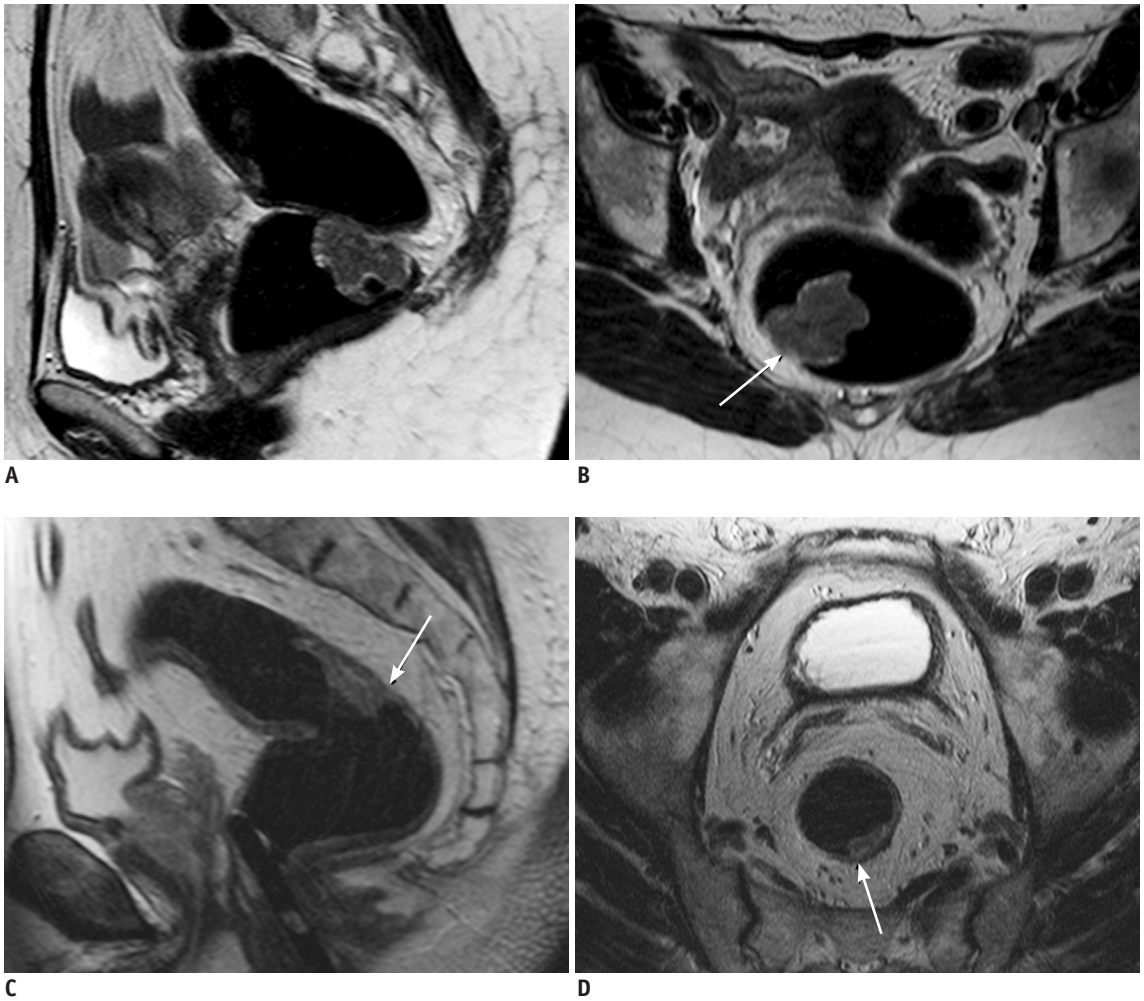
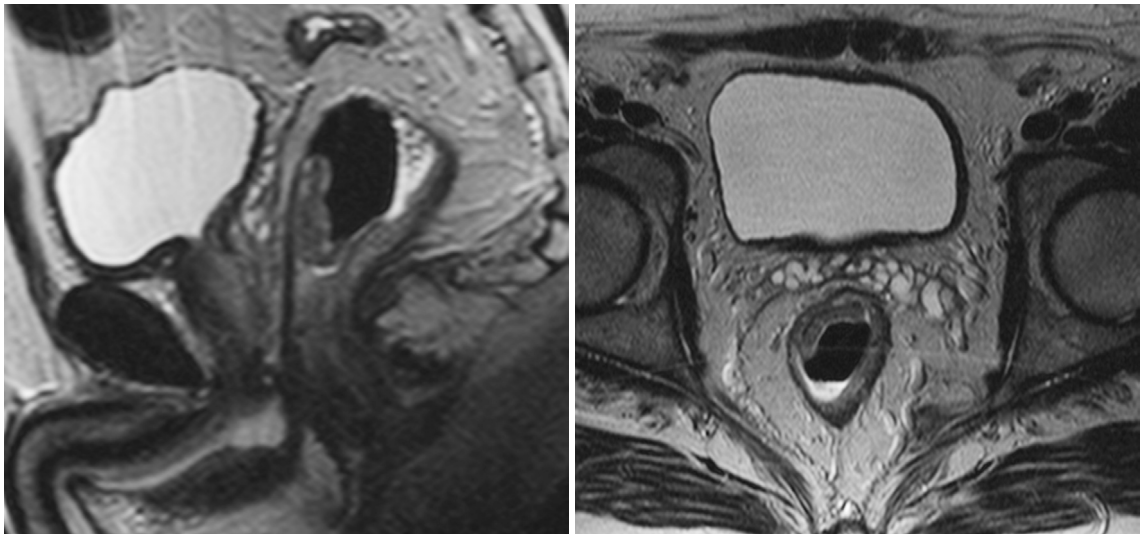
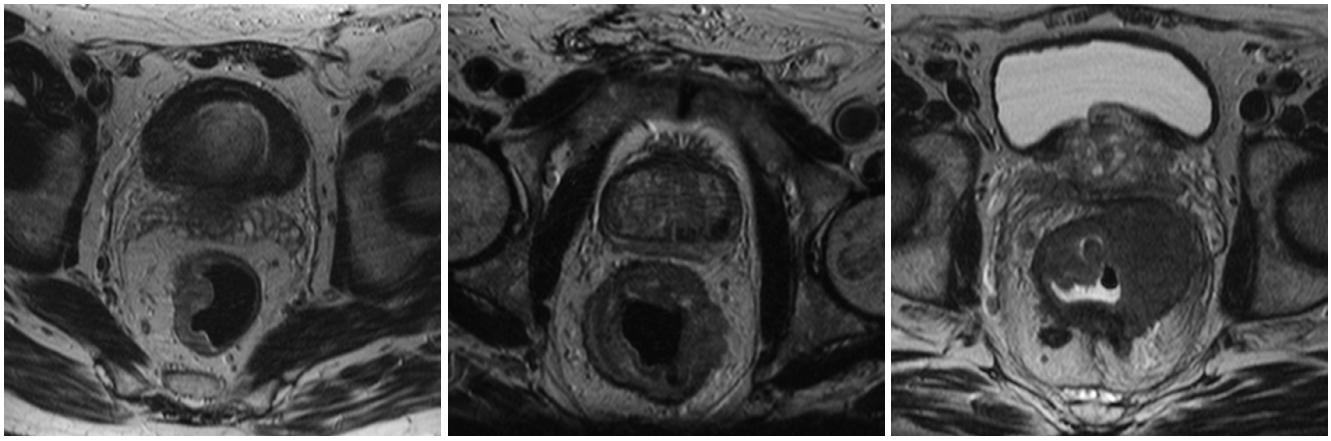


Fig. 1. Two intramural rectal cancers.
High-resolution TSE T2-weighted scans on sagittal **(A)** and axial plane **(B)** show intramural rectal cancer: distention of rectal lumen allows good delineation of polipoid lesion with normal aspect of muscular layer (arrow). Histo-pathological specimen detected pT1 lesion. In another patient high-resolution TSE T2-weighted scans on sagittal **(C)** and axial plane **(D)** demonstrate tumor confined to muscular layer (arrows) without any involvement of perirectal adipous tissue. Histo-pathological specimen detected pT2 lesion. TSE = Turbo Spin Echo



A B

Fig. 2. High-resolution Turbo Spin Echo T2-weighted scans on sagittal (A) and axial plane (B) show T2-stage low rectal cancer.
Muscular layer appears normal both on sagittal and axial scan and insufflation of rectal lumen does not modify detection of mesorectal fat tissue anteriorly.



A B C

Fig. 3. High-resolution Turbo Spin Echo T2-weighted axial scan of T3 rectal cancer in three different patients.
In first patient **(A)** early T3 lesion is depicted with spiculations spreading through muscular layer into perirectal fat; lymph-node is located in mesorectum on right side. In second patient **(B)** MRI shows circumferential rectal mass with deep parietal infiltration spreading in perirectal fat tissue, without any involvement of CRM (> 2 mm). In third patient **(C)** axial scan shows large rectal mass with deep extra-mural neoplastic infiltration that involves mesorectal fascia both on anterior and left lateral side with positive CRM; some metastatic lymph nodes are depicted in mesorectal fat tissue. CRM = circumferential resection margin

with the inked CRM < 1 mm distant from the tumour was regarded as having positive CRM. All lymph nodes were sampled and those close to the inked margin were sampled separately. Histological classification of the tumours was done according to WHO. Staging was performed according to TNM 6th edition (2002) (16) and with the 7th edition since 2010 (17).

Statistical Analysis

The overall MRI T staging accuracy was calculated.

The accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) for each T stage, as well as for the predicting CRM invasion and lymph node involvement, were calculated using the histopathological results as the gold standard. The agreement between MRI and histological results was assessed using weighted-kappa statistics.

RESULTS

All the 73 lesions were well visualized and high quality MR images for all of them were obtained. The histopathological

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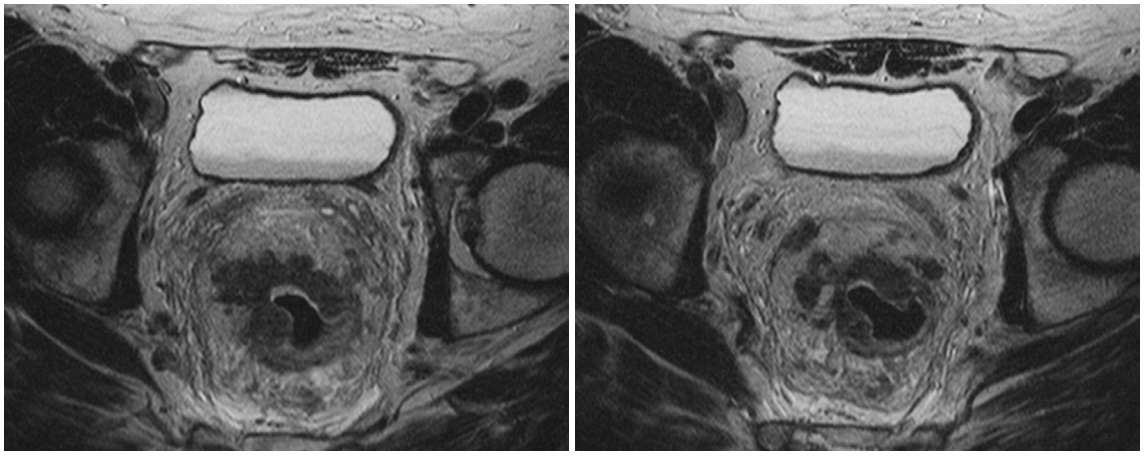


A B

Fig. 4. T3 rectal cancer involving circumferential resection margin.
High-resolution Turbo Spin Echo T2-weighted axial scans at two different level show circumferential rectal mass spreading widely into perirectal fat **(A)**. Tumor's deposits in mesorectum are less than 2 mm from mesorectal fascia **(B)** and involvement of circumferential resection margin was established.

Table 1. Agreement between MRI and Histological Analysis

	Weighted Kappa	95% CI
T staging	0.85	0.74-0.96
CRM	0.86	0.72-0.99
N staging	0.40	0.21-0.58

Note.— CI = confidence interval, CRM = circumferential resection margin

results of resected tumours showed adenocarcinoma in all patients. The pathological T stage of cancers was T1 in 7 patients, T2 in 22 patients, T3 in 37 patients and T4 in 7 patients.

Pathological N stage was pN0 in 45 patients, pN1 in 15 patients and pN2 in 13.

The CRM was involved in 19 patients found by pathology: 12 of the pT3 tumors and, by definition, all seven pT4 cancers.

T Staging

MRI correctly assessed the rectal wall tumour invasion in 25/29 intramural lesions, ≤ T2, in 35/37 pT3 and in 6/7 pT4. Four T2 lesions were overstaged as T3 due to a 1-2 mm reactive tissue or a desmoplastic reaction that could not be differentiated from a true mesorectal tumour invasion. Two patients with pT3 tumours were understaged due to a minimal mesorectal invasion that couldnot be depicted. One out of the seven pT4 tumours was understaged as T3, because the cervix invasion was not recognized.

The overall MRI accuracy of T staging was 93.6% {k = 0.85 (95% confidence interval [CI]: 0.74-0.96)} (Table 1). The accuracy, sensitivity, specificity, PPV and NPV for each T stage were as follows: 91.8%, 86.2%, 95.5%, 92.6% and 91.3% for the group ≤ T2 tumours; 90.4%, 94.6%, 86.1%, 87.5% and 94% for T3 tumours; 98,6%, 85.7%, 100%, 100% and 98.5% for T4 tumours, respectively.

Circumferential Resection Margin

MRI correctly predicted a tumour-free CRM in 52/54 patients. Two false-positives occurred in anterior located tumours. An involved CRM was assessed in 17 out of the 19 histological positive findings. Two false-negative cases were due to failure to identify a metastatic node less than 5 mm close to the mesorectal fascia and in a low rectal cancer.

The accuracy of the CRM status, sensitivity, specificity, PPV and NPV were 94.5% (k = 0.86 [95% CI: 0.72-0.99]), 89.5%, 96.3%, 89.5%, and 96.3% respectively.

N Staging

Twenty-eight out of the 73 patients with rectal cancer, showed metastatic nodes at histological exam (1pT1, 2pT2, 24pT3, 1pT4). Twenty-four of them were correctly categorized by MRI; on the other hand 19 false-positive cases were due to reactive lymph nodes greater than 5 mm. The accuracy, sensitivity, specificity, PPV and NPV were: 68.49% (k = 0.4 [95% CI: 0.21-0.58]), 85.71%, 57.78%, 55.81% and 86.67% respectively.

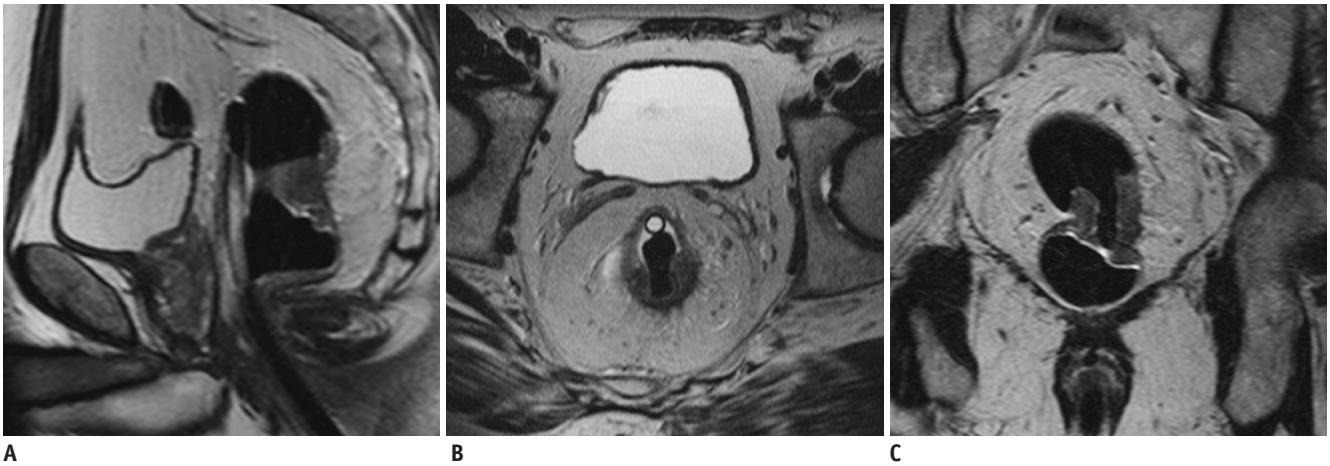
DISCUSSION

Surgical resection with TME is the mainstay of treatment for non metastatic rectal cancer. Tumours with transmural

invasion, lymph node and CRM involvement are at risk of local recurrence and are better treated with preoperative chemoradiotherapy that is proved to be more effective in reducing the local recurrence rate with lower morbidity (3). Hence, preoperative imaging is crucial to select patients for appropriate treatment. MRI with phased array surface coil, combining high spatial resolution and large fields of view, represents the most advanced staging modality able to depict the extramural tumour extension as well as the CRM that are crucial points in the therapeutic planning of locally advanced tumours (19-24). The MR protocol is quite standardized and the HR TSE T2 sequences acquired in at least two planes are considered to be the fundamental part of the exam (25, 26); the axial plane orthogonal to the rectal tumor is essential, while gadolinium enhanced T1 sequences do not appear to be an effective approach (27). However the best study technique to use both for staging rectal cancer and for assessing an involved CRM is controversial. Several authors prefer to perform the exam without rectal lumen distension, hypothesizing that it may alter the distance between the tumour and the mesorectal fascia and potentially compromise the CRM evaluation (8). Other authors advocate rectal distension with water, methylcellulose, superparamagnetic iron oxide solutions or warm US gel to improve depiction of the primary tumour (11, 14, 15).

The rationale for our technique is that the insufflation of approximately 60-80 mL room air stretches the rectal wall, causes an endoluminal signal void increasing the tumour to rectal wall contrast ratio; it allows a good delineation of the lesion, resulting in an accurate tumour's staging without altering the CRM depiction. All patients showed good compliance to the rectal distention with air and moreover this procedure is inexpensive. In our hands this technique showed good correlation between preoperative MR staging and histopathological results, with an overall accuracy of 93.6%. In previous studies the agreement between MR and histology for T staging has ranged from 66% to 94% (9, 11, 19, 28). However the differentiation between intramural tumours and T3 borderline lesions was still a diagnostic problem. This is because it is often not possible to distinguish a true mesorectal tumour invasion from desmoplastic reaction or inflammatory peritumoral tissue that may or may not contain tumour cells. In our study the overstaging represented the main cause of errors, as four pT2 were interpreted as pT3 (Fig. 5). However, it has been suggested that this is not crucial for patient management (29, 30), as it is much more important to distinguish a borderline T3 lesion from an advanced T3 cancer with a potential involvement of the CRM (6, 20). Accordingly, T3 tumours form a heterogeneous group, not all T3 lesions would require a neoadjuvant therapy but only tumours at risk of CRM involvement, which represents the most powerful predictor for local recurrence (Figs. 3, 4). Further studies are needed to assess this matter.

A better technique for evaluating CRM is up for debate. The study published by Slater et al. (8) assesses that rectal distension reduces the distance between the rectal wall and the mesorectal fascia, suggesting that this procedure should be avoided; however this study was focused on comparing



A B C

Fig. 5. Borderline T3 rectal cancer.
High-resolution Turbo Spin Echo T2-weighted scans on sagittal **(A)**, axial **(B)** and coronal plane **(C)** show borderline T3-stage rectal neoplasm. Hypointense strands into mesorectum are difficult to characterize. Differentiation between mesorectal tumour infiltration and desmoplastic reaction is often unfeasible. Histological specimen detected pT2 neoplasm.

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CRM measurement at the same level in two groups of patients with and without rectal distension. The authors did not investigate whether that reduction would really influence the detection of an involved CRM in rectal cancer.

Pathologists consider any specimen showing tumour ≤ 1 mm from the mesorectal fascia as having a positive margin (2, 18), although the criteria of ≤ 2 mm (6) has been proposed as more reliable. It has been suggested that MRI with phased array surface coil can predict an uninvolved CRM with a distance of 1-2 mm between the lesion and the mesorectal fascia (10) or, in a more cautious approach, 5-6 mm distance (31).

In our study, a specimen with the inked CRM ≤ 1 mm distant from the tumour was regarded as having a positive CRM; because of rectal distension a cut-off distance of 2 mm was considered essential for MR to predict a clear margin, according to other authors who use a similar technique (11). A cut off distance of 5-6 mm is not a suitable criterion using rectal distension, as many cases would be classified as involved CRM. Even though the luminal insufflation can induce some mesorectal compression, the results we obtained with an overall MRI accuracy of 94.5% in predicting the CRM status, showed that such evaluation is not compromised by rectal distention. The two false -positives that occurred in anterior located tumours, were due to the thin adipose tissue in the perirectal anterior site that can lead to a misinterpretation of a tumour-free margin. One false-negative occurred in a low rectal cancer due to the gradual tapering of the mesorectal tissue. It has been pointed out that the MR accuracy in predicting the CRM involvement in lower tumours decreases due to technical difficulties in the anatomical evaluation of this region (32).

No improvement in predicting the regional lymph nodes involvement was achieved. Our results were comparable to other studies performed without rectal distention. To date, there is no imaging modality that can evaluate the lymph node status with a clinically relevant degree of accuracy.

Actually, the optimal and standardized criteria to define local lymph-node metastatic involvement have not yet been established as highlighted in a recent meta-analysis that included 21 articles (33). Considering that our study mainly focused on T staging and CRM evaluation, the use of lymph-nodes size as the only criteria for the diagnosis of nodal metastasis was an acceptable proposal. Our results showed a sensitivity of 85.7%, comparable to studies that used other criteria.

There is one limitation in our study because no comparison between patients without and with rectal distention has been made.

In summary, the preoperative evaluation of primary rectal cancer is still a topic of great interest among surgeons, oncologists, radiologists and pathologists, because there are many points to consider in order to achieve the correct management of the patient. An accurate preoperative staging is therefore essential. MRI with phased array surface coil performed with rectal lumen distention, has proved to be an effective technique both for rectal cancer staging and for predicting an involved CRM. The detection of a potentially involved margin is not affected by rectal insufflation. MRI represents an accurate diagnostic tool to help the clinician in order to select patients who may benefit from neoadjuvant therapy and to avoid overtreatment in those patients who can proceed directly to surgery.

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