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Pelvic MRI after induction chemotherapy and before long-course chemoradiation therapy for rectal cancer: What are the imaging findings?

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Abstract

Objectives To determine the appearance of rectal cancer on MRI after oxaliplatin-based chemotherapy (ICT) and make a preliminary assessment of MRI's value in predicting response to total neoadjuvant treatment (TNT).

Methods In this IRB-approved, HIPAA-compliant, retrospective study between 1 January 2010–20 October 2014, pre- and post-ICT tumour T2 volume, relative T2 signal intensity (rT2SI), node size, signal intensity and border characteristics were assessed in 63 patients (65 tumours) by three readers. The strength of association between the reference standard of histopathological percent tumour response and tumour volume change, rT2SI and lymph node characteristics was assessed with Spearman's correlation coefficient and Wilcoxon's rank sum test. Cox regression was used to assess association between DFS and radiological measures.

Results Change in T2 volume was not associated with TNT response. Change in rT2SI showed correlation with TNT response for one reader only using selective regions of interest (ROIs) and borderline correlation with response using total volume ROI. There was a significant negative correlation between baseline and post-ICT node size and TNT response (r = -0.25, $p = 0.05$; r = -0.35, $p = 0.005$, readers 1 and 2, respectively). Both baseline and post-induction median node sizes were significantly smaller in complete responders ($p = 0.03$, 0.001; readers 1 and 2, respectively). Change in largest baseline node size and decrease in post-ICT node signal heterogeneity were associated with 100% tumour response ($p = 0.04$). Nodal sizes at baseline and post-ICT MRI correlated with DFS.

Conclusion In patients undergoing post-ICT MRI, tumour volume did not correlate with TNT response, but decreased lymph node sizes were significantly associated with complete response to TNT as well as DFS. Relative T2SI showed borderline correlation with TNT response.

Key Points

- *MRI-based tumour volume after induction chemotherapy and before chemoradiotherapy did not correlate with overall tumour response at the end of all treatment.*
- *Lymph node size after induction chemotherapy and before chemoradiotherapy was strongly associated with complete pathological response after all treatment.*
- *Lymph node sizes at baseline and post-induction chemotherapy MRI correlated with disease-free survival.*

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Keywords Rectal cancer · Chemotherapy · MRI · Total neoadjuvant treatment

Abbreviations

CapeOX	Capecitabine-oxaliplatin
CRT	Chemoradiotherapy
DCE-MRI	Dynamic contrast-enhanced sequences
DFS	Disease-free survival
DWI	Diffusion-weighted imaging
FOLFIRINOX	5-Fluorouracil-irinotecan-oxaliplatin
FOLFOX 5	5-Fluorouracil-leucovorin-oxaliplatin
ICT	Upfront chemotherapy ('induction')
IQR	Interquartile range
mrTRG	Magnetic resonance tumour regression grade
pCR	Pathological complete response
rT2SI	Relative T2 signal intensity
TME	Total mesorectal excision
TNT	Total neoadjuvant treatment
XELOX	Xeloda-oxaliplatin

Introduction

Pelvic MRI has proven value in the assessment of response to multimodality treatment for locally advanced rectal cancer, which consists of chemoradiotherapy (CRT) followed by surgery and postoperative ('adjuvant') chemotherapy [1, 2]. Imaging evaluations are performed at baseline and again after CRT. However, some institutions have moved to the administration of total neoadjuvant treatment (TNT), which includes upfront chemotherapy ('induction'; ICT) before CRT followed by total mesorectal excision (TME) [3]. Induction chemotherapy was added as an option for treatment in 2015 for stages II/III rectal cancer and is included in the 2017 National Comprehensive Cancer Network (NCCN) guidelines, but is not included in the European Society for Medical Oncology (ESMO) guidelines at this time [4, 5]. While much has been published on MRI response appearances and criteria after CRT, there is a paucity of published material on post-ICT MRI appearances [6, 7].

Such findings as tumour downsizing with scar formation and nodal downsizing and disappearance have prognostic value when noted on post-CRT MRI [1, 8]. Recently, induction chemotherapy has been shown to confer advantages over adjuvant chemotherapy such as better patient tolerance and earlier targeting of micrometastases. A trial from our institution [3] showed excellent rates of tumour regression, administration of planned therapy and attainment of pathological complete responses. Although few centres use the induction treatment paradigm, it has become the preferred treatment option at Memorial Sloan Kettering Cancer Center (MSKCC) over the past decade, and MRI, in addition to endoscopy, is frequently performed to monitor patients' responses.

Given the growing use of TNT as a favourable strategy, and the potential to intervene earlier in the treatment course if interim imaging offered relevant information, we undertook this investigation with the hypothesis that MRI after chemotherapy only (ICT) would offer prognostic information for subsequent response to all treatment (TNT) that could potentially inform management decisions. We found a paucity of published material on MRI appearances after chemotherapy alone, and thus the purpose of our study was to determine the appearance of primary rectal cancer and lymph nodes on MRI after 5-fluorouracil-leucovorin-oxaliplatin (FOLFOX)-based induction chemotherapy (ICT) and to make a preliminary assessment of the value of post-ICT MRI in predicting response to total neoadjuvant treatment (TNT).

Materials and methods

Patients

This HIPPA-compliant, IRB-approved, retrospective study, was issued a waiver of the need for patient consent, and no author reported a conflict of interest. A computerised search was conducted to identify consecutive patients with newly diagnosed locally advanced rectal cancer who underwent a rectal MRI examination between 1 January 2010 and 20 October 2014 and who also received oxaliplatin chemotherapy in that time frame. The start date for the search was chosen because it reflects the time-frame when administration of ICT and MRI evaluation of response to this treatment became more frequent in this institution. The search yielded 257 patients. A radiological computerised search was performed on this group to isolate consecutive patients with at least three rectal MRIs, ensuring identification of patients reimaged after induction therapy, as many patients were evaluated at baseline and then only after chemoradiation and so received only two MRIs. This search yielded 164 patients. A search of the hospital clinical information system was conducted to confirm at least 75% administration of the induction chemotherapy regimen prior to the follow-up rectum MRI. After consultation with our medical oncology service, this was deemed to reflect the minimum dosage at which overall treatment effect of the neoadjuvant chemotherapy was likely to be achieved. In total

101 patients were excluded, and 63 were included in the final cohort (Fig. 1). There were 36 males (mean age 58 years, range 31–81) and 27 females, (mean age 51 years, range 24–70).

Treatment

Oxaliplatin is the key component of 5-fluorouracil-leucovorin-oxaliplatin (mFOLFOX6) (oxaliplatin 85 mg/m^2 and leucovorin 400 mg/m^2, and fluorouracil 400 mg/m^2 day 1 with fluorouracil 1,200 mg/m^2/day constant IV infusion over 24 h days 1 and 2, every 2 weeks for eight cycles) and capecitabine-oxaliplatin (CapeOX) (oxaliplatin 100 mg/m^2 every 3 weeks with capecitabine 1,000–1,250 mg/m^2 twice daily 14 days on and 7 days off for five cycles), the routine induction chemotherapy regimens used at our institution.

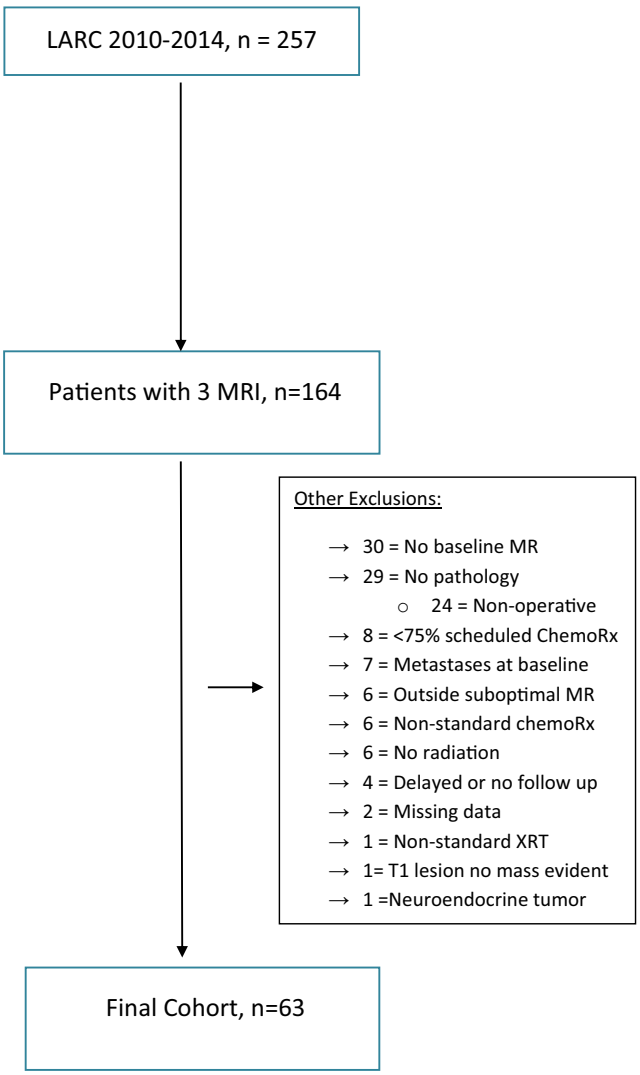

Fig. 1 Patient inclusion/exclusion flow chart

MRI performance

Rectal MRI examinations were performed on different MRI scanners manufactured by GE Healthcare at a field strength of 1.5 Tesla or 3 Tesla using a standardised MRI protocol that included standard high-resolution T2-weighted imaging in axial, sagittal, coronal and oblique orientation (TR: 4,400–5,000; TE: 90–110; echo train length: 12–24; slice thickness: 3–4 mm; interslice gap: 1 mm; FOV: 20 cm; matrix: 320 x 160; NEX: 2), an axial DW sequence (single-shot spin-echo EPI sequence, b-values: 0 and 750–1,000 s/mm^2; TR: 1,800–5,550 ms; TE: 60–112 ms; slice thickness: 3–5 mm; interslice gap: 1 mm; FOV: 18–40 cm; matrix: 96–256 x 96–128; NEX: 3–6; mean acquisition time: 2.4 min) and a sagittal DCE-MRI sequence (TR: 3.1–7.9 ms; TE: 0.9–4.2 ms; slice thickness: 4–10 mm; no interslice gap; FOV: 20–34 cm; matrix: 256–320 x 128–192; mean temporal resolution: 8.3 (5–11.5) s; 30–40 phases; mean acquisition time: 5.2 min). A bolus of Gd-DTPA (Magnevist, Bayer Schering) at a constant dose of 0.1 mmol/kg was power injected at a rate of 2 ml/s followed by a saline flush for all patients [9].

MRI interpretation

Pre- and post-induction MRI rectal examinations were reviewed independently by three board-certified radiologists with 2 years (DB), 5 years (IB) and 7 years (NC) experience reading rectal MRI, respectively, blinded to the histopathological reference standard. Readers interpreting post-ICT MRI were unblinded to baseline MRI. The following parameters were assessed by two readers (IB, NC) in the primary tumour: T2 volume (tumour volume = volume on every axial slice x [slice thickness +gap]) (Tera Recon, v.4.4.12.138) as well as relative T2 signal intensity (rT2SI) (signal intensity from representative tumour using approximately 1-cm circular region-of-interest (ROI)/circular 1-cm ROI obturator internus) [10]. (A subsequent estimation of rT2SI was performed by a third reader (DB), in a post-hoc analysis, using whole tumour volume SI on every slice, based on the differing results of the two readers using the 1-cm ROI methodology.) The three largest locoregional lymph nodes (mesorectal/superior rectal and obturator/internal iliac) were measured in maximum short-axis diameter and the presence or absence of heterogeneous node borders and heterogeneous internal nodal signal intensity was recorded [11, 12].

Statistical analysis

Percent tumour response at histopathology, a validated variant of tumour regression grade used at our institution, was the reference standard as reported in the electronic medical record by several specialist gastrointestinal pathologists with access to all clinical information and index tests [13, 14]. Change in

T2 volume and rT2SI as well as baseline, post-ICT and change in nodal size were tested for association with Spearman's correlation coefficient for percent fibrosis and with Wilcoxon rank sum test for complete response (100% fibrosis) versus incomplete response (<100% fibrosis). Presence of lymph node heterogeneity was tested for its association with percent tumour response using Wilcoxon's rank sum test and with Fisher's exact test for categorical response. The nonparametric intra-class correlation coefficient was calculated to assess agreement between T2 volume and lymph node size measures for two readers. Disease-free survival is defined as the time from the start of chemotherapy to recurrence or death, and is analysed using the Kaplan-Meier method. The log-rank test is used to compare disease-free survival between groups. Cox regression is used to assess association between DFS and radiological measures. All tests were evaluated for statistical significance at an alpha level of 0.05. Statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC, USA), except calculation of nonparametric intra-class coefficient, which was done using the nopaco package in R.

Results

Patient demographics

Of the 63 patients, 76% (48/63) were imaged after eight cycles of FOLFOX (range 0–26 days after cycle 8), 16% (10/63) were imaged after seven cycles (range 5–14 days after cycle 7) and 8% (5/63) were imaged after six cycles (range 6–13 days after cycle 6). Two patients underwent a full dose (five cycles) of CAPEOX (capecitabine plus oxaliplatin). Five patients had clinical stage II and 58 had clinical stage III rectal cancer (Table 1). All patients underwent chemoradiotherapy with 5,040 Gy and 5FU/leucovorin. There were 9/63 complete responses (14%). Incomplete responses ranged from 0% to 99%. The post-induction MRI was obtained within 30 days (median 8, range 0–26 days; unknown for two patients) after 75–100% of the intended chemotherapy regimen, before commencement of chemoradiation. No adverse events were recorded from MRI.

Disease-free survival

Disease-free survival curves are shown in Fig. 2. In the cohort of 63 patients, 12 experienced a disease recurrence (lung; n = 5, liver; n = 3, local; n = 2, bone, n = 1 and retroperitoneal lymph node; n = 1) and one died with no recurrence. Median follow-up time for recurrence-free survivors was 4.7 years (range: 1.3–7.4). Overall 4-year disease-free survival (DFS) was 82.3% (95% CI: 70.3–89.8). DFS was significantly worse by increasing cT-stage (log-rank p = 0.001; Fig. 2b). The highest stage group (T3/T4) had significantly worse DFS compared to the lowest stage (T0/TIS/T1) and middle stage (T2) groups (adjusted pairwise log-rank p = 0.001 and 0.04, respectively) and DFS was not significantly worse in the T2 group compared to the lowest stage group (p = 0.62). DFS was not significantly different by cN-stage (log-rank p = 0.45; Fig. 2c).

Table 1 Baseline, post-chemotherapy and pathological T and N stage

	Baseline	Post-chemotherapy	Pathological stage
T stage			
T0	0	11	10
TIS	-	-	3
T1	0	0	5
T1/2	2	10	-
T2	1	0	26
T2/3	5	5	-
T3	50	33	18
T4	5	4	1
N stage			
N0	5	21	45
N+	58	42	-
N1	-	-	13
N2	-	-	5

Reported for 63 patients. Two patients with two tumours each were staged once according to the highest stage tumour

Primary rectal tumour correlations with subsequent CRT response by pathology

T2 tumour volumetry and relative T2 signal intensity (rT2SI)

Summary values for tumour volume and rT2SI at baseline, post-chemotherapy and decrease from baseline to post-chemotherapy are given in Table 2. Radiological tumour volumes decreased after induction chemotherapy as measured by each reader and as expected. Readers showed excellent agreement for T2 volume measures at baseline (ICC = 0.90) and post-chemotherapy (ICC = 0.82). Nine patients had no measurable tumour after induction therapy and rT2SI with respect to the obturator muscle is based on 56 patients in total. Median decrease in absolute volume was greater for patients with higher T and N stage (Table 3).

There was no significant correlation between pathological tumour response and tumour volume change for either reader (Table 4). No significant correlation was also noted for patients with near complete response (90% and 95% tumour fibrosis). Change in rT2SI showed no correlation with percent tumour response on a continuous scale (Table 4). For tumour response

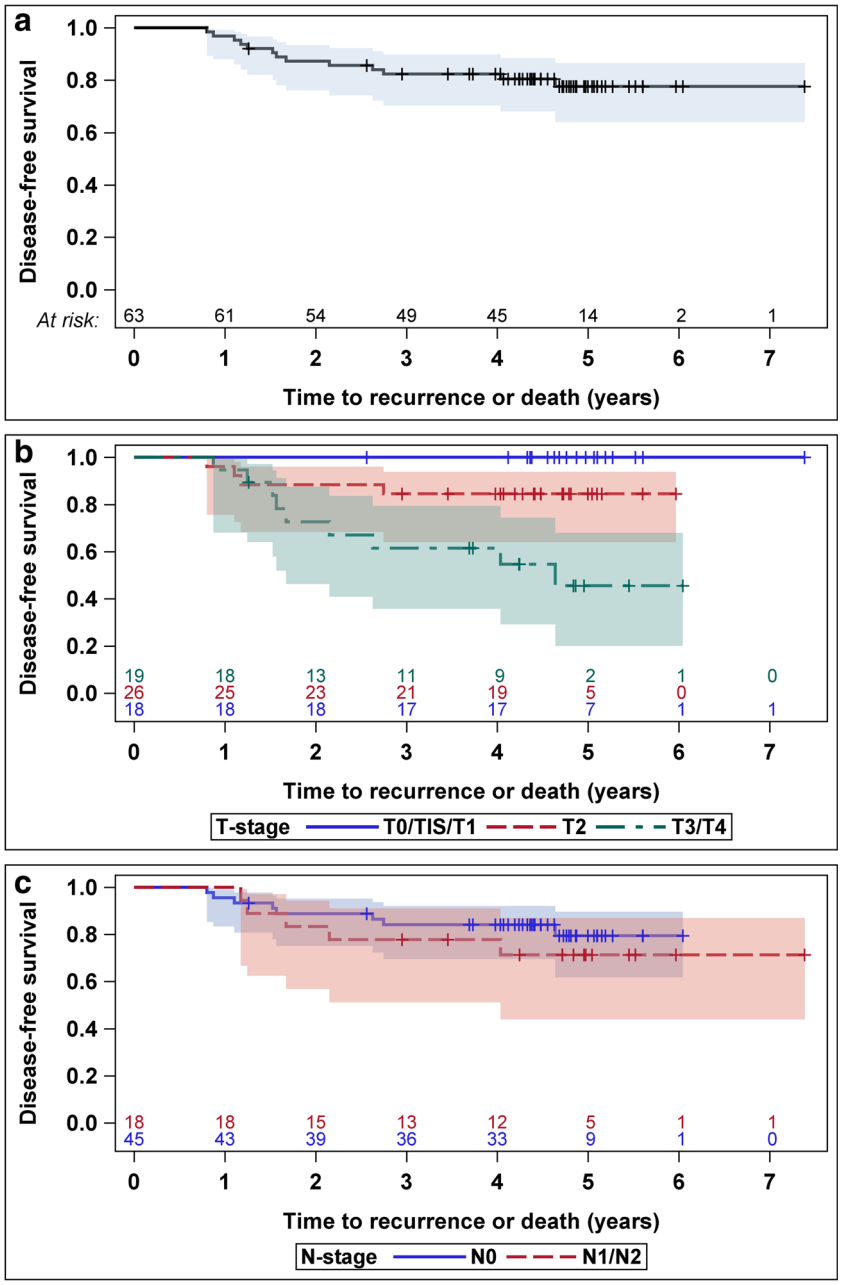

Fig. 2 Disease-free survival, overall and by pathological T and N stage. **a** Overall. **b** By pathological T stage. **c** By pathological N stage

categories, using the 1-cm selective ROI method, there was a significant decrease (3.92 vs. 0.23, $p = 0.04$) in rT2SI for those with and without complete response for reader 1. For reader 2 there was no correlation between signal change and percent tumour response. No significant correlation was also noted for patients with near complete response (90% and 95% tumour fibrosis). In the *post hoc* analysis, using the third reader and whole-volume ROI, however, patients with complete response had a borderline significantly larger decrease in rT2SI compared with those with incomplete response (median 1.60 vs. 0.12, $p = 0.05$). Change in volume was not significantly associated with DFS for reader 1 (HR for 1 cm^3 decrease: 0.98, 95% CI: 0.95–1.02, $p = 0.28$) nor for reader 2 (HR: 0.99, 95% CI: 0.96–1.03, $p = 0.68$), and change in rT2SI was not significantly associated with DFS (reader 3; HR for 1 unit decrease: 1.3, 95% CI: 0.94–1.72, $p = 0.12$).

Lymph node correlations with subsequent CRT response by pathology

Lymph node size

Lymph node size decreased after induction chemotherapy as measured by each reader. Readers showed good agreement for

Table 2 Rectal tumour measures at baseline, post-chemotherapy and change

	Baseline (IQR)	Post-chemotherapy (IQR)	Change Median decrease (IQR)
T2* volume (cm^3) (reader 1)	29.8 (17.2–49.9)	7.3 (3.9–15.5)	18.9 (8.2–33.9)
T2 volume (cm^3) (reader 2)	29.7 (15.1–42.7)	4.9 (2.0–9.7)	19.6 (9.3–32.2)
rT2SI^ (reader 3)	2.65 (2.22–3.13)	2.33 (1.79–2.67)	0.37 (-0.36–1.20)

*T2-weighted MR imaging

^ Relative T2 signal intensity

lymph node size measures at baseline (ICC = 0.69) and post-chemotherapy (ICC = 0.68).

For one reader, baseline lymph node size showed a borderline negative correlation with tumour response on a continuous scale (rho = -0.25, $p = 0.05$; Table 5). Both readers found that baseline lymph node size was significantly smaller for complete responders (median 4–5 mm vs. 7 mm; $p = 0.001$ and 0.004). One of the readers also found that baseline lymph node size was significantly smaller for near complete responders (95% fibrosis; median 5 mm vs. 7 mm; $p = 0.05$).

Smaller post-chemotherapy lymph nodes were associated with a larger percent tumour response (Spearman correlation coefficient: -0.35 and -0.29; $p = 0.005$ and 0.02, respectively) and both readers found that patients with complete response had smaller post-chemotherapy lymph nodes (median 3 mm vs. 5 mm). Both readers also found that patients with near complete response (95% fibrosis) had smaller post-chemotherapy lymph nodes (median 4 mm vs. 5 mm; $p = 0.03$ and 0.009, respectively).

Change in lymph node size did not correlate with percent tumour response on a continuous scale for either reader; however, for reader 1, the change in size of the largest lymph node was borderline significantly different between complete and incomplete responders (median 1 mm vs. 3 mm; $p = 0.05$).

Larger pre-chemotherapy lymph nodes were significantly associated with an increased hazard in DFS for both readers (HR (95% CI) per 1 mm^3 increase for reader 1: 1.07 (1.01–1.1.3), $p = 0.02$; reader 2:1.09 (1.02–1.17), $p = 0.009$) as were larger post-chemotherapy nodes (HR (95% CI) for reader 1:1.19 (1.004–1.41), $p = 0.04$; reader 2: 1.21 (1.03–1.41), $p = 0.02$). Change in lymph node size was significantly associated with DFS for reader 1 (HR (95% CI): 1.14 (1.02–1.28), $p = 0.02$) and not significantly associated for reader 2 (HR (95% CI): 1.09 (0.99–1,19), $p = 0.06$).

Lymph node border irregularity or signal heterogeneity

For both readers, the number and percentage of heterogeneous or irregularly bordered lymph nodes decreased after induction therapy; however, these nodal features at baseline did not correlate with tumour response (Table 5). One reader found that heterogeneity post-chemotherapy was significantly more common in incomplete responders (59% vs. 22%, $p = 0.04$). Heterogeneity post-chemotherapy was not significantly associated with DFS for reader 1 (HR: 0.98, 95% CI: 0.27–3.57, $p = 0.98$) or for reader 2 (HR: 2.20, 95% CI: 0.68–7.16, $p = 0.19$).

Discussion

In this cohort of patients who received induction chemotherapy (ICT) before chemoradiotherapy (CRT) as part of total neoadjuvant treatment (TNT), a new paradigm now gaining traction for the treatment of rectal cancer, we explored the MRI findings after chemotherapy only (ICT) as they related to response at histopathology after all treatment (TNT). Our principal finding was that T2 volume change showed no correlation with response. RT2SI correlated with 100% fibrosis (complete response), but this was method-dependent.

Table 3 Rectal tumour measures by T and N stage

		T2 volume (reader 1, cm^3)	T2 volume (reader 2, cm^3)	T2 signal intensity (reader 3)
pT stage	N	Median decrease (IQR)	Median decrease (IQR)	Median decrease (IQR)
T0/TIS/T1	18	16.2 (7.8–31.1)	14.1 (12.1–32.2)	0.16 (-0.09–1.38)
T2	27	18.9 (8.2–33.9)	17.0 (8.4–29.4)	0.56 (-0.67–0.79)
T3/T4	20	23.5 (8.0–41.8)	26.1 (6.4–38.7)	0.29 (-0.36–1.37)
pN stage				
N0	47	17.3 (7.8–38.0)	15.9 (10.2–32.2)	0.58 (-0.23–1.41)
N1/N2	18	19.4 (14.5–31.1)	26.0 (6.9–37.0)	-0.06 (-0.59–0.83)

Table 4 Rectal tumour measures with subsequent CRT response by pathology

Change in T2 volume versus tumour response (reader 1)			
	N	Spearman's ρ	p
Tumour response	65	0.077	0.54
	N	Median decrease (IQR)	Wilcoxon p
Complete response	9	16 (6–16)	0.31
Incomplete response	56	20 (9–35)	
Change in T2 volume versus tumour response (reader 2)			
	N	Spearman's ρ	p
Tumour response	65	0.023	0.86
	N	Median decrease (IQR)	Wilcoxon p
Complete response	9	13 (9–20)	0.44
Incomplete response	56	21 (10–32)	
Change in relative T2 signal intensity versus tumour response (reader 3)			
	N	Spearman's ρ	p
Tumour response	56	0.092	0.50
	N	Median decrease (IQR)	Wilcoxon p
Complete response	5	1.60 (0.74–3.08)	*0.05
Incomplete response	51	0.12 (-0.41–1.03)	

* ≤ 0.05

However, lymph node sizes at baseline and after ICT were significantly smaller in patients achieving pathological complete response (pCR). Specifically, patients with nodes that were less than 4 mm were more likely to achieve complete response after all treatment. Baseline and post-ICT lymph node size correlated with DFS, whereas tumour volume and signal intensity did not. Change in size of the largest lymph node and heterogeneity of the largest lymph node showed variable association with pCR and DFS amongst readers.

Unlike MRI studies that have shown correlation between response to chemoradiotherapy and T2 volume reduction [15], diffusion-weighted imaging (DWI) volume reduction [16] and rT2SI [10], our study of MRI after chemotherapy only did not show similar correlations with T2 volume (both readers) or rT2SI changes (for one reader). This finding is hard to explain given the growing evidence for enhanced treatment efficacy using ICT [3]. It suggests that although we often saw significant tumour shrinkage after ICT, CRT was the great equaliser even if a poor response to ICT occurred, thus confounding our ability to show an association. In other words, there must be tumours that are sensitive to CRT that are poorly responsive to ICT. We did not investigate further volume reduction or signal change due to CRT, as that was not our purpose. Such a study would be of interest to assess the relative contribution of these components of TNT to overall tumour shrinkage. In an early study on the use of induction chemotherapy, MRI-based assessment found an 83% objective response rate after chemotherapy alone and further response after CRT with objective response rates of 96% [17]. It is unclear how this determination was made. The authors claim to have used RECIST for MRI assessment, but RECIST is not applicable or reliable for the hollow GI tract. The disagreement on T2 signal changes between readers using the selective ROI method underlies the subjective nature of this method compared with full volume tumour interrogation, which was subsequently performed using a third reader. In general we have observed that T2 tumour darkening after ICT alone is less common than after CRT. This may correlate with the established knowledge that fibrosis is induced by radiation. A potentially useful finding in our cohort was that pre- and post-treatment node-sizes correlated with TNT treatment outcomes. It is known that nodal response tends to follow in parallel with tumour response in rectal cancer [8], and thus these findings are in keeping with what is understood about tumour biology.

Our findings differ from other post-ICT MRI studies. In the Pan-Ex pooled analysis [6], the T2 signal intensity changes [called 'magnetic resonance tumour regression grade' (mrTRG)] showed correlation with DFS, an association not consistently found in our results, and overall survival (OS), an outcome we could not specifically test. Also, we do not use the mrTRG system per se, but the concept is similar and related to T2-signal darkening, only formalised in that system. One possible limitation was our use of representative ROIs for tumour signal intensity rather than whole-volume signal intensity. We used this method since, visually, in our experience, rectal tumours are most often homogeneous with a paucity of necrosis or mixed signal intensity foci. Regarding volumetric changes to ICT, Nougaret et al found 68% accuracy of post-ICT volumetry with response in 16 patients receiving 8 weeks of 5-fluorouracil-irinotecan-oxaliplatin (FOLFIRINOX) [18]. Aiba et al found 70% accuracy in a 40-patient study using either 4 weeks of xeloda-oxaliplatin (XELOX) or 8 weeks of FOLFOX [19], and Seierstad et al found an accuracy of 78% in 69 patients undergoing 4 weeks of Nordic 5-fluorouracil-leucovorin-oxaliplatin (FLOX) chemotherapy. Perhaps the earlier time

Table 5 Lymph node size and heterogeneity with subsequent CRT response by pathology (results presented for reader 1 (left columns) and reader 2 (right columns))

Largest lymph node size (baseline) versus tumour response					
	N	Spearman's ρ	p	Spearman's ρ	p
Tumour response	63	-0.25	*0.05	-0.13	0.29
	N	Median size, mm (IQR)	Wilcoxon p	Median size, mm (IQR)	Wilcoxon p
Complete response	9	4 (4–5)	*0.001	5 (4–5)	*0.004
Incomplete response	54	7 (5–9)		7 (4–5)	
Largest lymph node size (post-chemotherapy) versus tumour response					
	N	Spearman's ρ	p	Spearman's ρ	p
Tumour response	63	-0.35	*0.005	-0.29	*0.02
	N	Median size, mm (IQR)	Wilcoxon p	Median size, mm (IQR)	Wilcoxon p
Complete response	9	3 (3–4)	*0.003	3 (2–4)	*0.006
Incomplete response	54	5 (4–6)		5 (3–6)	
Change in largest lymph node size versus tumour response					
	N	Spearman's ρ	p	Spearman's ρ	p
Tumour response	63	-0.10	0.43	0.10	0.42
	N	Median size, mm (IQR)	Wilcoxon p	Median size, mm (IQR)	Wilcoxon p
Complete response	9	1 (1–2)	*0.05	2 (2–2)	0.45
Incomplete response	54	3 (1–4)		2 (1–4)	
Lymph node heterogeneity (baseline) versus tumour response					
	N		Wilcoxon p		Wilcoxon p
Tumour response	63		-		0.74
	N	Heterogeneity Frequency (%)	Fisher's Exact p	Heterogeneity Frequency (%)	Fisher's Exact p
Incomplete response	54	100%	-	41 (76%)	0.20
Complete response	9	100%		5 (56%)	
Lymph node heterogeneity (post-chemotherapy) versus tumour response					
	N		Wilcoxon p		Wilcoxon p
Tumour response	63		0.29		0.44
	N	Heterogeneity Frequency (%)	Fisher's Exact p	Heterogeneity Frequency (%)	Fisher's Exact p
Incomplete response	54	42 (78%)	0.99	32 (59%)	*0.04
Complete response	9	7 (78%)		2 (22%)	

* ≤ 0.05

periods used in these studies were better at separating responders from non-responders [20], but for all studies, due to different ICT regimens and timing of MRI used, the results are not directly comparable. Regarding lymph node assessment after chemotherapy only, the GEMCAD 0801 study [7] found that although MR lymph node stage correlated with DFS and recurrence on univariate analysis, correlation was not maintained at multivariate analysis. That study found that mrEMVI and its regression were more important factors after chemotherapy only. We did not analyse EMVI, a possible limitation of our study. Other node-for-node validation studies have found that size-criteria are more successful predictors of nodal involvement after treatment than before [21]. In the studies of both Lahaye [21] and Sassen [8], use of a 5-mm cut-off post-treatment, while not perfect, allowed an accuracy of 86% and 89%, respectively. We also found similar size cut-offs helpful, even at this mid-point of treatment, after chemotherapy and before chemoradiotherapy, in keeping with the concept that nodal regression during therapy may be a surrogate response marker.

It may be premature to draw conclusions on the clinical implications of our results. The lack of good correlation between primary tumour measurements and response might suggest a lack of efficacy for MRI at this time period, but this conclusion can only specifically be made regarding FOLFOX for 16 weeks, since other investigators using other agents and schedules did find MRI useful after chemotherapy only. However, our nodal data could prove useful if validated in another, larger, prospective study. Forty-three percent (27/63) of patients had lymph nodes greater than or equal to 5 mm after ICT and none went on to achieve a complete response. Of patients who had lymph nodes smaller than 5 mm, 25% (9/36) went on to achieve a complete response. The emergence of new treatment options, such as selective use of radiation or even non-operative treatment for rectal cancer has prompted

many studies to identify who will respond well or achieve a complete response early in treatment. As such, information on lymph nodes mid-treatment could potentially inform the treatment strategy if it were found to be reproducible. In the ongoing Phase II/III trial of Neoadjuvant FOLFOX With Selective Use of Combined Modality Chemoradiation Versus Preoperative Combined Modality Chemoradiation for Locally Advanced Rectal Cancer Patients Undergoing Low Anterior Resection with Total Mesorectal Excision (PROSPECT) study, for example, chemoradiotherapy is only selectively used if chemotherapy alone is found to be inadequate in shrinking the primary tumour [22].

Our study is limited by its size and retrospective nature. As our oncologists became more comfortable with using induction chemotherapy and obtained more MRI scans to evaluate its effects, we felt the need to audit these studies. However, strict criteria were not applied as to which patients would receive induction chemotherapy or MRI. We believe that both were more likely to be obtained on patients with more advanced disease, requiring more aggressive downstaging and to ensure that the delay to CRT would not be detrimental, and thus this cohort of patients is likely skewed towards those with more advanced disease. A strength of our study lies in the double readings, allowing more confident conclusions about findings when made by both readers. This strength manifested itself in a number of interpretations that produced conflicting findings between two readers and thus prevented a false-positive conclusion.

In conclusion, in a cohort of patients undergoing total neoadjuvant treatment for rectal cancer with 16 weeks of FOLFOX, and in whom MRI was performed after this treatment and prior to CRT, volumetric changes were not associated with tumour response, and there was disagreement on the association of T2 signal changes using selective ROI placement. Using whole-tumour volume ROI, a more robust method as previously described [23, 24], an inverse association between signal intensity and tumour response was noted by one reader and, though encouraging, would require further validation. Nodal sizes before and after chemotherapy were strongly associated with complete tumour response to TNT as well as with DFS. Validation of these data using a larger patient cohort and particularly in a prospective study would be the best approach to further explore the potential prognostic use of MRI in the management of patients undergoing total neoadjuvant treatment for rectal cancer.

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Methodology
- Retrospective
- Cross-sectional study/observational
- Performed at one institution

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