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ORIGINAL ARTICLE

The neoadjuvant rectal score and a novel magnetic resonance imaging based neoadjuvant rectal score are stage independent predictors of long-term outcome in locally advanced rectal cancer

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Abstract

Aim: Neoadjuvant rectal (NAR) score is an early surrogate for longer-term outcomes in rectal cancer undergoing radiotherapy and resection. In an era of increasing organ preservation, resection specimens are not always available to calculate the NAR score. Post-treatment magnetic resonance imaging (MRI) re-staging of regression is subjective, limiting reproducibility. We explored the potential for a novel MRI-based NAR score (mrNAR) adapted from the NAR formula.

Methods: Locally advanced rectal cancer patients undergoing neoadjuvant therapy (nCRT) and surgery were retrospectively identified between 2008 and 2020 in a single cancer network. mrNAR was calculated by adapting the NAR formula, replacing pathological (p) stages with post-nCRT MR stages (*ymr*). Cox regression assessed relationships between clinicopathological characteristics, NAR and mrNAR with overall survival (OS) and recurrence-free survival (RFS).

Results: In total, 381 NAR and 177 mrNAR scores were calculated. On univariate analysis NAR related to OS (hazard ratio [HR] 2.05, 95% confidence interval [CI] 1.33–3.14, $p = 0.001$) and RFS (HR 2.52, 95% CI 1.77–3.59, $p = 0.001$). NAR 3-year OS <8 was 95.3%, 8–16 was 88.6% and >16 was 80%. mrNAR related to OS (HR 2.96, 95% CI 1.38–6.34, $p = 0.005$) and RFS (HR 2.99, 95% CI 1.49–6.00, $p = 0.002$). 3-year OS for mrNAR <8 was 96.2%, 8–16 was 92.4% and >16 was 78%. On multivariate analysis, mrNAR was a stage-independent predictor of OS and RFS. mrNAR corresponded to NAR score category in only 15% (positive predictive value 0.23) and 47.5% (positive predictive value 0.48) of cases for categories <8 and >16, respectively.

Conclusions: Neoadjuvant rectal score is validated as a surrogate end-point for long-term outcomes. mrNAR categories do not correlate with NAR but have stage-independent prognostic value. mrNAR may represent a novel surrogate end-point for future neoadjuvant treatments that focus on organ preservation.

KEYWORDS
cCR, clinical complete response, LARC, MRI, mrNAR score, NAR score, neoadjuvant, organ preservation, pathological complete response, pCR, rectal cancer, surrogate end-point, watch and wait

INTRODUCTION

The incidence of rectal cancer reflects around 15–25 cases/100 000 population per year in Europe [1]. Early rectal cancers can be managed by resection alone. A significant proportion present locally advanced (LARC), for which a standard management is neoadjuvant radiotherapy ± chemotherapy (nCRT) followed by total mesorectal excision (TME) [1].

The extent of radiotherapy response is an important prognosticator in LARC [2]. There is a spectrum of response, however, varying considerably in patients of the same disease stage. Approximately 14.9% of patients can achieve pathological complete response (pCR) after nCRT, with no specimen evidence of tumour or positive nodes [3]. Three-year disease-free survival (DFS) is 92.3%, 77.6% and 64.6% for complete, intermediate and poor regression (Dworak classification) respectively [4].

LARC trials historically rely on local recurrence (LR), overall survival (OS) and DFS outcomes. With clear links between nCRT response and long-term oncological outcomes, interest has grown to develop rapid and easily attainable surrogate end-points to increase trial efficiency and pace. They could also guide follow-up.

Magnetic resonance imaging (MRI) remains the standard for LARC local staging and post-nCRT re-staging [1, 5]. TNM downstaging alone, however, is not a consistent indicator of outcomes. Although pCR (epitome of good response) has been used as a study end-point, a meta-analysis of 22 trials confirmed that pCR lacks validity as a 5-year OS surrogate [6]. Pathological (pTRG) and MRI (mrTRG) tumour regression grading have shown promise as they associate with OS and DFS [2, 7–9]. TRG assessments remain subjective, however, with limited inter-observer agreement, and thus reproducibility of prognostic information remains unclear [1, 7, 10–12]. mrTRG has therefore not been adopted as a preoperative surrogate end-point [13].

The neoadjuvant rectal (NAR) score was proposed by George et al. as a short-term trial end-point [14]. It will henceforth be referred to as pathological NAR (pNAR). It incorporates weighted clinical (c) T stage and post-nCRT pathological (*yp*) T and N stages from resection specimens. It is a pseudo-continuous variable with 24 possible outcomes [14]. pNAR is calculated as demonstrated in Figure 1A and is adapted from Valentini et al. nomogram data on rectal cancer recurrence and survival [15]. It aims to serve as a DFS and OS surrogate with higher scores representing a poorer prognosis, for example 0 (*yp*CR from cT4) to 100 (progression from cT1 to *yp*T4N2) [14, 16]. The pNAR score has been validated in retrospective studies [17–22], phase II [16] and phase III trials [10]; however, some report no additional value as an OS end-point compared with *yp*TNM [23, 24].

Pathologically derived surrogates have several issues in modern rectal cancer management. They are irrelevant with respect to organ preservation and cannot help inform preoperative conversations. Preoperative surrogates may allow opportunity for nCRT optimization or provide a window of consideration for salvage preoperative management. They could also prove invaluable during informed consent for higher risk patients considering surgery associated with greater morbidity.

What does this paper add to the literature?

We present an imaging-based neoadjuvant rectal (NAR) score (mrNAR) of response to therapy. Extent of response is an important prognosticator and this novel mrNAR score is a stage-independent predictor of recurrence-free and overall survival. It does not rely on resection specimens so has use in an era of organ preservation.

(A)

$$\mathrm{NAR} = \frac{[5ypN - 3(cT - ypT) + 12]^2}{9.61}$$

(B)

$$\mathrm{mrNAR} = \frac{[5ymrN - 3(cT - ymrT) + 12]^2}{9.61}$$

FIGURE 1 (A) Equation for George et al. neoadjuvant rectal score (NAR) (referred to as pNAR within this work). Clinical tumour staging was based on the initial diagnostic MRI T stage. (B) Equation for our novel proposed mrNAR score; *c*T, clinical tumour stage; *ymr*N, post-nCRT MRI nodal N stage; *ymr*T, post-nCRT MRI tumour T stage.

A specific description of MRI TN assessment after nCRT is a more accurate, less subjective assessment of re-staging. We hypothesize that an MRI NAR score (mrNAR), using the same parameters as the validated pNAR score, could satisfy the need for an early, preoperative surrogate of longer-term outcomes.

In this study we aimed to validate the prognostic value of George et al.'s [14] pNAR score within our cohort and explore the prognostic accuracy of a novel mrNAR score for future use as a preoperative marker of outcomes.

METHODS

Consecutive LARC patients were retrospectively identified from a prospectively maintained database held by our regional cancer centre

between nCRT start dates 13 February 2008 to 28 December 2020. Clinicopathological characteristics, data and outcomes were collected retrospectively from electronic records by a single investigator (RKM). Patients were included if they underwent nCRT and proceeded to curative intent resection within a single National Health Service (NHS) health board. Selection for nCRT consideration was made following regional multidisciplinary team (MDT) meetings and regimens were delivered at the treating oncologist's discretion. Radiotherapy was most frequently delivered over 5 weeks (45–54 Gy in 25 fractions) usually with concomitant fluoropyrimidine-based chemotherapy regimens including oral capecitabine or intravenous 5-fluorouracil. Alternatively, a short-course schedule was delivered (25 Gy in 5 fractions) over a week, potentially followed by systemic chemotherapy.

Patients were excluded if transanal excision, contact or brachytherapy was performed, if they received palliative or postoperative radiotherapy, if they did not progress to curative intent surgery for any reason, or no staging MRI performed. Distant metastases at diagnosis (TxNxM1) or preoperatively (yTxNxM1) were excluded.

LARC was defined as MRI T3–T4 and/or locoregional nodes and/or circumferential resection margin threatening. Colonoscopy biopsy confirmed histological diagnosis of adenocarcinoma. MRI and computed tomography were used for local and distant staging respectively. Post-nCRT (y) MRI (mr), with documented inclusion of *ymr*TN re-staging, was not performed in all, as outlined in Results. TME was performed by open or laparoscopic techniques. The median time from nCRT start date to date of surgery was 18 weeks.

George et al.'s pNAR was calculated as described in Figure 1A [14]. Our post-nCRT mrNAR score was calculated by adjusting the pNAR calculation as follows: *c*T, clinical tumour T stage; *ymr*T, post-nCRT MRI T stage; and *ymr*N, post-nCRT MRI nodal stage (Figure 1B) [14]. Clinical T-staging was based on the diagnostic MRI. As previously described by George et al., pNAR was categorized into three risk groups: low (NAR <8), intermediate (NAR 8–16) and high (NAR >16) [14]. For reproducibility, this was replicated for mrNAR.

MRI assessment

A standardized MRI protocol was performed on a variety of 1.5 T MRI scanners. The protocol includes large field of view sagittal and axial images with 4–6 mm slice thickness, small field of view true axial and coronal tumour images with slice thickness of 3–3.5 mm, and axial diffusion-weighted sequences performed with *b* value ranges of 0–50, 300–800 and 800–1000 (s/mm^2). Post-nCRT scans were performed on the same scanner as initial staging for any given patient. No routine rectal cleansing or insufflation was performed. MRI staging was performed pre-nCRT in all patients and post-nCRT from 2016 as outlined in Results. Pre- and post-nCRT T-staging, N-staging and circumferential resection margin status was assessed using the MERCURY mrTRG proforma from 2016 to 2019 [9, 25] and the ESGAR proforma from 2019 [26]. As per proforma, pre-nCRT nodal assessment was based on size and morphological criteria (shape, signal intensity heterogeneity and margin regularity). For post-nCRT, either no remaining nodes or nodes <5 mm were considered N0 and the presence of any nodes with a short axis diameter ≥5 mm was considered N+. All scans were performed within a single NHS Scotland Health Board, NHS Greater Glasgow and Clyde. The mean time between the end of CRT and re-staging MRI was 8.84 weeks. All MRI scans were reported by a consultant radiologist and re-reviewed and presented at the colorectal MDT by subspecialist gastrointestinal radiologists. Information from the final MDT reports were accessed retrospectively and categorized using the TNM classification (8th edition) [1].

Pathological evaluation

Pathology reports followed the Royal College of Pathologists (RCP) TNM classification guidelines [27]. Reports were accessed retrospectively having been released at the time of resection. 'Vascular invasion' was deemed present if there was evidence of intramural, extramural or both venous invasions. Specimens were considered to be margin positive/R1 if there was tumour encroachment (direct involvement or nodal) ≤1 mm from non-peritonealized 'circumferential' or longitudinal margins. pCR was defined in line with RCP guidelines as the absence of viable tumour locally (*ypT0*) and in lymph nodes (*ypN0*) [27, 28]. The reporting pathologist's impression of tumour regression was reviewed retrospectively. Tumour regression grading followed the recommended four-tier system by the American Joint Committee on Cancer/RCP guidelines. This is based on a modification of TRG described by Ryan et al. as follows: TRG0, no viable cancer cells (complete response); TRG1, single or rare small groups of cancer cells (near-complete response); TRG2, residual cancer with evident tumour regression but more than single or rare small groups of cancer cells (partial response); TRG3, extensive residual cancer with no evident tumour regression (poor or no response) [27, 29].

Recurrence/survival

The following definitions were used: overall survival (OS), nCRT start date to any death; recurrence-free survival (RFS), nCRT start date to any recurrence; local recurrence (LR) refers to pelvic or intra-luminal recurrence only (isolated) or to both isolated local and distant recurrence together (occurring simultaneously or at different time points before death or end of follow-up); distant recurrence (DR) was defined as any recurrence outside the pelvis alone.

Statistical analysis

Descriptive statistics were used for baseline clinicopathological characteristics. χ^2 was used to assess the associations between both pNAR

TABLE 1 Association with clinicopathological characteristics and pathological NAR ($n = 381$, median FU 52 months) and MRI NAR ($n = 177$, median FU 38 months).

	Pathological NAR					MRI NAR				
Clinicopathological characteristics	***n* = 381 (%)**	**pNAR <8 (%)**	**pNAR 8–16 (%)**	**pNAR >16 (%)**	***p***	***n* = 177 (%)**	**MRI NAR <8 (%)**	**MRI NAR 8–16 (%)**	**MRI NAR >16 (%)**	***p***
Age										
<55	68 (17.8)	15 (17.6)	29 (16.5)	24 (20)	0.738	37 (20.9)	6 (23.1)	21 (22.8)	10 (16.9)	0.673
55–75	247 (64.8)	55 (64.7)	117 (66.5)	75 (62.5)		110 (62.1)	18 (69.2)	50 (54.3)	42 (71.2)	
>75	66 (17.3)	15 (17.6)	30 (17)	21 (17.5)		30 (16.9)	2 (7.7)	21 (22.8)	7 (11.9)	
Median age	66					65				
Gender										
Female	149 (39.1)	40 (47.1)	58 (33)	51 (42.5)	0.699	63 (35.6)	12 (46.2)	29 (31.5)	22 (37.3)	0.682
Male	232 (60.9)	45 (52.9)	118 (67)	69 (57.5)		114 (64.4)	14 (53.8)	63 (68.5)	37 (62.7)	
Clinical										
Clinical TNM										
I	10 (2.6)	1 (1.2)	6 (3.4)	3 (2.5)	0.001	3 (1.7)	0	3 (3.3)	0	0.062
II	87 (22.8)	27 (31.8)	50 (28.4)	10 (8.3)		35 (19.8)	6 (23.1)	23 (25)	6 (10.2)	
III	284 (74.5)	57 (67.1)	120 (68.2)	107 (89.2)		139 (78.5)	20 (76.9)	66 (71.1)	53 (89.8)	
Radiotherapy										
SCRT	34 (8.9)	7 (8.2)	15 (8.5)	12 (10)	0.644	25 (14.1)	1 (3.8)	14 (15.2)	10 (16.9)	0.162
LCRT	347 (91.1)	78 (91.8)	161 (91.5)	108 (90)		152 (85.9)	25 (96.2)	78 (84.8)	49 (83.1)	
Tumour height										
Low	171 (44.9)	40 (47.1)	84 (48)	47 (39.2)	0.212	81 (45.8)	9 (34.6)	45 (48.9)	27 (45.8)	0.929
Mid	133 (34.9)	29 (34.1)	59 (33.5)	45 (37.5)		60 (33.9)	12 (46.2)	30 (32.6)	18 (30.5)	
Upper	77 (20.2)	16 (18.8)	33 (18.8)	28 (23.3)		36 (20.3)	5 (19.2)	17 (18.5)	14 (23.7)	
Postoperative										
*yp*TNM										
pCR	59 (15.5)	59 (69.4)	0	0	0.001	23 (13)	4 (15.4)	15 (16.3)	4 (6.8)	0.001
I	79 (20.7)	21 (24.7)	57 (32.4)	1 (0.8)		45 (25.4)	11 (42.3)	25 (27.2)	9 (15.3)	
II	124 (32.5)	0	113 (64.2)	11 (9.2)		50 (28.2)	5 (19.2)	27 (29.3)	18 (30.5)	
III	119 (31.2)	5 (5.9)	6 (3.4)	108 (90)		59 (33.3)	6 (23.1)	25 (27.2)	28 (47.5)	
Path regression										
TRG 0–1	110 (28.9)	74 (87.1)	28 (15.9)	8 (6.7)	0.001	45 (25.4)	6 (23.1)	26 (28.3)	13 (22)	0.720
TRG 2–3	271 (71.1)	11 (12.9)	148 (84.1)	112 (93.3)		132 (74.6)	20 (76.9)	66 (71.7)	46 (78)	

TABLE 1 (Continued)

Clinicopathological characteristics	Pathological NAR					MRI NAR				
	n = 381 (%)	pNAR <8 (%)	pNAR 8–16 (%)	pNAR >16 (%)	*p*	*n* = 177 (%)	MRI NAR <8 (%)	MRI NAR 8–16 (%)	MRI NAR >16 (%)	*p*
y pathological differentiation										
pCR	59 (15.5)	59 (69.4)	0	0	0.001	23 (13)	4 (15.4)	15 (16.3)	4 (6.8)	0.002
Well/moderate	300 (78.7)	25 (29.4)	167 (94.9)	108 (90)		140 (79.1)	22 (84.6)	74 (80.4)	44 (74.6)	
Poor	22 (5.8)	1 (1.2)	9 (5.1)	12 (10)		14 (7.9)	0	3 (3.3)	11 (18.6)	
Vascular invasion										
No	224 (58.8)	83 (97.6)	103 (58.5)	38 (31.7)	0.001	97 (54.8)	15 (57.7)	53 (57.6)	29 (49.2)	0.357
Yes	157 (41.2)	2 (2.4)	73 (41.5)	82 (68.3)		80 (45.2)	11 (42.3)	39 (42.4)	30 (50.8)	
R1										
No	344 (90.3)	85 (100)	158 (89.8)	101 (84.2)	0.001	165 (93.2)	24 (92.3)	90 (97.8)	51 (86.4)	0.093
Yes	37 (9.7)	0	18 (10.2)	19 (15.8)		12 (6.8)	2 (7.7)	2 (2.2)	8 (13.6)	

Note: χ^2 test; significance level $p < 0.05$.

Abbreviations: FU, follow-up; LCRT, long-course radiotherapy regime; MRI, magnetic resonance imaging; NAR, neoadjuvant rectal score; pCR, pathological complete response; R1, margin positive disease; SCRT, short-course radiotherapy regime; TNM, Tumour Node Metastases classification 8th edition; TRG, tumour regression grade; *y*, post neoadjuvant therapy.

and mrNAR with clinicopathological characteristics. A p value ≤0.05 was considered significant. Cox regression analysis was used to determine relationships at 3 years between OS, RFS and clinicopathological characteristics including pNAR and mrNAR. Postoperative pathological factors with p value ≤0.01 on univariate analysis were included in the multivariate model. Kaplan–Meier and log-rank tests were used to assess survival probability difference between pNAR, mrNAR categories and survival outcomes. Spearman's rank correlation coefficient assessed the relationship between pseudo-continuous mrNAR and pNAR scores, and the magnitude of the percentage error was calculated as [(mrNAR − pNAR)/pNAR] × 100. Dichotomous χ^2 analysis for trend and positive predictive values (PPVs) were used to describe the association of mrNAR to pNAR risk categories as well as *ymr*TNM to *yp*TNM. A Bland–Altman plot was used to analyse agreement between pNAR and mrNAR scores. Statistical analysis was performed using SPSS software (version 26.0; SPSS Inc.).

RESULTS

Clinicopathological characteristics

Between 2008 and 2020, following exclusions, 381 patients were available for analysis with pNAR scores. Post-nCRT MRI with TNM re-staging since 2016 was available in 177/381 (46.5%) with mrNAR scores calculated.

Baseline demographics are summarized in Table 1. Most patients were men (60.9%), median age 66; 74.5% were node positive/TNM III at diagnosis. A minority (8.9%) underwent a short-course radiotherapy regime. 52.2% underwent sphincter-preserving surgery versus permanent stoma in 47.8%. Tumour positions were 44.9%, 34.9% and 20.2% for low (<5 cm), mid (5–10 cm) and upper (>10 cm) distances respectively from the anorectal junction. The predominant adenocarcinoma grade was moderately differentiated.

The relationships between pNAR, mrNAR and clinicopathological characteristics are summarized in Table 1. 15.5% patients achieved pCR. There was no association between age, gender and pNAR or mrNAR. Post-treatment (*yp*)TNM was associated with pNAR as expected given it is a component of the formula. Although not a component of the mrNAR formula, *yp*TNM significantly associated with mrNAR risk categories ($p = 0.001$) indicating re-staging MRI accuracy. Higher pNAR scores were significantly associated with known determinants of poor prognosis: higher pTRG ($p = 0.001$), vascular invasion ($p = 0.001$) and R1 ($p = 0.001$). A higher mrNAR category did not significantly associate with these.

Survival outcomes

From the nCRT start date, median follow-up time was 52 months for the whole cohort and 38 months for the 177 patients who also had mrNAR scoring. Median time to any death was 38 months. The observed OS 3-year death rate was 48/381 (12.6%).

TABLE 2 Univariate analysis of preoperative and postoperative clinicopathological factors for 3-year OS and RFS.

Clinicopathological characteristics		Overall survival at 3 years (OS)				Any recurrence at 3 years (RFS)			
n = 381	*N* (%)	Events (*n* = 48)	% (SE)	HR (95% CI)	*p*	Events (*n* = 75)	% (SE)	HR (95% CI)	*p*
Age									
<55	68 (17.8)	6	91 (4)			12	81 (5)		
55–75	247 (64.8)	35	84 (2)			51	77 (3)		
>75	66 (17.3)	7	86 (5)	1.07 (0.67–1.71)	0.777	12	80 (5)	1.01 (0.69–1.47)	0.946
Gender									
Female	149 (39.1)	11	91 (3)			30	78 (4)		
Male	232 (60.9)	37	82 (3)	2.39 (1.22–4.69)	0.011	45	78 (3)	1.03 (0.65–1.64)	0.889
Clinical									
Clinical TNM									
I	10 (2.6)	1	88 (12)			2	78 (14)		
II	87 (22.8)	5	93 (3)			18	76 (5)		
III	284 (74.5)	42	83 (2)	2.4 (0.96–4.36)	0.064	55	78 (3)	0.98 (0.63–1.52)	0.933
Radiotherapy									
SCRT	34 (8.9)	1	96 (4)			3	87 (7)		
LCRT	347 (91.1)	47	85 (2)	3.31 (0.46–24.09)	0.237	72	77 (2)	2.02 (0.64–6.43)	0.233
Tumour height									
Low	171 (44.9)	27	81 (3)			41	72 (4)		
Mid	133 (34.9)	12	89 (3)			24	80 (4)		
Upper	77 (20.2)	9	88 (4)	0.76 (0.5–1.12)	0.160	10	86 (4)	0.68 (0.49–0.94)	0.019
Postoperative									
*yp*TNM									
pCR	59 (15.5)	1	95 (3)			1	98 (2)		
I	79 (20.7)	4	92 (4)			7	90 (4)		
II	123 (32.3)	18	84 (4)			28	74 (4)		
III	120 (31.5)	23	78 (4)	1.69 (1.24–2.34)	0.001	39	64 (5)	2.12 (1.61–2.81)	0.001
pTRG									
TRG 0–1	110 (28.9)	8	91 (3)			10	90 (3)		
TRG 2–3	271 (71.1)	40	83 (2)	2.17 (1.02–4.64)	0.030	65	73 (3)	2.99 (1.54–5.82)	0.001
Vascular invasion									
No	97 (54.8)	22	88 (2)			26	87 (2)		
Yes	80 (45.2)	26	82 (3)	1.83 (1.04–3.23)	0.037	49	65 (4)	3.18 (1.97–5.12)	0.001
R1									
No	344 (90.3)	37	88 (2)			57	81 (2)		
Yes	37 (9.7)	11	67 (9)	2.90 (1.48–5.69)	0.002	18	49 (8)	3.59 (2.11–6.11)	0.001
pNAR									
<8	85 (22.3)	4	95 (2)			3	96 (2)		

TABLE 2 (Continued)

Clinicopathological characteristics		Overall survival at 3 years (OS)				Any recurrence at 3 years (RFS)			
n = 381	*N* (%)	Events (*n* = 48)	% (SE)	HR (95% CI)	*p*	Events (*n* = 75)	% (SE)	HR (95% CI)	*p*
8–16	176 (46.2)	20	87 (3)			33	79 (3)		
>16	120 (31.5)	24	77 (4)	2.05 (1.33–3.14)	0.001	39	64 (5)	2.52 (1.77–3.59)	0.001
MRI NAR (*n* = 177)									
<8	26 (14.7)	1	95 (5)			2	91 (6)		
8–16	92 (52)	7	91 (3)			7	91 (3)		
>16	59 (33.3)	13	75 (6)	2.96 (1.38–6.34)	0.005	16	68 (7)	2.99 (1.49–6.00)	0.002

Note: Cox (proportional hazards) regression, significance level $p \leq 0.01$.

Abbreviations: CI, confidence interval; HR, hazard ratio; LCRT, long-course radiotherapy regime; MRI, magnetic resonance imaging; NAR, neoadjuvant rectal score; pCR, pathological complete response; R1, margin positive disease; SCRT, short-course radiotherapy regime; TNM, Tumour Node Metastases classification 8th edition; TRG, tumour regression grade; *y*, post neoadjuvant therapy.

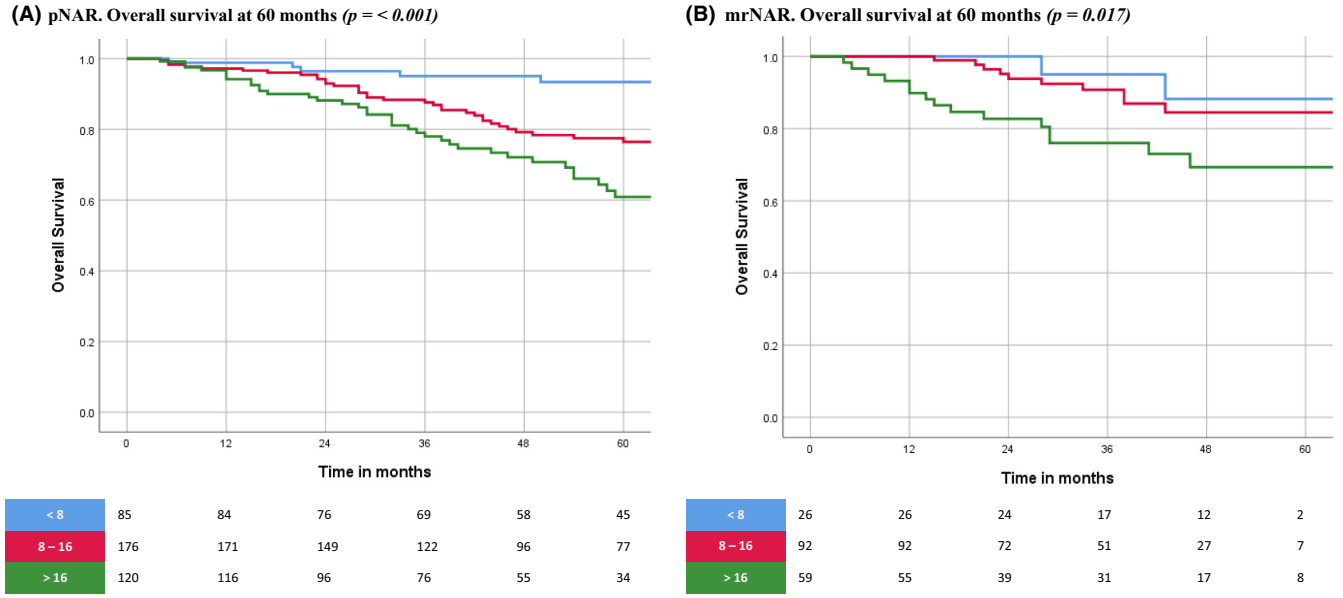

FIGURE 2 Kaplan–Meier plots for survival; statistical significance using log-rank test. (A) Survival analysis and prognostic significance of pNAR risk category score for OS up to 60 months with corresponding lifetables ($n = 381$). (B) Survival analysis and prognostic significance of mrNAR risk category score for OS up to 60 months with corresponding lifetables ($n = 177$).

Table 2 summarizes clinicopathological characteristics, including pNAR and mrNAR, and 3-year OS. On univariate analysis, gender and tumour position did not meet criteria ($p \leq 0.01$) for association with OS. Postoperative variables that associated with OS included *yp*TNM (hazard ratio [HR] 1.69, 95% confidence interval [CI] 1.24–2.34, $p = 0.001$) and R1 (HR 2.90, 95% CI 1.48–5.69, $p = 0.002$).

We analysed the prognostic significance of pNAR for survival in our cohort. pNAR was a marker for OS (HR 2.05, 95% CI 1.33–3.14, $p = 0.001$) on univariate analysis (Table 2). Despite lower event numbers, mrNAR was also significant for OS (HR 2.96, 95% CI 1.38–6.34, $p = 0.005$) (Table 2). Survival analysis revealed that the pNAR risk categories significantly stratified OS ($p < 0.001$) up to 60 months (Figure 2A). mrNAR categories also stratified for OS ($p = 0.017$) (Figure 2B).

Multivariate analysis was performed to compare *yp*TNM, R1 and pNAR score as pathological surrogate markers of OS (Table 3). On multivariate backward stepwise Cox regression, R1 (HR 2.28, 95% CI 1.15–4.52, $p = 0.018$) and pNAR (HR 1.90, 95% CI 1.23–2.95, $p = 0.004$) were independently associated with 3-year OS.

To test the role of mrNAR as a surrogate end-point for OS, pNAR was replaced by mrNAR in a second multivariate analysis with R1 and *yp*TNM (Table 4). In this multivariate analysis, R1 (HR 3.56, 95% CI 1.26–10.03, $p = 0.017$) and mrNAR (HR 2.53, 95% CI 1.18–5.42, $p = 0.017$) were independently associated with 3-year OS.

TABLE 3 Multivariate analysis of postoperative pathological factors for 3-year OS and RFS.

		Overall survival at 3 years (OS)				Any recurrence at 3 years (RFS)			
Multivariate Cox regression	*N* (%)	Events *n* = 48	% (SE)	HR (95% CI)	*p*	Events *n* = 75	% (SE)	HR (95% CI)	*p*
Pathological									
*yp*TNM									
pCR	59 (15.5)	1	95 (3)			1	98 (2)		
I	79 (20.7)	4	92 (4)			7	90 (4)		
II	123 (32.3)	18	84 (4)			28	74 (4)		
III	120 (31.5)	23	78 (4)	1.27 (0.70–2.31)	0.430	39	64 (5)	1.78 (1.32–2.41)	0.001
pTRG									
TRG 0–1	110 (28.9)	–	–	–	–	10	90 (3)		
TRG 2–3	271 (71.1)	–	–	–	–	65	73 (3)	0.98 (0.45–2.13)	0.959
Vascular invasion									
No	97 (54.8)	–	–	–	–	26	87 (2)		
Yes	80 (45.2)	–	–	–	–	49	65 (4)	1.96 (1.19–3.22)	0.008
R1									
No	344 (90.3)	37	88 (2)			57	81 (2)		
Yes	37 (9.7)	11	67 (9)	2.28 (1.15–4.52)	0.018	18	49 (8)	2.20 (1.28–3.79)	0.004
pNAR									
<8	85 (22.3)	4	95 (2)			3	96 (2)		
8–16	176 (46.2)	20	87 (3)			33	79 (3)		
>16	120 (31.5)	24	77 (4)	1.90 (1.23–2.95)	0.004	39	64 (5)	1.01 (0.52–1.97)	0.971

Note: Backwards stepwise Cox regression, significance level $p \leq 0.01$.

Abbreviations: CI, confidence interval; HR, hazard ratio; NAR, neoadjuvant rectal score; pCR, pathological complete response; R1, margin positive disease; TNM, Tumour Node Metastases classification 8th edition; TRG, tumour regression grade; *y*, post neoadjuvant therapy.

Recurrence outcomes

Table 2 summarizes the relationship of clinicopathological factors with recurrence. Three-year recurrence rates were 19.6%. Median time to any recurrence was 18 months.

On univariate analysis *yp*TNM, pTRG, vascular invasion and R1 were all significantly associated with 3-year RFS (Table 2). pNAR (HR 2.52, 95% CI 1.77–3.59, $p = 0.001$) and mrNAR (HR 2.99, 95% CI 1.49–6.00, $p = 0.002$) were also associated with RFS.

Multivariate analysis of RFS was performed with possible pathological surrogate markers (p value ≤0.01 inclusion criterion) *yp*TNM, pTRG, vascular invasion, R1 and pNAR. *yp*TNM (HR 1.78, 95% CI 1.32–2.41, $p = 0.001$), vascular invasion (HR 1.96, 95% CI 1.19–3.22, $p = 0.008$) and R1 (HR 2.20, 95% CI 1.28–3.79, $p = 0.004$) remained independently associated with 3-year RFS (Table 3). When pNAR was replaced by mrNAR in multivariate analysis, only *yp*TNM (HR 2.12, 95% CI 1.27–3.55, $p = 0.004$) and mrNAR (HR 2.39, 95% CI 1.19–4.82, $p = 0.015$) remained independently associated with 3-year RFS (Table 4).

Survival analysis demonstrated that pNAR risk categories stratified RFS ($p = 0.001$), DR ($p = 0.008$) and LR ($p = 0.001$) up to 60 months (Figure 3A). Although RFS events for mrNAR were infrequent ($n = 25/177$, 14.1%), stratification was still evident up to 60 months on Kaplan–Meier but not significant for DR or LR (Figure 3B).

pNAR versus mrNAR

Explorative analysis of the 177 patients with pNAR and mrNAR scores was performed. As a pseudo-continuous variable, pNAR and mrNAR scores had a low correlation coefficient ($r = 0.22$, $p = 0.002$). The median magnitude of percentage error was 71.9% comparing pNAR to mrNAR scores. Dichotomous χ^2 analysis and PPVs calculated revealed that mrNAR matched the corresponding pNAR score category with 15% (PPV 0.23), 52.6% (PPV 0.45) and 47.5% (PPV 0.48) sensitivity for <8, 8–16 and >16, respectively. On comparison of *ymr*T stage accuracy to *yp*T stage, 37.7% sensitivity (PPV 0.64) for T1–2 and 77.6% sensitivity (PPV 0.74) for T3–4 disease was achieved. Identification of pathological positive nodes in yMRI was 48.4% (PPV 0.58). Bland–Altman analysis suggested good limits of agreement between pNAR and mrNAR scores, with no significant proportional bias on linear regression analysis ($p = 0.930$) (Figure S1).

TABLE 4 Multivariate analysis of postoperative pathological factors and mrNAR for 3-year OS and RFS.

		Overall survival at 3 years (OS)				Any recurrence at 3 years (RFS)			
Multivariate Cox regression	*N* (%)	Events *n* = 48	% (SE)	HR (95% CI)	*p*	Events *n* = 75	% (SE)	HR (95% CI)	*p*
Pathological									
*yp*TNM									
pCR	59 (15.5)	1	95 (3)			1	98 (2)		
I	79 (20.7)	4	92 (4)			7	90 (4)		
II	123 (32.3)	18	84 (4)			28	74 (4)		
III	120 (31.5)	23	78 (4)	1.39 (0.84–2.31)	0.200	39	64 (5)	2.12 (1.27–3.55)	0.004
pTRG									
TRG 0–1	110 (28.9)	–	–	–	–	10	90 (3)		
TRG 2–3	271 (71.1)	–	–	–	–	65	73 (3)	0.88 (0.22–3.51)	0.856
Vascular invasion									
No	97 (54.8)	–	–	–	–	26	87 (2)		
Yes	80 (45.2)	–	–	–	–	49	65 (4)	1.92 (0.74–5.00)	0.181
R1									
No	344 (90.3)	37	88 (2)			57	81 (2)		
Yes	37 (9.7)	11	67 (9)	3.56 (1.26–10.03)	0.017	18	49 (8)	2.33 (0.83–6.50)	0.106
MRI NAR (*n* = 177)									
<8	26 (14.7)	1	95 (5)			2	91 (6)		
8–16	92 (52)	7	91 (3)			7	91 (3)		
>16	59 (33.3)	13	75 (6)	2.53 (1.18–5.42)	0.017	16	68 (7)	2.39 (1.19–4.82)	0.015

Note: Backwards stepwise Cox regression, significance level $p \leq 0.01$.

Abbreviations: CI, confidence interval; HR, hazard ratio; MRI, magnetic resonance imaging; NAR, neoadjuvant rectal score; pCR, pathological complete response; R1, margin positive disease; TNM, Tumour Node Metastases classification 8th edition; TRG, tumour regression grade; *y*, post neoadjuvant therapy.

DISCUSSION

In this study we sought to validate George et al.'s NAR score (pNAR) and explore the prognostic utility of a novel, non-subjective mrNAR score for use preoperatively.

pNAR

For the first time in a UK cohort, our study contributes to and supports the view of the current literature that pNAR associates with survival outcomes [18, 22]. We confirmed pNAR risk categories consistently predicted survival and recurrence. This was apparent through regression analysis and stratification by pNAR risk category on survival analysis up to 60 months.

On multivariate analysis, pNAR achieved independent status for OS at 3 years above *yp*TNM and pTRG. For recurrence, *yp*TNM, R1 and vascular invasion were independent risk factors over pNAR. Our findings dispute the findings of van der Valk et al. who determined their combined model of cT, *yp*T and *yp*N variables a superior predictor over pNAR for OS [23]. Imam et al. also concluded that the pNAR score gave no more prognostic information than *yp*T and *yp*N combined, but still believed pNAR to be of clinical value [18]. We consider pNAR to be a useful tool, with readily available parameters, that can be expanded to 1 of 24 pseudo-continuous scores to provide extra prognostic information. Further study is required to truly understand pNAR use within an era of personalized treatment; for example, should patients with NAR >16 be preferentially considered for adjuvant chemotherapy? We did not deem the wide 2008–2020 interval range a limitation in our study of pNAR. Simple T-staging (TNM I–IV) and vascular invasion status has not differed significantly in MRI or pathological reporting in this period, nor did the distribution of pNAR scores across years in our cohort.

mrNAR

Habr-Gama et al. first described similar long-term survival rates when comparing pCR to those in the so-called watch-and-wait

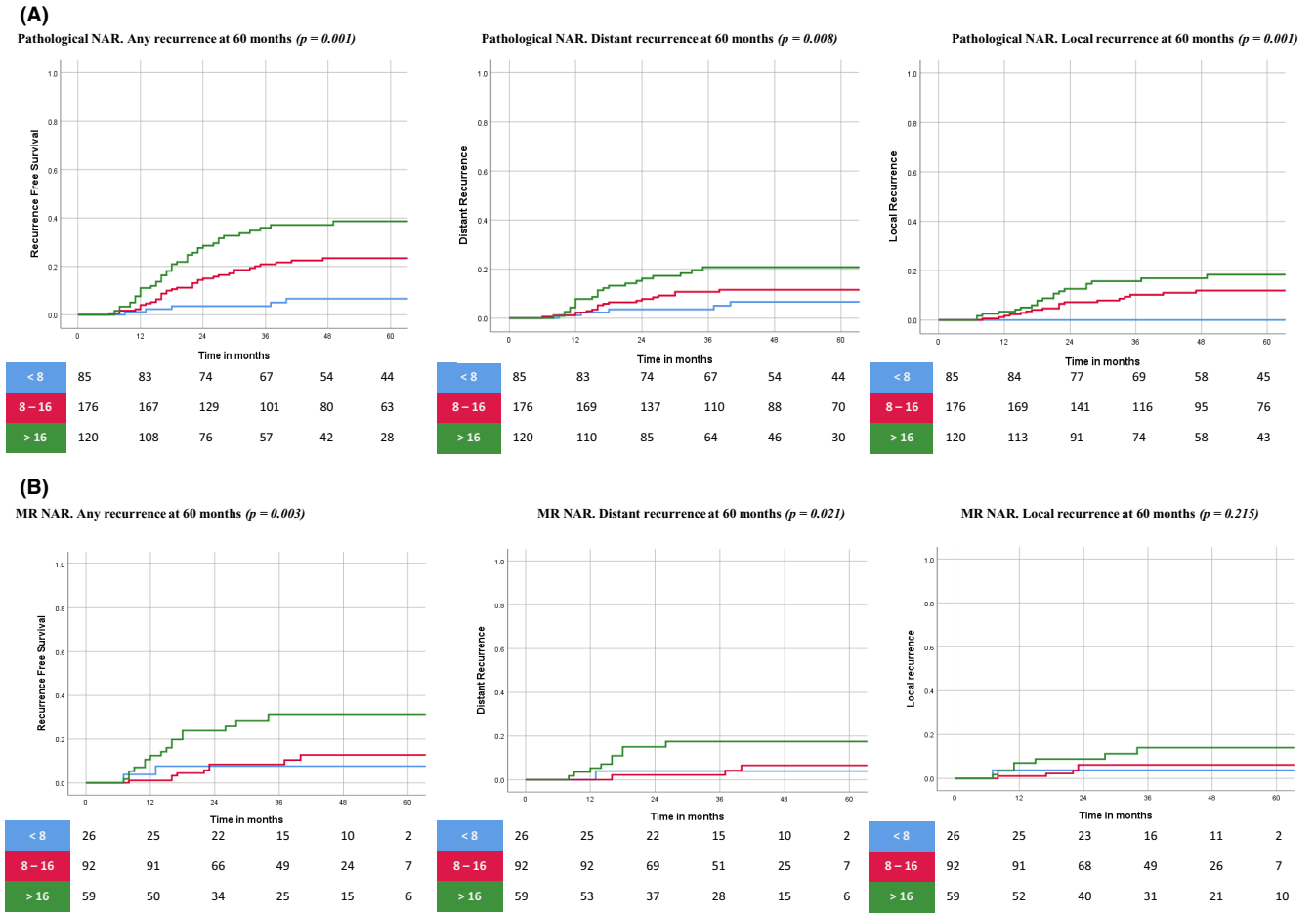

FIGURE 3 Kaplan–Meier plots for recurrence; statistical significance using log-rank test. (A) Recurrence analysis of pNAR risk categories for RFS, DR, LR up to 60 months with corresponding lifetables ($n = 381$). (B) Recurrence analysis of mrNAR risk categories for RFS, DR, LR up to 60 months with corresponding lifetables ($n = 177$).

(W&W) pathway who did not progress to surgery having archived cCR [30]. Regrowth can occur after cCR. The largest study to date of 880 W&W patients reported 25.2% 2-year cumulative incidence of local regrowth [31]. Most regrowths after cCR (83.8%) can progress to TME [32]. Therefore, there is an evident move towards organ preservation within the field and trials looking at total neoadjuvant therapy only increase the need for preoperative surrogate endpoints. Currently, only mrTRG exists as a non-pathologically derived reflection of response.

Our exploration of a novel, non-subjective MRI NAR score has yielded encouraging results as risk categories significantly associated with survival outcomes. Kaplan–Meier plots stratified mrNAR risk groups with statistical significance. Of interest, there was particular separation on plots in the >16 category, perhaps an early indication of mrNAR >16 as a surrogate for high-risk disease. Only one death occurred in mrNAR <8.

mrNAR has shown early promise as a predictor of recurrence. Risk categories were independently associated with RFS on multivariate analysis. Similar to OS Kaplan–Meier plots, >16 appeared to separate from the other two closely linked categories which were 91% and 95% for intermediate and low categories respectively. We hypothesize separation of these categories with increased cohort size.

Despite known limitations of post-nCRT MRI, particularly nodal re-staging [5, 33–35], we demonstrated that mrNAR was associated with *yp*TNM ($p = 0.001$) despite its formula not containing pathological parameters (Table 1). Dichotomous χ^2 analysis supported previous reports that *y*MRI was more accurate for *y*T, particularly *y*T3–4, than *y*N re-staging [35]. In our cohort, MR was more sensitive (48.4%) for detecting pathological N+ disease compared to 42% sensitivity in a study of 2062 Swedish colorectal cancer patients [35]. The poor ability of mrNAR to match the corresponding pNAR risk category could be explained by the cumulative inaccuracies that develop when combining T and N within the formula. This is supported as <8 risk category groups were least compatible (15% sensitivity, PPV 0.23) of all, highlighting MRI limitations to assess lower T stages and negative nodes. mrNAR, however, did demonstrate good agreement of outcome with pNAR on Bland–Altman analysis (Figure S1), supporting its witnessed utility as a prognosticator.

Despite evident limitations of MR re-staging, mrNAR consistently predicts survival and recurrence outcomes in our cohort. This non-subjective, simple and novel score could aid nCRT optimization and possibly influence decisions to proceed to surgery with considerable morbidity. In addition, and perhaps most applicable, it could have use in trials optimizing nCRT. An example is the phase II trial by Rahma et al. investigating the addition of pembrolizumab to total neoadjuvant therapy. They utilized pNAR as an end-point but could not score those not progressing to resection with 13.9% versus 13.6% achieving cCR in the pembrolizumab versus control arm [16]. This highlights the need for a preoperative surrogate marker in trials.

All scans included in mrNAR were reported by a consultant radiologist with specialist rectal cancer interest. It should be highlighted that all patients within this study underwent surgery and so are not a true population of W&W patients. Our study was limited by the small number of end events within the 177 mrNAR cohort, with 38 months median follow-up. However, this is approximately the same length of follow-up used in many randomized controlled trials which report on median 3-year outcomes [36–39]. Moreover, we decided not to include an mrTRG comparison to mrNAR given the large heterogenicity of mrTRG reporting methods witnessed in our cohort.

Nevertheless, we see potential for mrNAR to aid with optimization of nCRT and possibly influence the decision to proceed to surgery and risk considerable morbidity. It is also imperative that a surrogate end-point exists for trials in an era of organ preservation. This score would allow for all trial patients to be categorized, regardless of progression to surgery.

The mrNAR has potential for use in meta-analysis of treatment response across multiple radiotherapy randomized controlled trials. It requires more mature data and external validation through assessment within a larger prospective cohort prior to clinical application.

AUTHOR CONTRIBUTIONS

Ross K. McMahon: Conceptualization; data curation; formal analysis; investigation; writing – original draft. **Sean M. O'Cathail:** Conceptualization. **Harikrishnan Nair:** Data curation; formal analysis; investigation. **Jonathan J. Platt:** Investigation. **Michael Digby:** Investigation.

CONFLICT OF INTEREST STATEMENT

No funding or conflicts of interest to declare from any authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Study approved by NHS Scotland regional ethics committee (REC-ref: 20/ES/0012). Written informed consent waived by the institutional review board.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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