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CLINICAL INVESTIGATION **Rectum**

EVALUATING MESORECTAL LYMPH NODES IN RECTAL CANCER BEFORE AND AFTER NEOADJUVANT CHEMORADIATION USING THIN-SECTION T2-WEIGHTED MAGNETIC RESONANCE IMAGING

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Purpose: To apply thin-section T2-weighted magnetic resoance imaging (MRI) to evaluate the number, size, distribution, and morphology of benign and malignant mesorectal lymph nodes before and after chemoradiation treatment compared with histopathologic findings.

Methods and Materials: Twenty-five patients with poor-risk adenocarcinoma of the rectum treated with neoadjuvant chemoradiation were evaluated prospectively. Thin-section T2-weighted MR images obtained before and after chemoradiation treatment were independently reviewed in consensus by 2 expert radiologists to determine the tumor stage, nodal size, nodal distribution, and nodal stage. Total mesorectal excision surgery after chemoradiation allowed MR nodal stage to be compared with histopathology using κ statistics. Nodal downstaging was compared using the Chi-square test.

Results: Before chemoradiation, 152 mesorectal nodes were visible (mean, 6.2 mm; 100 benign, 52 malignant) and 4 of 52 malignant nodes were in contact with the mesorectal fascia. The nodal staging was 7/25 N0, 10/25 N1, and 7/25 N2. After chemoradiation, only 29 nodes (mean, 4.1 mm; 24 benign, 5 malignant) were visible, and none were in contact with the mesorectal fascia. Nodal downstaging was observed: 20/25 N0 and 5/25 N1 ($p < 0.01$, Chi-square test). There was good agreement between MRI and pathologic T-staging ($\kappa = 0.64$) and N-staging ($\kappa = 0.65$) after chemoradiation.

Conclusions: Neoadjuvant chemoradiation treatment resulted in a decrease in size and number of malignant- and benign-appearing mesorectal nodes on MRI. Nodal downstaging and nodal regression from the mesorectal fascia were observed after treatment. MRI is a useful tool for assessing nodal response to neoadjuvant treatment.

Magnetic resonance imaging, Rectal cancer, Lymph nodes, Neoadjuvant, Chemoradiation.

INTRODUCTION

Neoadjuvant chemoradiation in patients with rectal cancer aims to downsize and downstage tumor and nodal disease before surgery (1, 2), to reduce the risk of a tumor positive circumferential surgical margin and local disease recurrence. However the degree of nodal downstaging is impossible to determine based on histopathology alone, as the true pathologic stage cannot be ascertained before treatment. Indirect evidence that nodal regression occurs has been from observing the mean nodal count at histopathology (3) and magnetic resonance imaging (MRI) (4) after treatment. More recently, nodal regression grading at histopathology has been proposed as a method of assessing nodal response (5). However distinguishing residual nodal tissue from satellite tumor deposits can be challenging, and complete nodal regression may be overlooked at pathology.

Thin-section MRI is now used to identify rectal cancer patients with poor prognostic features that would benefit from neoadjuvant chemoradiation (6). MRI can accurately stage rectal tumors as well as assess the relationship of tumor and lymph nodes to the mesorectal fascia (7–9). Although transrectal sonography is still widely used for local staging of rectal cancer, MRI imaging has been shown to be more cost- and clinically effective compared with digital rectal examination and endorectal ultrasound by selecting appropriate patients for neoadjuvant therapy (10). Hence MRI can be recommended for the local staging of rectal cancers. Positron emission tomography (PET) using 18-flurodeoxyglucose

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tracer is applied to evaluate metastatic or recurrent disease (11), but its role in assessing mesorectal nodes is not clearly defined. In addition avid tracer uptake by the primary tumor can obscure visualization of mesorectal nodes that lie close to the primary tumor, leading to false-negative results (12).

From pathologic studies, complete response of primary rectal tumor has been observed to be 20% to 30% (13, 14) after chemoradiation. There is usually accompanying reduction in the number of malignant and nonmalignant nodes recovered from the surgical specimen (3). Interesting the response of the primary tumor frequently parallels that of the nodal response (14).

T2-weighted MRI is useful in demonstrating downsizing and downstaging of primary rectal tumor after chemoradiation (4, 6). Using computed tomography (CT) imaging, nodal downstaging reportedly occurs in up to 60% (15). However the effects of neoadjuvant chemoradiation on mesorectal lymph nodes have not been specifically investigated using MRI. In addition to nodal staging, thin-section MRI performed before and after chemoradiation provides an opportunity to observe changes in the number, size, distribution, and morphology of mesorectal lymph nodes. Accurate noninvasive MRI assessment of regression of poor-prognosis stage N2 disease to N0 or N1 can indicate effective therapy. Furthermore the demonstration of nodal as well as tumor regression away from the mesorectal fascia/potential circumferential resection margin (CRM), can also help to predict a favorable surgical outcome.

Thus the aim of this study was to apply thin-section T2-weighted MRI to evaluate the number, size, distribution, and morphology of radiologically benign and malignant mesorectal lymph nodes before and after chemoradiation treatment compared with histopathology findings.

METHODS AND MATERIALS

The study was approved by the scientific review and the ethics committee at our institution. Written consent was obtained from all patients before the study.

Study population

Twenty-five patients with adenocarcinoma of the rectum who were candidates to receive neoadjuvant chemoradiation treatment in our institution were prospectively evaluated in this study (6). The clinical eligibility criteria were as follows: MRI-defined, poor-risk, histologically proven adenocarcinoma of the rectum; no previous chemotherapy or radiotherapy; no evidence of metastatic disease on clinical examination and CT of the chest, abdomen, and pelvis; World Health Organization performance status 0 to 2; and adequate hematologic (white blood cell count $>3 \times 10^9$/L, neutrophil $>1.5 \times 10^9$/L, and platelet $>100 \times 10^9$/L), renal (serum creatinine $1\times$ upper limit of normal or calculated creatinine clearance >50 ml/min), and liver function (serum bilirubin $<1.5\times$ upper limit of normal).

Patients were considered to have poor-risk disease on the basis of high-resolution, thin-slice (3-mm) MRI of the pelvis. The MRI criteria for poor-risk disease were: tumor extending to within 1 mm of or beyond the mesorectal fascia (*i.e.,* CRM involved or threatened), T3 low-lying tumor at or below the levators, tumor extending 5 mm or more into perirectal fat, tumor invading surrounding structures or peritoneum (T4), and T1-4N2 tumors. Patients with contraindications to MR scanning were excluded.

MR examination

Magnetic resonance imaging was performed using thin-section (3-mm) high–spatial resolution, T2-weighted technique on 1.5-T MR systems (Siemens Vision, Erlangen, Germany; Philips Intera, Best, The Netherlands) before and within 6 weeks after chemoradiation treatment.

At each study, T2-weighted sagittal images (TR >5,000 ms, TE = 128 ms, ETL = 16, 3-mm thickness, 350-cm FOV, 512×512 matrix, NEX = 3, scan duration = 4 min) of the rectum were first obtained to enable planning of the axial sections. Contiguous T2-weighted, axial 3-mm images of the pelvis (TR >5000 ms, TE = 128 ms, ETL=16, 3-mm thickness, 185-mm FOV, 256×256 matrix, NEX = 3, scan duration = 3–12 min) were acquired in a plane perpendicular to the rectal wall, from the anorectal junction along the length of the mesorectum. Coronal imaging was also performed parallel to the anal canal using similar scan parameters as the axial imaging.

Therapeutic regimen

Neoadjuvant chemotherapy. A 12-week course of neoadjuvant chemotherapy was administered. Oxaliplatin (130 mg/m^2) was delivered every 3 weeks, and capecitabine was administered orally at a dose of 2,000 mg/m^2/d divided into two split doses for 14 days followed by 7 days of rest repeated every 3 weeks.

Synchronous chemoradiation. On completion of 12 weeks of neoadjuvant chemotherapy, patients were treated with chemoradiation. Radiotherapy was delivered by a two-phase technique; both phases were conformally planned using CT. Phase 1 delivered a total of 45 Gy in 25 daily fractions and encompassed the primary tumor and pelvic lymph nodes. During phase 2, the aim was to deliver 9 Gy in five fractions covering the tumor, either clinically palpable or visible on imaging, with a 2-cm margin in all directions. Patients received concomitant capecitabine at a reduced dose of 1,650 mg/m^2/d continuously without interruption. If patients already had dose reduction to capecitabine during neoadjuvant chemotherapy, the same proportional dose reduction was made during synchronous radiotherapy.

Surgery. Total mesorectal excision was performed 6 weeks after the completion of chemoradiotherapy. The final choice of surgical procedure (abdomino-perineal or anterior resection) was made by the surgeon.

Image interpretation

All images were assessed by in consensus by two radiologists (D.M., G.B.) who have more than 10 years experience in body MRI. The images were reviewed blinded to the pathologic and surgical findings. The studies before and after neoadjuvant chemoradiation treatment were assessed separately. At each imaging review, the following were recorded.

Tumor stage. The TNM T-stage of the tumor as assessed by MRI was recorded.

Nodal number and size. The total number of lymph nodes identified in each patient was recorded. The maximum short axis diameter of each node was measured on a workstation (e-film, Merge Healthcare, Milwaukee, WI).

Nodal distribution. The position of each node was recorded as below the inferior tumor margin, at the level of the tumor, or above the superior border of the tumor.

Nodal status and stage. Each node identified at MRI was determined to be malignant or nonmalignant using morphologic criteria (16, 17). Such criteria have been shown to be more accurate than size measurement in discriminating between malignant and nonmalignant lymph nodes. A node was considered to be malignant if it showed irregular outlines or internal signal heterogeneity (16). The nodal stage on a patient-by-patient basis was also recorded using the TNM classification system as N0 (no malignant nodes), N1 (one to three malignant nodes), or N2 (four or more malignant nodes).

After the analysis of the pretreatment and posttreatment images was completed, all the images were reviewed together (by D.M., G.B.) to enable matching of the individual mesorectal nodes. Nodes that were visible pretreatment but no longer visible post-treatment were deemed to have completely regressed. By comparing results of the pre- and post-treatment T2-weighted MR images, the frequency of tumor and nodal stages on a per-patient basis was computed before and after treatment.

Radiologic–pathologic comparison

After total mesorectal excision surgery, the surgical specimen allowed the MR tumor (T) and nodal stage (N) after chemoradiation to be directly compared with the histopathologic T and N staging.

Statistical analysis

All statistical analysis was performed using MedCalc for Windows, version 9.2.0.0 (MedCalc Software, Mariakerke, Belgium). The agreement between post-treatment MRI and histologic T-staging was compared using κ statistics.

The nodal size before and after chemoradiation was compared using the Student's t test. The distribution of MR nodal stage before and after chemoradiation treatment was compared using the Chi-square test. The degree of agreement between post-chemoradiation MRI and histologic nodal stage was assessed using κ statistics. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of MRI in determining the post-chemoradiation nodal stage were computed. A p value of <0.01 was considered statistically significant for all analyses.

RESULTS

Tumor stage

Before chemoradiation, 2 of 25 patients had Stage T2 tumor, 19 of 25 had Stage T3 tumor with 5 mm or greater extramural disease extension, and 4 of 25 patients had Stage T4 disease by MRI assessment. The disease was located in the lower rectum in 5 of 25 patients, mid-rectum in 11 of 15, and upper rectum in 9 of 25. The mean length of the tumor was 48 mm (95% CI, 39–56 mm). The tumor morphology was polypoidal in 6 of 25 patients and annular in 19 of 25.

After chemoradiation, there was downward migration in the T-stage of tumors on MRI as follows: 6 of 25, T0; 3 of 25, T1; 3 of 25, T2; 12 of 25, T3; and 1 of 25, T4. Comparison of the T-staging by MRI after chemoradiation with the pathologic T-staging indicated that there was good agreement (Table 1) (weighted $\kappa = 0.64$).

Table 1. Agreement in the local T-staging of tumor after chemoradiation treatment by magnetic resonance imaging (MRI) compared with histopathology

		Histopathology					
		T0	T1	T2	T3	T4	
MR imaging	T0	3	1	1	1	0	6
	T1	1	1	1	0	0	3
	T2	1	0	1	1	0	3
	T3	1	0	1	10	0	12
	T4	0	0	0	0	1	1
		6	2	4	12	1	25

Weighted $\kappa = 0.64$.

Nodal number and size

A total 152 nodes were visible at MRI before chemoradiation. The mean maximum short-axis diameter of these nodes on T2-weighted MRI was 6.2 mm (95% CI, 5.9–6.6 mm; range, 3–21 mm). After chemoradiation only 29 nodes were visible at MR imaging with a mean maximum short axis diameter of 4.1 mm (95% CI, 3.5–4.6 mm, range, 2–6 mm). Mesorectal nodes visible on MRI were measurably smaller in diameter after chemoradiation treatment ($p = 0.002$, Student's t test).

Nodal distribution

Before chemotherapy, 93 of 152 (62.5%) of mesorectal nodes were found at the level of the tumor, with another 26 of 152 (17%) found within 2 cm proximal of the tumor. In all, 149 of 152 nodes (98%) were found at or within 5 cm proximal of the tumors. Only 3 of 152 nodes (2%) were found below the distal tumor margin.

After chemoradiation, the majority of mesorectal nodes (20 of 29, 69%) were found at the level of the tumor, with another 4 of 29, 14%) found within 2 cm proximal to the tumor. All visible nodes at T2-weighted MRI were located at or within 5 cm proximal to the tumor. No nodes were visible below the distal tumor margin.

Nodal status and nodal stage

Of the 152 mesorectal nodes detected at baseline MRI, 100 appeared benign and 52 appeared malignant based on morphologic criteria. Of the 52 malignant nodes, four were found to be in contact with the mesorectal fascia at MRI. On a per-patient basis, the nodal stage was as follows: N0 (7/25), N1 (10/25), and N2 (7/25).

After chemoradiation, only 29 mesorectal lymph nodes were visible at T2-weighted MRI (Fig. 1). Of these, 24 appeared benign and five were malignant by morphologic criteria. There was nodal downstaging on a per-patient basis: N0 (20/25) and N1 (5/25) ($p < 0.01$, Chi-square test). In four cases of MR determined N1 disease, there was MR evidence of residual Stage T3 disease at the site of tumor.

All four malignant nodes that were in contact with the mesorectal fascia completely regressed after treatment (Fig. 2). None of the nodes visualized after chemoradiation treatment was in contact with the mesorectal fascia. Three malignant nodes showed increased in T2 signal intensity after chemoradiation, in keeping with mucinous change (Fig. 3), which was confirmed at histopathology.

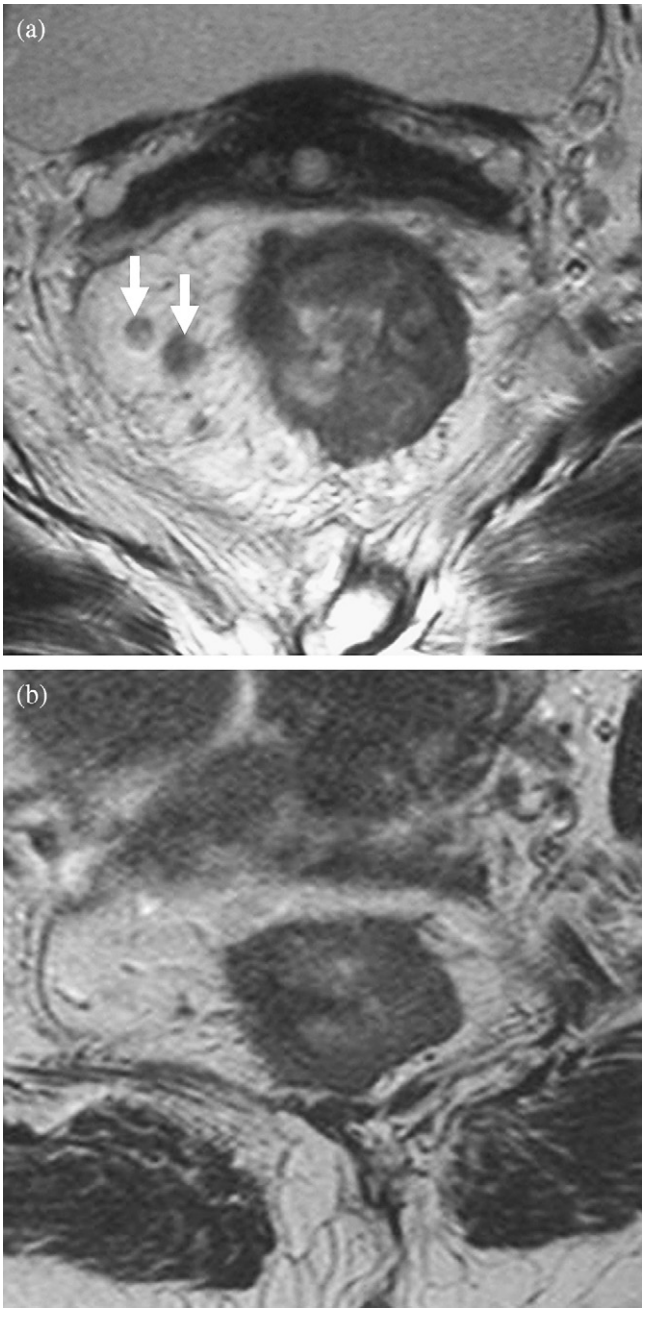

Fig. 1. Nodal downstaging after chemoradiation. (a) Pretreatment T2-weighted magnetic resonance image showing several malignant nodes in the right mesorectum (arrows) and a polypoidal mass in the mid-rectum. (b) After chemoradiation treatment, there was downsizing of the primary tumor. In addition, the malignant nodes demonstrated on the pretreatment imaging showed complete regression. The nodal status was found to be N0 after surgery.

After chemoradiation treatment, all patients underwent surgery which enabled the post-treatment MR nodal stage to be compared with pathologic nodal stage. There was good agreement between the pathologic and the MR nodal stage after chemoradiation treatment on a per patient basis using morphologic criteria ($\kappa = 0.65$; 95% CI, 0.28–1.0) (Table 2). Compared with histopathology, MR imaging had 67% (95% CI, 24–94%) sensitivity, 95% (71–99%) specificity, 80% (30–99%) PPV, 90% (67–98%) NPV and 88% (70–96%) accuracy in detecting nodal disease after neoadjuvant treatment. All patients with residual nodal disease (N1) at pathology also showed pathologic evidence of residual disease at the site of primary tumor (5/6 T3, 1/6 T2).

DISCUSSION

By assessing the nodal morphology at MRI, malignant nodes can be detected with a greater degree of sensitivity (85%; 95% CI, 74–92%) and specificity (97%; 95% CI, 95–99%) compared with nodal size measurement (16), and this was

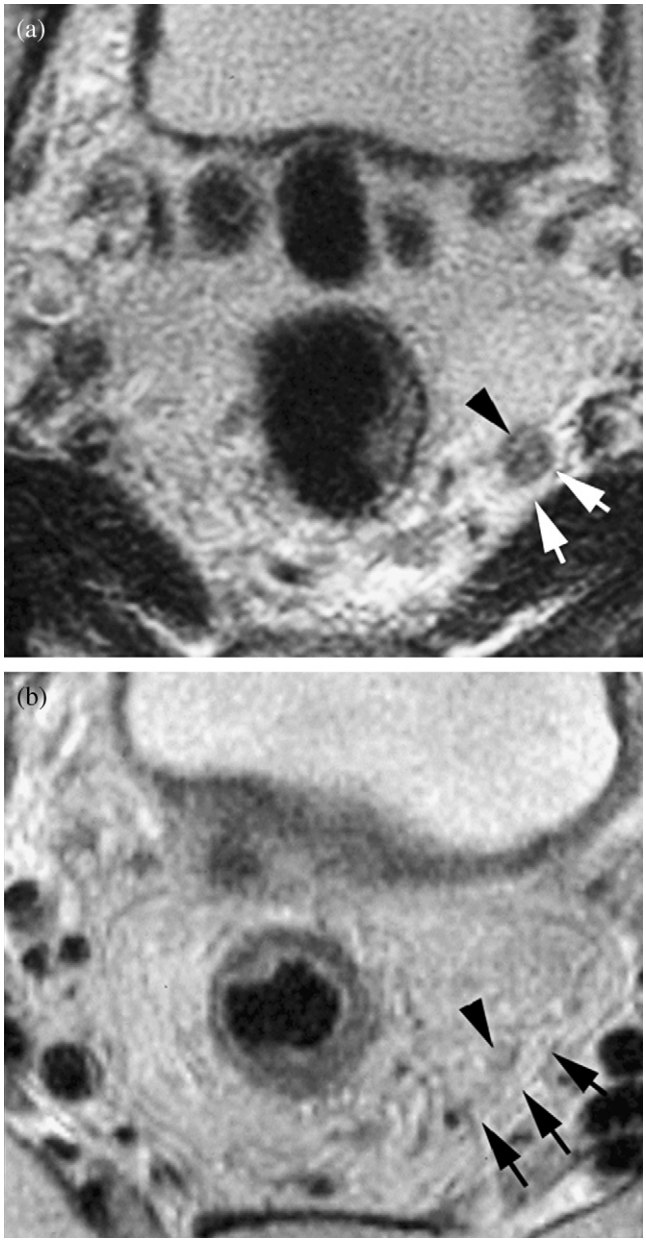

Fig. 2. Regression of lymph node from the mesorectal fascia. (a) Pretreatment T2-weighted magnetic resonance image showing a malignant node (arrowhead) with heterogeneous signal intensity and irregular outline in the left mesorectum close to the mesorectal fascia (arrow). (b) After chemoradiation treatment, there was regression of the node (arrowhead) from the mesorectal fascia (arrow).

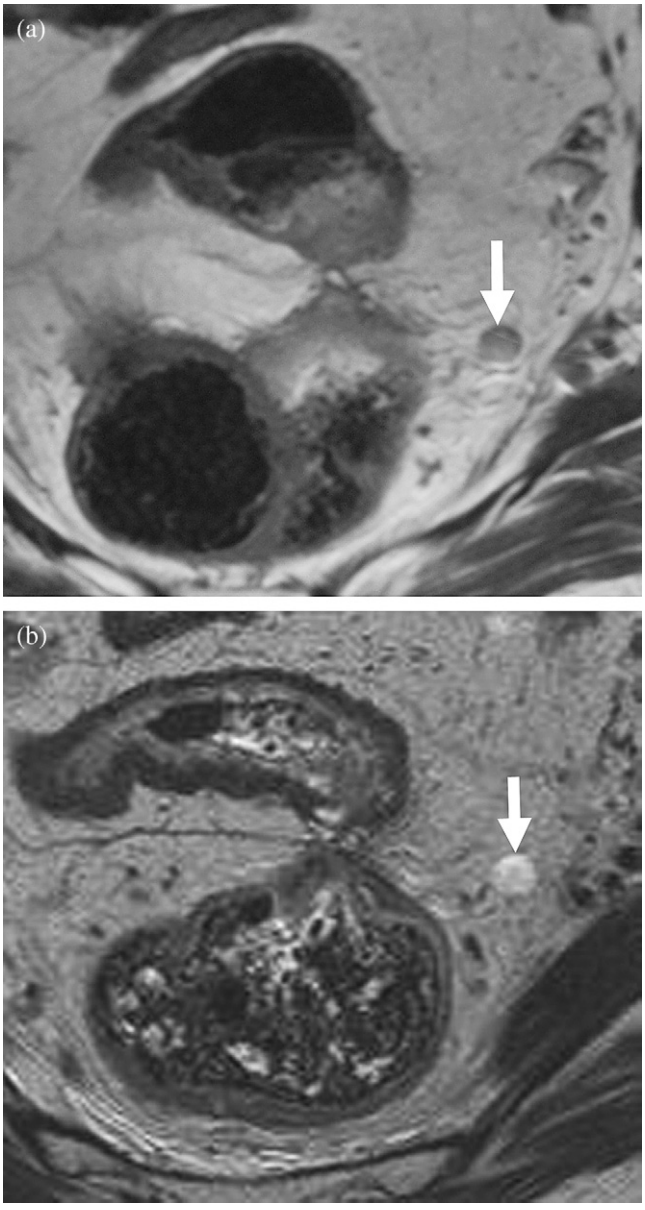

Fig. 3. Mucinous change after chemoradiation treatment. (a) Pretreatment T2-weighted image showing a malignant stricture of the rectosigmoid with a heterogeneous lymph node in the left mesorectum (arrow). (b) After chemoradiation treatment, the node returns uniform high signal intensity, indicating mucinous change (arrow).

applied in our study as the basis for discriminating between malignant and nonmalignant nodes.

In our study we found that the application of chemoradiation treatment resulted in a reduction in the size and number of both benign and malignant mesorectal lymph nodes observed at MR imaging. Interestingly the majority of nodes that regressed completely after chemoradiation treatment were initially benign appearing.

Nodal regression after chemoradiation was found to be associated with nodal downstaging on a per-patient basis. After treatment, there was downward nodal stage migration, with the majority of patients becoming Stage N0 and some Stage N1. Interestingly, no patient was found to have Stage N2

Table 2. Agreement in the local T-staging of tumor after chemoradiation treatment by magnetic resonance imaging (MRI) compared with histopathology.

		Histopathology nodal stage		
		N1	N0	
MR nodal stage	N1	4	1	5
	N0	2	18	20
		6	19	25

$\kappa = 0.65$.

disease after chemoradiation, and this observation was confirmed at histopathology. There was good agreement ($\kappa = 0.65$) between the pathologic and the MR nodal staging of disease after chemoradiation Furthermore MRI was found to have a high diagnostic accuracy for nodal stage after chemoradiation compared with histopathology.

In parallel with nodal downstaging, we observed that there was accompanying downstaging of the primary rectal tumors with chemoradiation. There was also good agreement in the MR assessment of the tumor pathologic stage after chemoradiation with histopathology (weighted $\kappa = 0.65$). These findings indicate the effectiveness of chemoradiation treatment in inducing both tumor and nodal regression, and suggest that MR imaging may be an appropriate tool to monitor the effects of treatment *in vivo*. However, despite the radiologic evidence of disease downsizing and downstaging, it is yet unclear how such response may be translated to disease survival. Clearly, follow-up of such a cohort of patient would be needed to evaluate long-term outcome and would provide valuable insights into the effectiveness of such a treatment.

Thin-section (3-mm) T2-weighted imaging enables clear visualization of primary tumor, satellite tumor deposits, or malignant lymph nodes that lie in close proximity to the mesorectal fascia, which may prompt the administration of neoadjuvant operative chemoradiation treatment with the aim of reducing the risk of a tumor-positive CRM. Mesorectal lymph nodes can be localized to less than 2 mm of the mesorectal fascia by *in vivo* MR imaging (9). Admittedly only a small percentage of malignant nodes are found in such close proximity to the mesorectal fascia, this being observed in only 4 of 152 cases (3%) in our study. However confidence in identifying such nodes would allow consideration for neoadjuvant treatment to induce tumor and nodal regression away from the mesorectal fascia, to minimize the risk of tumor-positive CRM at surgery. Indeed, all malignant-appearing nodes that were found in contact with the mesorectal fascia in our study regressed completely after chemoradiation treatment and were associated with a tumor-free R0 resection at surgery.

In terms of nodal distribution, we found that the majority of mesorectal nodes, after chemoradiation treatment, were located at the level of the tumor, with the rest of the remaining nodes seen just proximal to the tumor. This parallels the findings of the nodal distribution in patients reported before chemoradiation treatment (9).

A change in the morphologic appearance of mesorectal lymph nodes could also result from chemoradiation. Three malignant nodes in 3 patients demonstrated uniform high signal intensity after chemoradiation treatment, in keeping with mucinous change, findings that were confirmed on histopathology. In fact it has been shown that the identification of mucinous deposits in lymph nodes after chemoradiation with no viable tumor cells may be taken as evidence of lymph node downstaging (18).

Another interesting observation in our study was that after chemoradiation all the malignant nodes were identified in patients who still showed evidence of residual primary disease (T3/ T2) at histopathology. This observation is consistent with previously reported finding from pathologic study that patients with Stage T1 or T0 after chemoradiation treatment were not usually associated with nodal disease (19).

There were several limitations to this study. First, node-by-node correlation was not performed this study. Nevertheless we demonstrated good agreement between the MR determined nodal stage on a per-patient basis after chemoradiation and the histopathologic nodal stage. Second, it was not possible to verify definitively the nodal status of patients before chemoradiation. However morphologic criteria rather than size criteria were used this study, which should improve nodal staging accuracy over the conventional size criteria widely used for other imaging studies. Third, despite demonstrating nodal and tumor downstaging and downsizing after chemoradiation, it is unclear as yet how this may translate to better patient outcomes. Future studies should be planned to address this issue.

CONCLUSION

In conclusion, neoadjuvant chemoradiation treatment results in a decrease in size and number of benign and malignant mesorectal lymph nodes. Treatment also results in downstaging of nodal disease and regression of malignant nodes from the mesorectal fascia, which can be observed *in vivo* by thin-section T2-weighted MRI. Hence MRI is a useful tool for assessing nodal response to neoadjuvant treatment.

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