Prognostic implication of the neoadjuvant rectal score and other biomarkers of clinical outcome in Hong Kong Chinese patients with locally advanced rectal cancer undergoing neoadjuvant chemoradiotherapy

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ABSTRACT

Background: Neoadjuvant chemoradiotherapy is a standard treatment for locally advanced rectal cancer, for which pathological complete response is typically used as a surrogate survival endpoint. Neoadjuvant rectal score is a new biomarker that has been shown to correlate with survival. The main objectives of this study were to investigate factors contributing to pathological complete response, to validate the prognostic significance of neoadjuvant rectal score, and to investigate factors associated with a lower neoadjuvant rectal score in a cohort of Hong Kong Chinese.

Methods: Data of patients with locally advanced rectal cancer who received neoadjuvant chemoradiotherapy from August 2006 to October 2018 were retrieved from hospital records and retrospectively analysed.

Results: Of 193 patients who had optimal response to neoadjuvant chemoradiotherapy and surgery, tumour down-staging was the only independent prognostic factor that predicted pathological complete response (P<0.0001). Neoadjuvant rectal score was associated with overall survival (hazard ratio [HR]=1.042, 95% confidence interval [CI]=1.021-1.064; P<0.0001), disease-free survival (HR=1.042, 95% CI=1.022-1.062; P<0.0001), locoregional recurrence-free survival (HR=1.070, 95% CI=1.039-1.102; P<0.0001) and distant recurrence-free survival (HR=1.034, 95% CI=1.012-1.056; P=0.002). Patients who had pathological complete response were associated with a lower neoadjuvant rectal score (P<0.0001), but pathological complete response was not associated with survival. For patients with intermediate neoadjuvant rectal scores, late recurrences beyond 72 months from diagnosis were observed.

Conclusion: Neoadjuvant rectal score is an independent prognostic marker of survival and disease recurrence in a cohort of Hong Kong Chinese patients who received neoadjuvant chemoradiotherapy for locally advanced rectal cancer.

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Introduction

Early-stage rectal cancer is primarily treated with total mesorectal excision surgery, while 'high-risk' rectal cancers can be treated with neoadjuvant short-course radiotherapy alone or concurrent chemotherapy and long-course radiotherapy (neoadjuvant chemoradiotherapy; NCRT).[1] High-risk rectal cancer is defined as the presence of T3 or T4 disease, node-positive disease, the presence of close or involved circumferential resection margin (CRM) by staging magnetic resonance imaging (MRI) and/or low-lying tumours involving the anal sphincters.[1] Randomised phase III trials have shown that neoadjuvant is more effective than adjuvant chemoradiotherapy, as it can improve disease-free survival (DFS), local tumour control, sphincter preservation and has better treatment compliance with fewer adverse drug effects.[2-4] Furthermore, the addition of 5-fluorouracil (5FU) to neoadjuvant radiotherapy has been shown to be more effective than radiotherapy alone with higher rates of pathological complete response (pCR) and lower local relapse rate.[5]

Historically, NCRT has been associated with 15% to 27% pCR rates that have been associated with progression-free survival and overall survival (OS).[6] Other prognostic markers such as the presence of tumour down-staging in terms of T stage and N stage,[7] tumour regression grading based on pathological and radiological criteria[6,8] and CRM status[9] have all been evaluated in clinical studies and correlated with predict survival and risk of cancer recurrence. However, a recently published meta-analysis has failed to show pCR rate as a significant surrogate marker of 5-year OS—an important primary endpoint in randomised trials, in patients with locally advanced rectal cancer (LARC) undergoing NCRT.[10] Therefore, a new endpoint known as the neoadjuvant rectal (NAR) score has been developed as a prognostic factor and study endpoint for clinical research in LARC. This is a composite endpoint consisting of both clinical and pathological information on T stage and N stage obtained before and after NCRT and has been validated in prospective clinical trials in Western populations.[11,12] The NAR score has also been shown to better predict OS in clinical trials on rectal cancer than pCR.[11]

The primary objective of the present study was to validate the prognostic significance of NAR score and pCR in a cohort of Hong Kong Chinese patients with LARC in terms of OS, DFS,

前導性直腸癌評分和其他臨床結果生物標記對接受前導性結合放射化療的局部侵襲性直腸癌香港患者的預後意義

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引言：手術前的前導性結合放射化療是局部侵襲性直腸癌的標準治療方法。切除後組織的病理完全緩解常用作研究內替代存活終點分析。前導性直腸癌評分是一個新的生物標記，已被證明與存活期相關。本研究旨在檢視導致病理完全緩解的因素，驗證前導性直腸癌評分的預後意義，以及檢視香港華人前導性直腸癌評分較低分數的相關原因。

方法：從醫院病歷中檢索由2006年8月至2018年10月接受前導性結合放射化療的局部侵襲性直腸癌患者資料，進行回顧性分析。

結果：在對前導性結合放射化療和手術有良好反應的193名患者中，腫瘤的期數改善是預測病理完全緩解的唯一獨立預後因素（P<0.0001）。前導性直腸癌評分與下列相關：總存活期（風險比=1.042，95%置信區間=1.021-1.064；P<0.0001）、無病存活期（風險比=1.042，95%置信區間=1.022-1.062；P<0.0001）、局部無復發存活期（風險比=1.070，95%置信區間=1.039-1.102；P<0.0001）和遠處無復發存活期（風險比=1.034，95%置信區間=1.012-1.056; P=0.002）。具有病理完全緩解的患者與較低的前導性直腸癌評分相關（P<0.0001），但病理完全緩解與存活期無關。在具有前導性直腸癌評分中等分數的患者中，發現有診斷後超過72個月的晚期復發。

結論：前導性直腸癌評分可作為局部侵襲性直腸癌的香港華人患者於接受前導性結合放射化療後，存活期和疾病復發的獨立預後標記。

New knowledge added by this study

- Neoadjuvant rectal (NAR) score is a validated prognostic marker of survival for patients with locally advanced rectal cancer. A lower NAR score is associated with subsequent achievement of pathological complete response to neoadjuvant chemoradiotherapy for locally advanced rectal cancer.
- Although pathological complete response is a surrogate endpoint of survival in clinical trials of neoadjuvant therapy for locally advanced rectal cancer, the present study failed to confirm this in a cohort of Chinese patients.

Implications for clinical practice or policy

- The NAR score should be incorporated as a study endpoint in clinical trials of neoadjuvant therapy for Chinese patients with locally advanced rectal cancer.
- The NAR score should be prospectively evaluated as a prognostic indicator in identifying patients who might benefit from more intensive adjuvant treatment.
- Moreover, the results of the present study suggest that longer follow-up for ≥72 months may be needed for patients with intermediate NAR scores.

locoregional recurrence-free survival (LRFS) and distant recurrence-free survival (DRFS). The second objective was to investigate associations between NAR score (or pCR) and known prognostic factors such as CRM status, tumour location, extramural vascular invasion (EMVI) and other treatment-related factors. The third objective was to investigate factors that might predict a lower NAR score.

Methods

The data of patients with LARC who were referred to the local multidisciplinary Lower Gastrointestinal Tumour Board and then underwent NCRT at the Prince of Wales Hospital, Hong Kong, from August 2006 to October 2018 were extracted from hospital records and retrospectively evaluated. Data were also retrieved from the records of the Lower Gastrointestinal Tumour Board meetings and the surgical new case database from the Prince of Wales Hospital.

Patient selection

Eligible patients had histologically confirmed LARC as defined by the presence of T3 or T4 tumour; or node-positive disease, and/or the presence of threatened CRM, and/or low-lying tumours involving the anal sphincters. All eligible patients underwent MRI and whole-body computed tomography (CT) scan staging before and after NCRT. Patients were excluded from the study who had distant metastasis at the time of diagnosis; who were not fit for NCRT or surgery due to poor performance status and/or presence of serious medical co-morbidities; or who had not completed the full course of NCRT.

Outline of oncological treatment, surgery, magnetic resonance imaging and pathological examination

All treatment decisions were jointly made by the Lower Gastrointestinal Tumour Board. At baseline, all patients underwent MRI staging and also systemic staging with contrast CT scan and/or positron emission tomography–CT imaging. Magnetic resonance imaging staging was determined by MRI radiologists and reported in a standardised format that contained information on T stage and N stage, presence of EMVI, CRM status and tumour regression grade response criteria.[13] For patients with MRI reports which did not contain the relevant data, the MRI scans were assessed retrospectively in order to obtain the study information.

All patients were treated according to the institutional radiotherapy protocol at the Prince of Wales Hospital, as represented by a long-course pelvic radiotherapy up to a total dose of 45 Gy at 1.8 Gy per day, five fractions per week for 5 weeks with boost 5.4 Gy at 1.8 Gy per day for three fractions. The majority of patients received concurrent chemotherapy with bolus intravenous 5FU and leucovorin that were given at week 1 and week 5 of radiotherapy, followed by adjuvant chemotherapy with 5FU and leucovorin or oxaliplatin-based chemotherapy.[14] Some patients also received neoadjuvant (modified) FOLFOXIRI regimen followed by concurrent capecitabine during pelvic radiotherapy as part of a prospective clinical trial.[15] All patients underwent total mesorectal excision surgery with curative intent, and pathologists at the New Territories East Cluster–affiliated hospitals performed pathological examination on all the resected surgical specimens. The presence of pCR was defined as the resolution of all tumour cells in all resected tissues including the lymph nodes.

Collection of clinical and radiological data

The following data were collected: age, sex, location of tumour from anal verge (defined as the endoscopic distance from anal verge as 'low' [0-5 cm], 'mid' [5-10 cm], 'high' [>10 cm]), tumour histology, neoadjuvant and adjuvant chemotherapy and the overall TNM (tumour, node, and metastasis) stage, as defined by the American Joint Committee on Cancer, 8th version. The date at histological diagnosis, cancer progression, locoregional and/or distant recurrence and the date of last follow-up examination or death were collected.

Pre- and post-treatment MRI data were collected: T stage (T2, T3 or T4), N stage (node positive or node negative), CRM (non-involved margin is defined as ≥2 mm; involved margin is defined as <2 mm from the anticipated surgical margin). The presence of EMVI was determined in the MRI scans of 152 patients.

Calculation of neoadjuvant rectal score

The NAR score was calculated according to the Valentini's nomograms for survival based on the following formula[16]:

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

where cT = clinical T stage before NRCT; pN = pathological nodal stage after NCRT and surgery; and pT = pathological T stage after NCRT and surgery.

The relationship between NAR scores and clinical outcome were analysed with NAR score as a continuous variable (24 discrete scores by the nomograms)[16] or in groups based on previous studies.[12,17] The NAR scores were grouped as: 'low' (NAR score <8), 'intermediate' (NAR score 8-16), and 'high' (NAR score >16), as previously published in the National Surgical Adjuvant Breast and Bowel Project 'R-04' trial,[11] or in quartiles according to the 'FORWARC' study.[17]

Statistical analysis

Overall survival was defined from the time of diagnosis to the time of death from any cause. Survival time will be censored at the last date the patient is known to be alive. Disease-free survival was defined from the time of diagnosis of rectal cancer to the time of disease recurrence and death from any cause. Locoregional recurrence-free survival was measured from the date of diagnosis to the date of locoregional recurrence and death from any cause. Distant recurrence-free survival was measured from the date of diagnosis to the date of distant metastasis and death from any cause.

Statistical analysis was performed using the SPSS (Window version 26; IBM Corp, Armonk [NY], United States). The Chi squared or Fisher's exact test was used for analysing categorical variables, *t* test for continuous variables and logistic regression was used to analyse the relationship between continuous variables and disease recurrence. Time-to-event endpoints include OS, DFS, LRFS and DRFS were estimated using the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazards model was used to evaluate any interaction between time-to-event endpoints and important covariates. The multivariable Cox regression with stepwise selection method was used to study NAR score and other prognostic factors. A value of P<0.05 was considered significant. The correlation between pCR and important covariates was obtained by using logistic regression. The odds ratio and the corresponding 95% confidence interval (CI) will be given.

Results

A total of 209 patients were found to be eligible, 16 of whom had suboptimal response to NCRT as defined by one or more of the following factors: persistently positive CRM, absence of significant tumour regression on MRI, or frank radiological progression (Fig 1). These patients were treated with consolidation chemotherapy after NCRT and of whom eight patients responded and underwent surgery with curative intent. The characteristics of the remaining 193 patients who had optimal response after NCRT had a mean age of 62 years, with a male and female ratio of 2.94:1 (Table 1). The median follow-up duration for all patients was 47.7 months (range, 42.7-53.5).

Prognostic significance of the neoadjuvant rectal score–survival rates

When the NAR score was analysed as 24 discrete scores by Valentini's nomograms,[16] it was found to be associated with OS (hazard ratio [HR]=1.042, 95% CI=1.021-1.064; P<0.0001), DFS (HR=1.042, 95% CI=1.022-1.062; P<0.0001), LRFS (HR=1.070, 95% CI=1.039-1.102; P<0.0001) and DRFS (HR=1.034, 95% CI=1.012-1.056; P=0.002).

To evaluate the effect of NAR score on survival rates, patients were arbitrarily divided into three groups according to NAR score: low (score <8; n=50), intermediate (score 8-16; n=99) and high (score >16; n=44) [Table 2]. There was a significant difference among the OS curves of low, intermediate, and high NAR score groups (P=0.004, Fig 2). Similarly, there was a significant difference among the DFS rates of the low, intermediate, and high NAR score groups (P<0.0001, Fig 3). The DFS was lower for the intermediate NAR score group than for the low NAR score group (HR=4.50, 95% CI=1.35-14.95; P=0.014), whereas the risk of progression was higher for the high NAR score group than for the low NAR score group (HR=8.14, 95% CI=2.40-27.65; P=0.001).

There was a significant difference among the LRFS rates of the low, intermediate, and high NAR score groups as shown in Figure 4 (P=0.002). Similarly, as shown in Figure 5, the DRFS rates of the three NAR score groups showed a statistical difference (P=0.013). The intermediate NAR score group had a lower DRFS than the low NAR score group (HR=4.04, 95% CI=1.21-13.50; P=0.023), while the high NAR score group had a higher risk

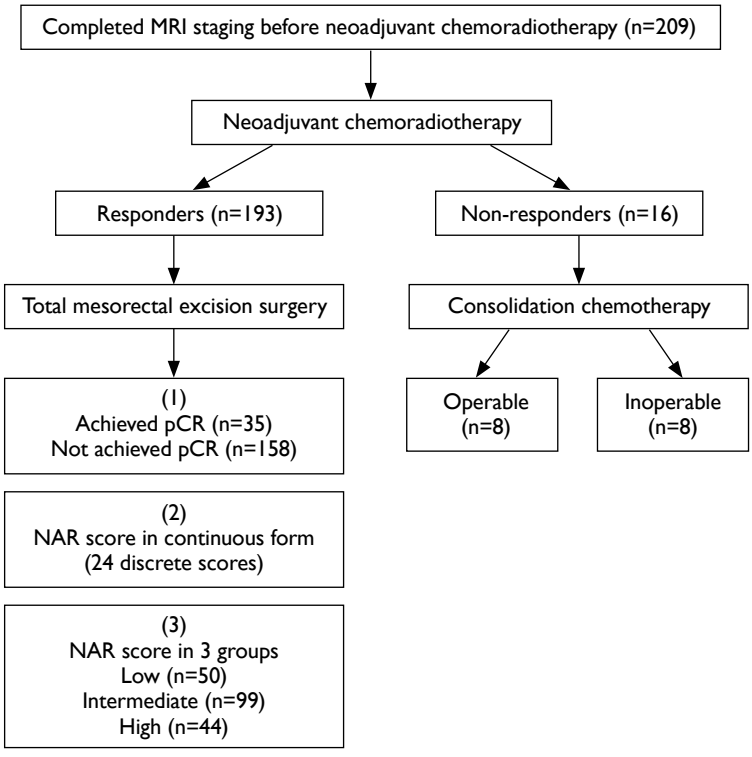

FIG 1. Flowchart showing selection of patients

Abbreviations: MRI = magnetic resonance imaging; NAR score = neoadjuvant rectal score; pCR = pathological complete remission

TABLE 1. Patient characteristics and associations between clinical factors and the rate of pCR in 193 patients who underwent neoadjuvant chemoradiotherapy and total mesorectal excision surgery

Variable	No. of patients (n=193)	Patients without pCR (n=158, 82%)	Patients with pCR (n=35, 18%)	P value*	OR	95% CI for OR	P value†
Age, mean, y		62.04	62.51	0.762‡	1.007	0.963-1.052	0.761
Sex							
Male	144	120	24	0.364	1.447	0.649-3.226	0.366
Female	49	38	11				
Tumour location							
Upper rectum	9	7	2	0.933	0.994	0.524-1.885	0.985
Middle rectum	103	85	18				
Lower rectum	81	66	15				
MRI T staging							
T2	5	3	2	0.291	0.627	0.249-1.577	0.321
T3	154	126	28				
T4	34	29	5				
MRI N staging							
Positive	160	134	26	0.135	0.517	0.216-1.240	0.139
Negative	33	24	9				
MRI tumour down-staging							
Yes	156	121	35	<0.0001			
No	37	37	0				
MRI EMVI (n=152)							
Positive	72	59	13	0.497	0.759	0.342-1.685	0.489
Negative	80	62	18				
MRI CRM involved							
Yes	124	103	21	0.562	0.801	0.378-1.698	0.563
No	69	55	14				

Abbreviations: 95% CI = 95% confidence interval; CRM = circumferential resection margin; EMVI = extramural vascular invasion; MRI = magnetic resonance imaging; OR = odds ratio; pCR = pathological complete remission

* P value by Chi squared test/Fisher's exact test for categorical variables or t test for continuous variables

† P value by Cox regression

‡ P value by *t* test

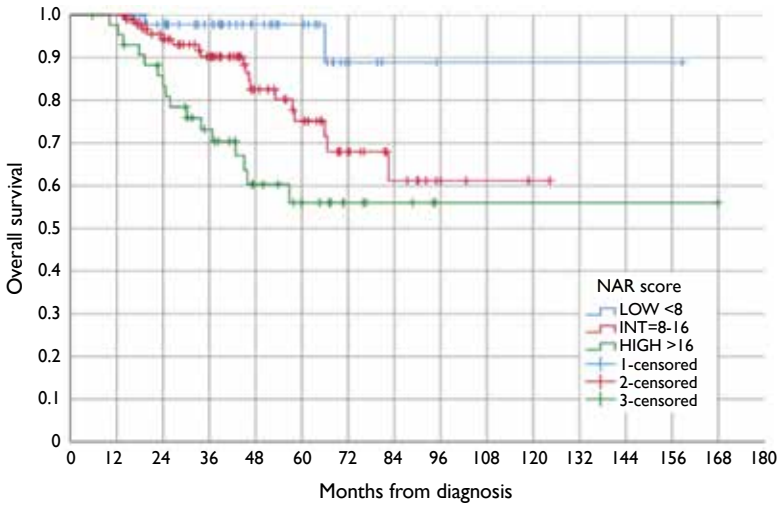

FIG 2. Kaplan–Meier curves showing overall survival of low (blue), intermediate (red), and high (green) NAR score groups

Abbreviations: censored = death from any cause; HIGH = high NAR score >16; INT = intermediate NAR score 8-16; LOW = low NAR score <8; NAR = neoadjuvant rectal score

of distant recurrence than the low NAR score group (HR=5.65, 95% CI=1.61-19.84; P=0.007).

Multivariate analysis of neoadjuvant rectal score and other prognostic factors

The NAR score was an independent prognostic factor for OS, DFS, LRFS and DRFS, irrespective of whether NAR score was analysed as a continuous variable or in groups of low, intermediate, and high NAR score (Tables 3 and 4). Other prognostic markers, such as age and MRI T stage, were predictive of OS, DFS and DRFS. The MRI tumour down-staging after NCRT was an independent prognostic factor for OS, DFS and LRFS. This study further evaluated the prognostic factors that might predict a low NAR score in subgroups of patients after NCRT. Of all the prognostic factors evaluated, only pCR was associated with a lower NAR score (NAR score ≤8 or >8) [Table 5].

TABLE 2. Survival analysis with patients stratified into three groups according to NAR score: low (<8); intermediate (8-16); and high (>16)

Outcome	NAR score	No. of patients	1-Year rates	3-Year rates	5-Year rates	P value*	HR	95% CI for HR	P value†
OS						0.004	2.50	1.50-4.17	<0.0001
	Low	50	100.0	97.8	97.8		1	-	-
	Intermediate	99	100.0	90.3	75.2		4.45	1.03-19.19	0.045
	High	44	97.7	73.2	56.0		9.12	2.10-39.66	0.003
DFS						<0.0001	2.36	1.52-3.67	<0.0001
	Low	50	98.0	93.3	93.3		1		
	Intermediate	99	90.9	79.4	73.7		4.50	1.35-14.95	0.014
	High	44	93.0	57.1	57.1		8.14	2.40-27.65	0.001
LRFS						0.002	4.02	1.73-9.34	0.001
	Low	50	100.0	100.0	100.0		1	-	-
	Intermediate	99	98.0	92.2	92.2		32439	-	0.912
	High	44	93.0	77.6	77.6		88295	-	0.902
DRFS						0.013	1.98	1.24-3.16	0.005
	Low	50	98.0	93.3	93.3		1	-	-
	Intermediate	99	90.9	79.9	73.6		4.04	1.21-13.50	0.023
	High	44	97.6	70.9	67.4		5.65	1.61-19.84	0.007

Abbreviations: 95% CI = 95% confidence interval; DFS = disease-free survival; DRFS = distant recurrence-free survival; HR = hazard ratio; LRFS = locoregional recurrence-free survival; OS = overall survival

* P value by log-rank test

† P value by Cox regression

Prognostic factors that predict pathological complete response after neoadjuvant chemoradiotherapy

In the 193 patients who had pCR to NCRT and surgery, MRI tumour down-staging was the only prognostic factor which was associated with the rate of pCR (P<0.0001) [Table 1].

Discussion

In the present study, NAR score was found to be a more power prognostic factor than pCR. Furthermore, patients who achieved pCR post NCRT tend to have lower NAR scores. Furthermore, the results of the present study indicate significant differences in the rates of OS, DFS, LRFS and DRFS among patients with low, intermediate, and high NAR scores in a Hong Kong Chinese population, which is consistent with observations from a study in Western populations.[12] Several interesting observations can be made in the survival rates among the low, intermediate, and high NAR score groups. The DFS and DRFS curves of the intermediate and high NAR score groups (Figs 3 and 5) crossed over around the 1-year mark, demonstrating that survival of the intermediate group was initially inferior to the high NAR score group. This trend might be explained by an imbalance in the sample size of patients were in the intermediate NAR score group (n=99) compared with the high NAR score group (n=44) [Fig 1]. The recurrence rate in the low NAR score group reached a plateau at around 3 years, whereas in the intermediate NAR score group, late recurrences (especially distant recurrence) could

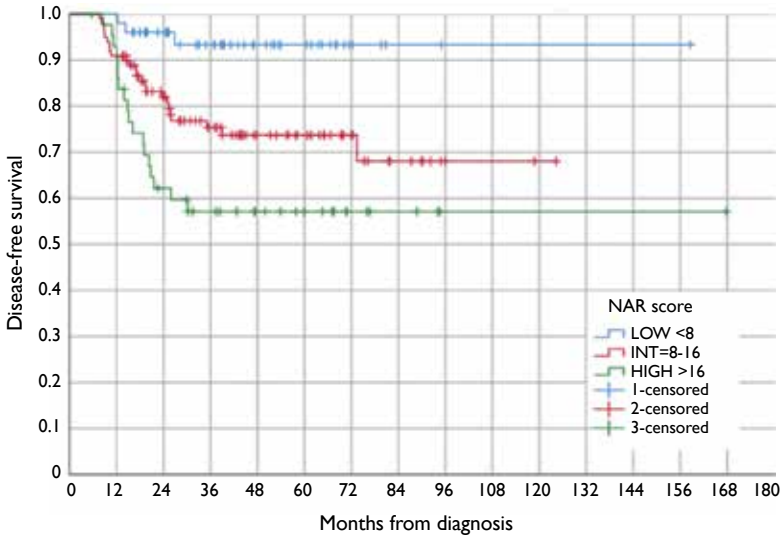

FIG 3. Kaplan–Meier curves showing disease-free survival of low (blue), intermediate (red), and high (green) NAR score groups

Abbreviations: censored = disease progression or death from any cause; HIGH = high NAR score >16; INT = intermediate NAR score 8-16; LOW = low NAR score <8; NAR = neoadjuvant rectal score

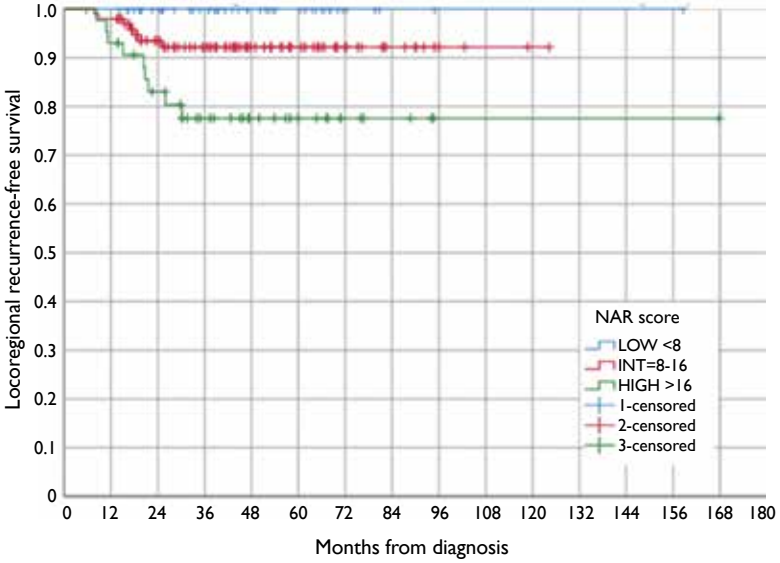

FIG 4. Kaplan–Meier curves showing locoregional recurrence-free survival of low (blue), intermediate (red), and high (green) NAR score groups

Abbreviations: censored = locoregional recurrence or death from any cause; HIGH = high NAR score >16; INT = intermediate NAR score 8-16; LOW = low NAR score <8; NAR = neoadjuvant rectal score

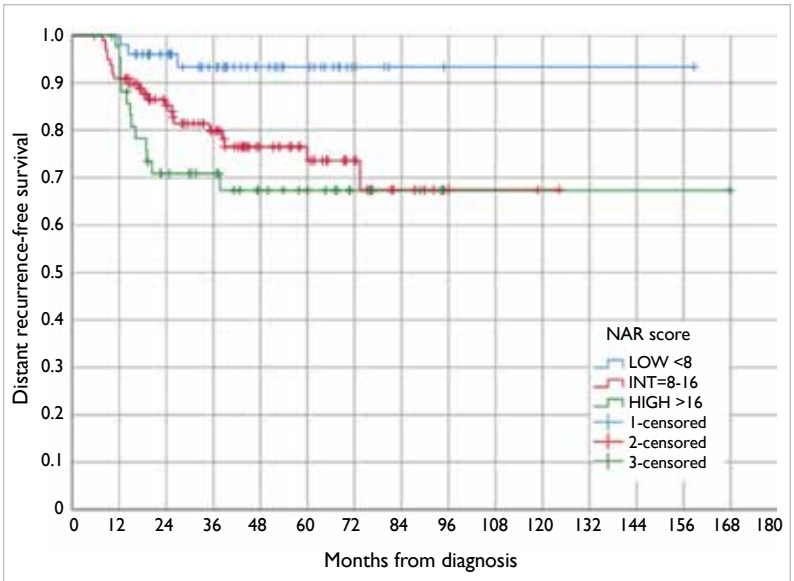

FIG 5. Kaplan–Meier curves showing distant recurrence-free survival low (blue), intermediate (red), and high (green) NAR score groups

Abbreviations: censored = distant recurrence or death from any cause; HIGH = high NAR score >16; INT = intermediate NAR score 8-16; LOW = low NAR score <8; NAR = neoadjuvant rectal score

occur well over 72 months after diagnosis. Therefore, this study suggests that longer follow-up duration for a period beyond 72 months may be needed for the intermediate NAR score group. This is in contrast to the recommendation in the European Society of Medical Oncology guideline which suggests a follow-up duration of up to 60 months.[18]

In this study, the NAR score (not pCR) was found to be an independent prognostic marker for survival and disease recurrence. It is possible that NAR score could better reflect the magnitude and dynamics of tumour regression over time, whereas pCR could give only dichotomised results observed at a single time-point after surgery.

There are several limitations to this retrospective study. The sample size was relatively small and there was an imbalance in the number of patients in the intermediate NAR score group compared with the other groups (Fig 1). Given the prognostic significance of MRI EMVI in LARC,[19] this study included this endpoint in the multivariate analysis. However, the MRI EMVI status could not be retrieved for some patients, especially those who had MRI imaging >5 years ago when this information was not captured at the time of imaging. Furthermore, the MRI N stage was only reported as either 'positive' or 'negative' in terms of nodal involvement without specifying the exact number of suspicious nodes. The CRM status and EMVI after NCRT and surgery has been shown in previous studies to affect prognosis and alter postoperative management.[20,21] However, information on these two prognostic factors could not be traced retrospectively, therefore only the pretreatment MRI CRM and MRI EMVI were included in the analysis. Nevertheless, the findings of this study are significant given the multicentre nature and also relatively long follow-up duration. Furthermore, it is consistent with the results of previous studies.[12,17]

Although NAR score is a consistent and validated prognostic marker, its determination relies on the availability of radiological and pathological assessments after surgery. In clinical practice, surgeons and oncologists have to rely heavily on MRI and/or endoscopic findings on assessing response to NRCT when making decisions on operability and preoperative consolidation chemotherapy after NRCT. Nevertheless, the NAR score is useful in the decision-making process with regard to the need for intensifying adjuvant chemotherapy and also length of follow-up duration. A study in Japan showed a benefit in administering adjuvant chemotherapy to patients with low NAR score (<16), but not in those with higher NAR score (≥16).[22] Further studies are needed to individualise adjuvant chemotherapy for Chinese patients using NAR scores after NCRT for LARC. Other more novel strategies such as personalised drug testing using rectal cancer organoid platforms in studying individual response to NCRT are on the horizon.[23]

Conclusion

The NAR score is an independent prognostic marker

TABLE 3. Multivariate analysis of prognostic factors (NAR score as continuous variable)

Factor	OS			DFS			LRFS			DRFS		
	HR	95% CI for HR	P value*	HR	95% CI for HR	P value*	HR	95% CI for HR	P value*	HR	95% CI for HR	P value*
Age	1.06	1.01-1.11	0.011	1.05	1.01-1.09	0.024	-	-	-	1.04	1.00-1.09	0.040
MRI T staging	2.51	1.21-5.22	0.014	2.50	1.32-4.75	0.005	-	-	-	3.49	1.78-6.85	<0.0001
MRI down-staging	4.82	1.50-15.47	0.008	3.85	1.46-10.15	0.006	4.43	1.08-18.19	0.039	-	-	-
Adjuvant chemotherapy		-	-	0.46	0.22-0.98	0.043	-	-	-	-	-	-
NAR score (continuous)	1.08	1.05-1.12	<0.0001	1.08	1.05-1.11	<0.0001	1.10	1.06-1.15	<0.0001	1.04	1.02-1.07	<0.0001

Abbreviations: 95% CI = 95% confidence interval; DFS = disease-free survival; DRFS = distant recurrence-free survival; HR = hazard ratio; LRFS = locoregional recurrence-free survival; MRI = magnetic resonance imaging; NAR score = neoadjuvant rectal score; OS = overall survival

* P value by Cox regression

TABLE 4. Multivariate analysis of prognostic factors (NAR score in three groups)

Factor	OS			DFS			LRFS			DRFS		
	HR	95% CI for HR	P value*	HR	95% CI for HR	P value*	HR	95% CI for HR	P value*	HR	95% CI for HR	P value*
Age	1.05	1.00-1.09	0.029	1.04	1.01-1.08	0.025	-	-	-	1.05	1.00-1.09	0.031
MRI T staging	2.15	1.07-4.35	0.033	2.13	1.16-3.93	0.015	-	-	-	2.70	1.41-5.19	0.003
NAR score (in 3 groups)	2.58	1.53-4.36	<0.0001	2.43	1.55-3.80	<0.0001	4.02	1.73-9.34	0.001	2.03	1.26-3.27	0.004

Abbreviations: 95% CI = 95% confidence interval; DFS = disease-free survival; DRFS = distant recurrence-free survival; HR = hazard ratio; LRFS = locoregional recurrence-free survival; MRI = magnetic resonance imaging; NAR score = neoadjuvant rectal score; OS = overall survival

* P value by Cox regression

TABLE 5. Prognostic factors that associated with a lower NAR score

NAR score	P value*
Age (< vs ≥ median age)	0.485
Sex (female vs male)	0.586
Location (upper, middle, lower)	0.734
MRI T staging (T2 and T3 vs T4)	0.383
MRI N staging (negative vs positive)	0.059
MRI CRM (not involved vs involved)	0.567
pCR (yes vs no)	<0.0001

Abbreviations: CRM = circumferential resection margin; MRI = magnetic resonance imaging; NAR score = neoadjuvant rectal score; pCR = pathological complete remission

* P value by Cox regression

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Conflicts of interest

All authors have disclosed no conflicts of interest.

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Ethics approval

This study was approved by the New Territories East Cluster–The Chinese University of Hong Kong (NTEC-CUHK) Ethics Committee (Ref NTEC-2019-0086). The requirement for patient consent was waived by the ethics board owing to the retrospective nature of the study.

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