Predicting Response to Total Neoadjuvant Treatment (TNT) in Locally Advanced Rectal Cancer Based on Multiparametric Magnetic Resonance Imaging: A Retrospective Study

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Research

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Abstract

Purpose: To investigate the potential value of magnetic resonance imaging (MRI) in predicting response relevance to total neoadjuvant treatment (TNT) in locally advanced rectal cancer.

Methods: We analyzed MRI of 71 patients underwent TNT from 2015 to 2017 retrospectively. We categorized the response of TNT as CR (complete response) and non-CR, and high, moderate and low sensitivity. Logistic regression analysis was used to identify the best predictors of response. Diagnostic performance was assessed using receiver - operating characteristic curve analysis.

Results: Post–ICT (induction chemotherapy) ΔTL (tumor length), post-CRT (concurrent chemoradiotherapy) ΔLNN (the numbers of lymph node metastases), post–CCT (consolidation chemotherapy) ΔS_{DWI} (maximum cross-sectional area of tumor on diffusion-weighted imaging), post-CCT ADC_T (the mean apparent diffusion coefficient values of tumor) and post-CCT ΔLNV (volume of lymph node) were the best CR predictors. Post-CRT EMVI (extramural vascular invasion) and post-CCT ΔS_{T2} (S on T2-weight) were the best significant factors for high sensitivity.

Conclusions: Post-ICT ΔTL and post-CRT EMVI may an early predictor of CR and high sensitivity to TNT, respectively. The grouping scheme of CR and non–CR was more suitable for predicting response by MRI parameters than high, moderate and low sensitivity.

Trial registration: retrospectively registered

Background

The standard treatment for patients with locally advanced rectal cancer (LARC) is neoadjuvant concurrent chemoradiotherapy, followed by surgical resection with total mesorectal excision (TME)(1). In fact, these patients have significant heterogeneity. Besides, the standard neoadjuvant therapy provided no better the overall survival (OS) and the disease-free survival (DFS) rates compared with surgery and adjuvant chemoradiotherapy(2). It is inappropriate to adopt the same therapeutic modality for all LARC patients. Recently, the National Comprehensive Cancer Network (NCCN) recommended total neoadjuvant treatment (TNT), which is an extensive and optimized therapeutic modality, as an acceptable treatment strategy for LARC. In the phase II clinical trial of TNT(3), patients received induction chemotherapy (ICT) followed by neoadjuvant concurrent chemoradiotherapy (CRT). After that, consolidation chemotherapy (CCT) were delivered. Some studies(2–5) demonstrated that TNT might improve the pathological complete response (pCR) rate and clinical complete response (cCR) rate ranging from 14–36% in the patients with LARC. However, there are still some patients who have poor sensitivity to neoadjuvant chemoradiotherapy(6, 7). It is of great significance to predict the response before or during treatment since the process of TNT is time-consuming. With the response predicted results, we would provide more precise and personalized treatment for patients. If the patients have good response to TNT, Wait & See strategy might be implemented. While those have not good response, we could implement other precision treatment programs that are more suitable for patients.

Magnetic resonance imaging (MRI) is an important method for accurate staging and evaluation of efficacy routinely. It provides parameters to reflect the characteristics of tumors. Some studies reported that MRI parameters such as T2 tumour volume change, relative T2 signal intensity, standardized index of shape, diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC) values, tumour volume, decreased lymph node sizes and extramural vascular invasion (EMVI) may be related to predicting response(8–12). However, the conclusions of various studies were inconsistent. There is still a lack of optimal MRI prediction parameters. Additionally, TNT is a new optimization strategy for LARC. There are few relevant studies that exploring the correlation between MRI parameters and response of TNT so far. Therefore, we need to make further exploration in order to provide new evidence for precision treatment and accurate prediction of the response to neoadjuvant CRT, especially to TNT. The objective of this study was to investigate the potential value of MRI in predicting response relevance to TNT in LARC.

Methods

Patient selection

The inclusive criteria were as follows. 1) Patients had histopathologically confirmed rectal cancer and diagnosed with stage II–III rectal cancer on MRI. 2) Patients must have completed TNT (neoadjuvant pelvic radiotherapy (a total dose of 50–50.4 Gy in 25–28 fractions) and at least 4 cycles of neoadjuvant chemotherapy). 3) MRI scans were performed before TNT (baseline), after at least 4 weeks from the end of CRT (post-CRT) and after CCT (post-CCT), respectively. 4) Patients must have at least two MRI images including $MRI_{baseline}$.

MR technique

All MR imagings were performed at a 3T Magnetom Skyra MR scanner (Siemens Healthcare). A standard T2WI was required by turbo spin-echo in sagittal, oblique coronal planes, and oblique axial. The oblique axial acquisition was performed using the following parameters: TR/TE, 6890/100; FOV, 236 × 260 mm; matrix, 313 × 384; and slice thickness = 3 mm. We used the multishot EPI performed with a reduced TE and encoding time for DWI. TR/TE, 5500/61; slice thickness = 4.5 mm; slice gap = 0.5 mm; FOV, 216 × 216 mm; matrix, 128 × 128; b values of 0, 600, and 1000s/mm^2; echo spacing = 0.4 ms; number of readout segments = 3. The ADC map was automatically generated during image reconstruction.

Data collection

We reviewed and collected MRI parameters, including distance of tumor (DIS), tumor length (TL), circumferential resection margin (CRM), EMVI, anal canal invasion (A), tumor stage (T stage), the mean apparent diffusion coefficient values of tumor (ADC_T), T2 adjusted values of tumor (T2a), maximum cross-sectional area of tumor on diffusion-weighted imaging (S_{DWI}) and T2-weight (S_{T2}), tumor thickness on DWI (TT_{DWI}) and T2-weight (TT_{T2}), tumor volume on T2-weight (TV), the numbers of lymph node metastases (LNN), diameter of lymph node (LND), the mean ADC values of the biggest lymph node (ADC_{LN}), and volume of lymph node on T2 - weight (LNV), which were measured together by two

experienced readers (two radiologists experience over ten years). If two readers have disagreement with each other, the discussion method will be adopted and the final consensus conclusion will be drawn. And the changes in MRI parameters relative to baseline were calculated including percentage change in some parameters between baseline and post-ICT / CRT / CCT MRI (ΔDIS, ΔTL, ΔADC_T, ΔT2a, ΔS_{DWI}, ΔS_{T2}, ΔTT_{DWI}, ΔTT_{T2}, ΔTV, ΔLNN, ΔLND, ΔADC_{LN} and ΔLNV), the downstage in other MRI parameters between baseline and post-ICT / CRT / CCT MRI (D_{CRM}, D_{EMVI}, D_A and $D_{T\ stage}$). (Supplementary file)

Maximum cross-sectional area of tumor was considered as the product of largest diameters and its perpendicular diameters. The EMVI status was determined by the pattern of tumor margin, the size of vessel, the location of vessel relative to the tumor, and caliber of vessel(13). A positive lymph node was defined as ≥ 8 mm in diameter and mixed signal intensity or irregular border on MRI(14–16). A maximum cross – sectional slice of tumor / lymph node was chosen as ROI which entire range delineated was used to measure the ADC value three times, and calculate the mean ADC value(17). TV or LNV = area of every axial slice × slice thickness (pinnacle software). T2a = T2 values of tumor / T2 values of gluteus maximus muscle.

Response evaluation

We categorized the efficacy of TNT as complete response (CR) group vs non-CR group, and high sensitive group vs moderate sensitive group vs low sensitive group.

The system used for TRG as recommended by the AJCC cancer Staging Manual, 8th Edition and the CAP Guidelines is that as modified from Ryan R, et al(18). It defined TRG 0, 1, 2, 3 as no remaining viable cancer cells, only small clusters or single cancer cells remaining, residual cancer remaining but with predominant fibrosis, minimal or no tumor kill in the primary lesion but regardless of lymph node status. PCR was defined as ypT0N0. PCR or patients sustained cCR for 12 months or longer while under non-operative surveillance represented CR(4), whereas the rest were non-CR.

The high sensitive group (H group) included TRG 0 and TRG 1. The moderate sensitive group (M group) defined as ether TRG 2 or patients with TRG 3 and tumor volume of MRI decreased by at least 20% from baseline(11, 19). The low sensitive group (L group) were considered as TRG 3 and tumor volume of MRI did not decrease by 20% from baseline.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and median (range). Categorical variables were expressed as a number (percentage). DIS, TL, ADC_T, T2a, S_{DWI}, S_{T2}, TT_{DWI}, TT_{T2}, LNN, LND, TV, LNV, ADC_{LN} and the percentage changes in MRI parameters between baseline and post-ICT / CRT / CCT MRI were compared between independent response subgroups using Wilcoxon's rank sum test. CRM, EMVI, A, T stage, and the downstage in other MRI parameters between baseline and post-ICT / CRT /CCT MRI between independent response groups were compared using Fisher's Exact test. Logistic regression analysis was used to identify the best predictors of response. Diagnostic performance of the best predictors were assessed using receiver-operating characteristic (ROC) curve analysis, and the sensitivity,

specificity, the optimal cut-off, negative predictive value (NPV), and positive predictive value (PPV) was calculated. The significance level was $P < 0.05$. Statistical analysis was conducted using PASW Statistics (version 25; SPSS, IBM Corp).

Results

Patients

Patients with LARC who underwent TNT before operation in our hospital from 2015 to 2017 were included. Table 1 demonstrated characteristics of patients. The search yielded 71 patients who had baseline MR images. The majority of these patients had MRI_{CRT} and MRI_{CCT} (55 (77.46%) and 49 (69.02%), respectively), 15 (21.13%) had MRI_{ICT}. There were 24 patients (33.80%) who achieved CR. 23 (32.39%) pCR in those who underwent surgery. 7 (9.86%) patients refused surgery after TNT and received Wait & See. Unfortunately, only one person (1.41%) sustained CR for 12 months. Among the 71 patients in the TNT cohort, the pathological TRG was TRG 0 in 24 (37.50%) patients, TRG 1 in 14 (21.88%), TRG 2 in 16 (25.00%) and TRG 3 in 10 (15.63%). According to TRG, 38 (59.38%) patients were classified as H group, 26 (40.63%) were classified as the M group, and no patients was L group (Fig. 1). There was a patient who was TRG 0 but ypN1. Therefore, we believe that he belongs to the high sensitive group and non-pCR group.

Table 1
Patient characteristics.

Variable	Numbers
Cycles of chemotherapy	
ICT	2 (0–5)
CRT	1 (1–3)
CCT	3 (0–5)
Clinical T classification	
T2	2 (2.82%)
T3	49 (69.01)
T4a	14 (19.72%)
T4b	6 (8.45%)
Clinical N classification	
N0	6 (8.45%)
N1	2 (2.82%)
N2	63 (88.73%)
Operation	64 (90.14%)
Wait & See	7 (9.86%)
ypT classification	
T0	24 (37.50%)
T1	2 (3.13%)
T2	11 (17.19%)
T3	26 (40.63%)
T4	1 (1.56%)
ypN classification	
N0	47 (73.44%)
N1	13 (20.31%)
N2	4 (6.25%)

Abbreviations ICT, induction chemotherapy; CRT, concurrent chemoradiotherapy; CCT, consolidation chemotherapy; pCR, pathological complete response; cCR, clinical complete response; H group, the high sensitive group; M group, the moderate sensitive group; L group, the low sensitive group.

Variable	Numbers
MRI	
$MRI_{baseline}$	71 (100%)
$MRI_{baseline}$ + MRI_{ICT}	15 (21.13%)
$MRI_{baseline}$ + MRI_{CRT}	55 (77.46%)
$MRI_{baseline}$ + MRI_{CCT}	49 (69.02%)
Response	
pCR	23 (32.39%)
cCR	1 (1.41%)
Non - pCR	41 (57.75%)
Non - cCR	6 (8.45%)
TRG	
0	24 (37.50%)
1	14 (21.88%)
2	16 (25.00%)
3	10 (15.63%)
Sensitivity	
H group	38 (59.38%)
M group	26 (40.62%)
L group	0 (0%)

Abbreviations ICT, induction chemotherapy; CRT, concurrent chemoradiotherapy; CCT, consolidation chemotherapy; pCR, pathological complete response; cCR, clinical complete response; H group, the high sensitive group; M group, the moderate sensitive group; L group, the low sensitive group.

Correlation between MRI parameters and response to TNT

No significant correlation was noted between response and baseline MRI parameters. Correlations between CR and post-ICT ΔTL (p = 0.008), post-ICT ΔLND (p = 0.019) and post-ICT ΔLNV (p = 0.019) were found. Post-ICT ΔTL was also correlated with high sensitivity to TNT with the p value 0.01 (Table 2).

Table 2
Logistic regression analysis of post - ICT predictive factors of CR and high sensitivity to TNT.

	Univariate (CR)	Multivariate (CR)		Univariate (H group)	Multivariate (H group)	
Parameters	P	95% CI	P	P	95% CI	P
Post - ICT ΔTL	0.008*	2.606–3.208	0.038*	0.01*		0.098
Post - ICT ΔLND	0.019*		0.988	0.300		0.770
Post - ICT ΔLNV	0.019*		0.988	0.188		0.980

Abbreviations ICT, induction chemotherapy; TL, tumor length; LND, diameter of lymph node; LNV, volume of lymph node on T2 – weight.

There were significant correlations between CR and post-CRT EMVI (p = 0.002), post-CRT LNN (p = 0.004), post-CRT LND (p = 0.021), post-CRT ΔLNN p = 0.002) and post-CRT ΔLND (p = 0.021). Only post-CRT EMVI was correlated with high sensitivity of LARC to TNT (p = 0.013) (Table 3).

Table 3
Logistic regression analysis of post - CRT predictive factors of CR and high sensitivity to TNT.

	Univariate (CR)	Multivariate (CR)		Univariate (H group)	Multivariate (H group)	
Parameters	P	95% CI	P	P	95% CI	P
post - CRT EMVI	0.002*		0.709	0.013*	1.55–52.266	0.014*
post - CRT LNN	0.004*		0.978	0.125		0.582
post - CRT LND	0.021*		0.896	0.272		0.719
post - CRT ΔLNN	0.002*	1.209–80.258	0.033*	0.252		0.650
post - CRT ΔLND	0.021*		0.896	0.242		0.591

Abbreviations CRT, concurrent chemoradiotherapy; EMVI, extramural vascular invasion; LNN, the numbers of lymph node metastases; LND, diameter of lymph node.

The following parameters of post-CCT MRI which were significant correlations between CR were evaluated: post-CCT ADC_T (p = 0.008), post-CCT TT_{DWI} (p = 0.031), post-CCT LNV (p = 0.003), post-CCT LNN (p = 0.016), post-CCT ΔS_{DWI} (p = 0.001), post-CCT ΔS_{T2} (p = 0.006), post-CCT ΔTT_{DWI} (p = 0.029), post - CCT ΔLNN (p = 0.008), post-CCT ΔLND (p = 0.046) and post-CCT ΔLNV (p = 0.002). There were many post-CCT MRI parameters had significant correlations between high sensitivity to TNT: post-CCT TL (p = 0.005), post-CCT S_{DWI} (p = 0.036), post-CCT S_{T2} (p = 0.008), post-CCT TT_{DWI} (p = 0.037), post-CCT TT_{T2} (p = 0.009), post-CCT LNV (p = 0.044), post-CCT ΔTL (p = 0.004), post-CCT ΔS_{DWI} (p = 0.009), post-

CCT ΔS_{T2} ($p = 0.001$), post-CCT ΔTT_{T2} ($p = 0.009$), post-CCT ΔTV ($p = 0.007$), post-CCT ΔLNN ($p = 0.016$), post-CCT ΔLNV ($p = 0.019$) and post-CCT $D_{T\ stage}$ ($p = 0.022$) (Table 4).

Table 4
Logistic regression analysis of post - CCT predictive factors of CR and high sensitivity to TNT.

	Univariate (CR)	Multivariate (CR)		Univariate (H group)	Multivariate (H group)	
Parameters	P	95% CI	P	P	95% CI	P
post - CCT ADC_T	0.008*	27.517–52.047	0.003*	0.063		0.392
post - CCT TT_{DWI}	0.031*		0.205	0.037*		0.290
post - CCT ΔTT_{DWI}	0.029*		0.28	0.056		0.231
post - CCT TT_{T2}	0.08		0.921	0.009*		0.89
post - CCT ΔTT_{T2}	0.048*		0.705	0.009*		0.221
post - CCT S_{DWI}	0.064		0.8	0.036*		0.631
post - CCT ΔS_{DWI}	0.001*	6.374–40.883	0.01*	0.009*		0.993
post - CCT S_{T2}	0.104		0.482	0.008*		0.933
post - CCT ΔS_{T2}	0.006*		0.058	0.001*	0.004–0.392	0.006*
post - CCT LNN	0.016*		0.998	0.103		0.68
post - CCT ΔLNN	0.008*		0.127	0.016*		0.209
post - CCT ΔLND	0.046*		0.067	0.056		0.217
post - CCT LNV	0.003*		0.358	0.044*		0.607
post - CCT ΔLNV	0.002*	35.108–61.120	0.017*	0.019*		0.439
post - CCT ΔTV	0.069		0.562	0.007*		0.338

Abbreviations CCT, consolidation chemotherapy; ADC_T, the mean apparent diffusion coefficient values of tumor; TT_{DWI}, tumor thickness on DWI; TT_{T2}, tumor thickness on T2 - weight; S_{DWI}, maximum cross - sectional area of tumor on diffusion-weighted imaging; S_{T2}, maximum cross - sectional area of tumor on T2 - weight; LNN, the numbers of lymph node metastases; LND, diameter of lymph node; LNV, volume of lymph node on T2 - weight; TV, tumor volume on T2 - weight; TL, tumor length; T stage, tumor stage.

	Univariate (CR)	Multivariate (CR)		Univariate (H group)	Multivariate (H group)	
post - CCT TL	0.053		0.618	0.005*		0.356
post - CCT ΔTL	0.098		0.839	0.004*		0.371
post - CCT D_T stage	0.022*		0.421	0.022*		0.561

Abbreviations CCT, consolidation chemotherapy; ADC_T, the mean apparent diffusion coefficient values of tumor; TT_{DWI}, tumor thickness on DWI; TT_{T2}, tumor thickness on T2 - weight; S_{DWI}, maximum cross - sectional area of tumor on diffusion-weighted imaging; S_{T2}, maximum cross - sectional area of tumor on T2 - weight; LNN, the numbers of lymph node metastases; LND, diameter of lymph node; LNV, volume of lymph node on T2 - weight; TV, tumor volume on T2 - weight; TL, tumor length; T stage, tumor stage.

Based on the results of above analysis, ultimately we selected using the method of binary logistic regression to build the response early predicting models. In the binary logistic regression analysis, post-ICT ΔTL (95% CI: 2.606–3.208, p = 0.038), post-CRT ΔLNN (95% CI: 1.209–80.258, p = 0.033), post-CCT ΔS_{DWI} (95% CI: 6.374–40.883, p = 0.01), post-CCT ADC_T (95% CI: 27.517–52.047, p = 0.003) and post-CCT ΔLNV (95% CI: 35.108–61.120, p = 0.017) were found to be the best predictors for CR. Moreover, post-CRT EMVI (95% CI: 1.55–52.266, p = 0.014) and post-CCT ΔS_{T2} (95% CI: 0.004–0.392, p = 0.006) were the best significant factors for high sensitivity to TNT (Table 2–4).

Prediction performances of MRI parameters for response

Based on logistic regression model, ROC curve analysis was used to explore the role of the best predictors. Figure 2 present ROC curve results for MRI parameters differentiating CR from non-CR. Besides, ROC curve results are reported that MRI parameters predicting H group in Fig. 3. Corresponding data are provided in Table 5. In terms of individual parameter prediction response, post-ICD ΔTL was selected as the best predictor of CR by logistic regression model (AUC 0.92, specificity 80%, sensitivity 100%, NPV 100%, PPV 71.4%, ACC 86.7%, p = 0.01). ROC analysis also showed that post-CCT ΔS_{T2} had a moderate predicting performance in identifying H group (AUC 0.78, specificity 80%, sensitivity 76.2%, NPV 76.2%, PPV 80%, ACC 78.3%, p = 0.001). In particular, the combination of post-CCT ΔS_{DWI}, post-CCT LNV and post-CCT ADC_T had best predicting performance of CR, with AUC 0.94, a sensitivity of 94.1%, and a specificity of 90.6% (Fig. 4).

Table 5
Multivariate analysis results about magnetic resonance imaging (MRI) findings for the prediction of CR and high sensitivity to TNT.

Parameters	AUC (95% CI)	SEN	SPE	PPV	NPV	ACC	P value
MRI findings for the prediction of CR							
Post-ICD ΔTL	0.92 (0.778–1.000)	100%	80%	71.4%	100%	86.7%	0.01
Post-CRT ΔLNN	0.75 (0.603–0.891)	71.4%	79.4%	68.2%	81.8%	76.4%	0.002
Post-CCT ΔS_{DWI}	0.78 (0.646–0.92)	70.6%	81.2%	66.7%	83.9%	77.6%	0.001
Post-CCT ADC_T	0.72 (0.672–0.866)	64.7%	75%	57.9%	80%	71.4%	0.012
Post-CCT ΔLNV	0.76 (0.629–0.899)	82.4%	71.9%	60.9%	88.5%	75.5%	0.003
Post-CCT ΔS_{DWI} + Post-CCT ADC_T	0.86 (0.766–0.962)	94.1%	68.7%	61.5%	95.7%	77.6%	< 0.001
Post-CCT ΔS_{DWI} + Post-CCT ΔLNV	0.87 (0.766–0.97)	76.5%	81.2%	68.4%	86.7%	79.6%	< 0.001
Post-CCT ADC_T + Post-CCT ΔLNV	0.88 (0.786–0.972)	100%	62.5%	58.6%	100%	75.5%	< 0.001
Post-CCT ΔS_{DWI} + Post-CCT ADC_T + Post-CCT ΔLNV	0.94 (0.873–1)	94.1%	90.6%	84.2%	96.7%	91.8%	< 0.001
MRI findings for the prediction of high sensitivity to TNT							
Post-CRT EMVI	0.69 (0.543–0.846)	100%	80%	76%	100%	68%	0.022

Abbreviations MRI, magnetic resonance imaging; ICT, induction chemotherapy; CRT, concurrent chemoradiotherapy; CCT, consolidation chemotherapy; TL, tumor length; LNN, the numbers of lymph node metastases; S_{DWI}, maximum cross - sectional area of tumor on diffusion-weighted imaging; ADC_T, the mean apparent diffusion coefficient values of tumor; LNV, volume of lymph node on T2 - weight; EMVI, extramural vascular invasion; S_{T2}, maximum cross - sectional area of tumor on T2 - weight.

Parameters	AUC (95% CI)	SEN	SPE	PPV	NPV	ACC	P value
Post-CCT ΔS_{T2}	0.78 (0.645–0.917)	80%	76.2%	80%	76.2%	78.3%	0.001

Abbreviations MRI, magnetic resonance imaging; ICT, induction chemotherapy; CRT, concurrent chemoradiotherapy; CCT, consolidation chemotherapy; TL, tumor length; LNN, the numbers of lymph node metastases; S_{DWI}, maximum cross - sectional area of tumor on diffusion-weighted imaging; ADC_T, the mean apparent diffusion coefficient values of tumor; LNV, volume of lymph node on T2 - weight; EMVI, extramural vascular invasion; S_{T2}, maximum cross - sectional area of tumor on T2 - weight.

Discussion

In the present study, MRI parameters of TNT patients in three different neoadjuvant treatment phases were used to predict response. It is the first study that using MRI parameters to predict response of TNT. Most studies have used good responder and poor responder according to TRG as an evaluation method(9, 20, 21). Actually, TRG is subjective(22). The sensitivity to TNT was grouped according to tumor volume reduction rate on MRI and TRG of LARC following treatment with TNT. In this study, there was no L group but only H group and M group, which may be because TNT is the strongest neoadjuvant therapy. More studies(3, 23–25) have reported that patients could achieve a high rate of CR. We used two modes to group the response to TNT. Compared with grouping scheme of H group vs M group vs L group, CR vs non-CR has more significant results in predicting response by MRI parameters, and this grouping mode is more suitable for it.

We found post-ICT ΔTL offered the good results for the detection of patients with a CR after TNT. Currently, there are very few researches that have described MRI parameters of post-ICT ΔTL for predicting a CR. The smaller post-nCRT tumor length predicted an increased pCR rate in the previous studies(20, 26, 27). FOWARC analyzed MRI images of 403 patients and found that baseline TL was a significant factor for predicting pCR probability and patients with TL (> 3 cm) may have a lower pCR

probability(28). In our study, there was significant difference of post-ICT ΔTL between CR and non-CR. During induction chemotherapy, the tumor length of CR and non-CR decreased by 33% (range: 17% – 39%) and 4% (range: -5% – 27%). Although our sample size is only 15 cases, integrating the result and practice experience we may conclude that the larger the post-ICT ΔTL predicted the more the tumor regression and the higher the probability of CR. Post-ICT ΔTL might be an early prediction parameter of CR. It has important reference value to help predict the sensitivity of neoadjuvant chemoradiotherapy and adjust the treatment plan as soon as possible.

Unlike other studies, we explored that post-CRT EMVI had a great predicting performance in identifying H group. When the post-CRT EMVI status was negative, sensitivity of patients to TNT was higher than positive. In previous literature by Lee et al(12), post-CRT EMVI was the only significant MRI factor in DFS. Long-term results from the GEMCAD 0801 trial(29) and Meng et al(30) considered baseline mrEMVI positivity was an independent prognostic indicator for DFS. Most previous studies have explored the relationship between EMVI and prognosis, yet we explored the correlation between EMVI and response and obtained good positive results. This maybe because radiation was effective in wiping out pathways of vascular spread in the pelvis(29).

Regarding the definition of lymph node, Brown et al(14) found that if a node was defined as suspicious because of an irregular border or mixed signal intensity. Koh et al(16) recommend the use of the short-axis diameter of 8 mm for positive pelvic nodes. So we combined the above two to define the positive lymph node. In the study, the more post-CRT ΔLNN and post-CCT ΔLNV provoked more chance of CR and high sensitivity to TNT in our study. At this point, patients who had post-CRT $\Delta LNN \geq 70\%$ would be more easier to achieve CR. Bustamante-Lopez et al(31) found only pCR showed a significant association with < 12 baseline LN. However, none of the previous studies had indicated correlation between post-CRT ΔLNN or post-CCT ΔLNV and response so far. It may be associated with the definition of positive lymph node is different and subjective.

DWI is increasingly incorporated in clinical rectal MRI exams worldwide(32). Moreover, the DWI-derived ADC values can be used for quantitative analysis of tumorous cellular density and extracellular space(17). ADC values are mainly negatively related to cell density and positively related to extracellular space(17, 20, 21). After consolidation chemotherapy, some tumor tissue was replaced by fibrous tissue. Post-CCT ADC_T reflects the tissue density after TNT rather than only the tumor cell. Fibrotic tissue generally has low ADC(21). Consequently, Post-CCT ADC_T may be a useful parameter for discriminating between CR and non-CR. Several articles focused on post-CRT ADC and post-CRT ΔADC(33–35). However, we found ADC_T of post-CCT MRI was associated with response. This differs from above studies.

There were a few limitations in the study that must be considered. Firstly, our study was a retrospective analysis with a small sample size, thus above conclusions need further validation and support. In addition, we did not compare the same parameter of post-ICT MRI, post-CRT MRI and post-CCT MRI to confirm that it can better reflect the response at a certain phase. Because many patients may have only

two phases of treatments. Thirdly, we assessed S_{DWI} and S_{T2} by measuring manually its long diameter and short diameter, and the area measured may be not accurate. Use of the image processing software may increase the accuracy.

Conclusions

Consequently, post-ICT ΔTL, post-CRT ΔLNN, post-CCT ΔS_{DWI}, post-CCT ADC_T and post-CCT ΔLNV were related to CR. Post-CRT EMVI and post-CCT ΔS_{T2} were correlated with high sensitivity to TNT. In addition, the combination of post-CCT ΔS_{DWI}, post-CCT LNV and post-CCT ADC_T had best predicting performance of CR. Instead of using more image information that can be deeply mined, such as radiomics(36-39) and deep learning mining image information(40-42), we use more common MRI parameters in clinic. Therefore, further studies are indicated to explore the best predictor of response.

Abbreviations

MRI	Magnetic resonance imaging
TNT	Total neoadjuvant treatment
ICT	Induction chemotherapy
CRT	Concurrent chemoradiotherapy
CCT	Consolidation chemotherapy
CR	Complete response
pCR	Pathological complete response
cCR	Clinical complete response
LARC	Locally advanced rectal cancer
TME	Total mesorectal excision
OS	Overall survival
DFS	Disease-free survival
NCCN	The National Comprehensive Cancer Network
DWI	Diffusion-weighted imaging
ADC	Apparent diffusion coefficient
EMVI	Extramural vascular invasion
DIS	Distance of tumor
TL	Tumor length
CRM	Circumferential resection margin
A	Anal canal invasion
T stage	Tumor stage
ADC_T	The mean apparent diffusion coefficient values of tumor
T2a	T2 adjusted values of tumor
S_{DWI}	Maximum cross-sectional area of tumor on diffusion-weighted imaging
S_{T2}	Maximum cross-sectional area of tumor on T2-weight
TT_{DWI}	Tumor thickness on DWI
TT_{T2}	Tumor thickness on T2-weight
TV	Tumor volume on T2-weight

LNN	The numbers of lymph node metastases
LND	Diameter of lymph node
ADC_{LN}	The mean ADC values of the biggest lymph node
LNV	Volume of lymph node on T2-weight
NPV	Negative predictive value
PPV	Positive predictive value
ROC	Receiver-operating characteristic
AUC	Area under the curve

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from Ethics committee on Biomedical Research, West China Hospital of Sichuan University (2020-903).

Patient consent to review their medical records was not required. The reasons for the waiver were as follows. Firstly, this is a retrospective study. There was no additional risk to patients. In the process of ethical approval, we have submitted to the ethics committee the application for exemption from informed consent of patients. Additionally, we abided by the Declaration of Helsinki. We collected de-identified data of patients. And the final results of the study would be anonymity.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Xin Wang, Ganlu Ouyang, Jin Yao and Xibiao Yang designed the study. Ganlu Ouyang designed the study, acquired the data, performed the statistical analysis and wrote the manuscript. Xibiao Yang acquired the data and conducted the quality control of data. Xiangbing Deng, Wenjian Meng and Yongyang Yu acquired and interpreted the data. Bing Wu provided imaging data. Dan Jiang provided pathological data. Pei Shu acquired the data and performed the statistical analysis. Ziqiang Wang, Jin Yao and Xin Wang critically revised the manuscript's intellectual content. All authors read and approved the final manuscript.

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Not applicable.

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Figures

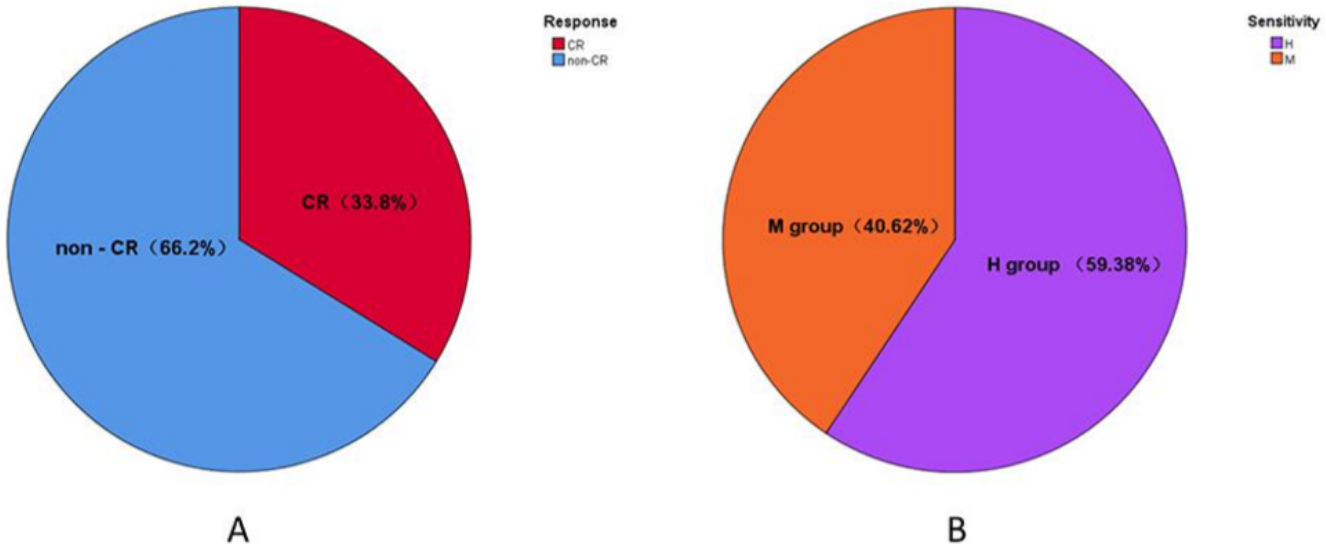

Figure 1

(A) Distribution of CR vs non – CR. (B) Distribution of the high sensitive group (H group) vs the moderate sensitive group (M group) vs the low sensitive group (L group).

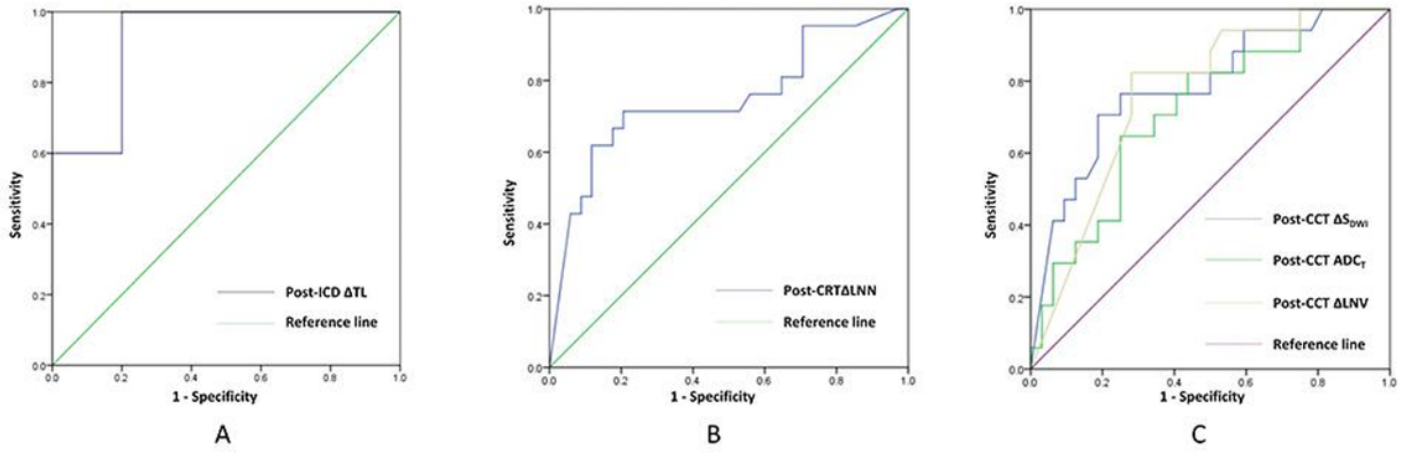

Figure 2

A) ROC curves of predicting CR in the post - ICT MRI cohorts. (B) ROC curves of predicting CR in the post - CRT MRI cohorts (C) ROC curves of predicting CR in the post - CCT MRI cohorts. Figure

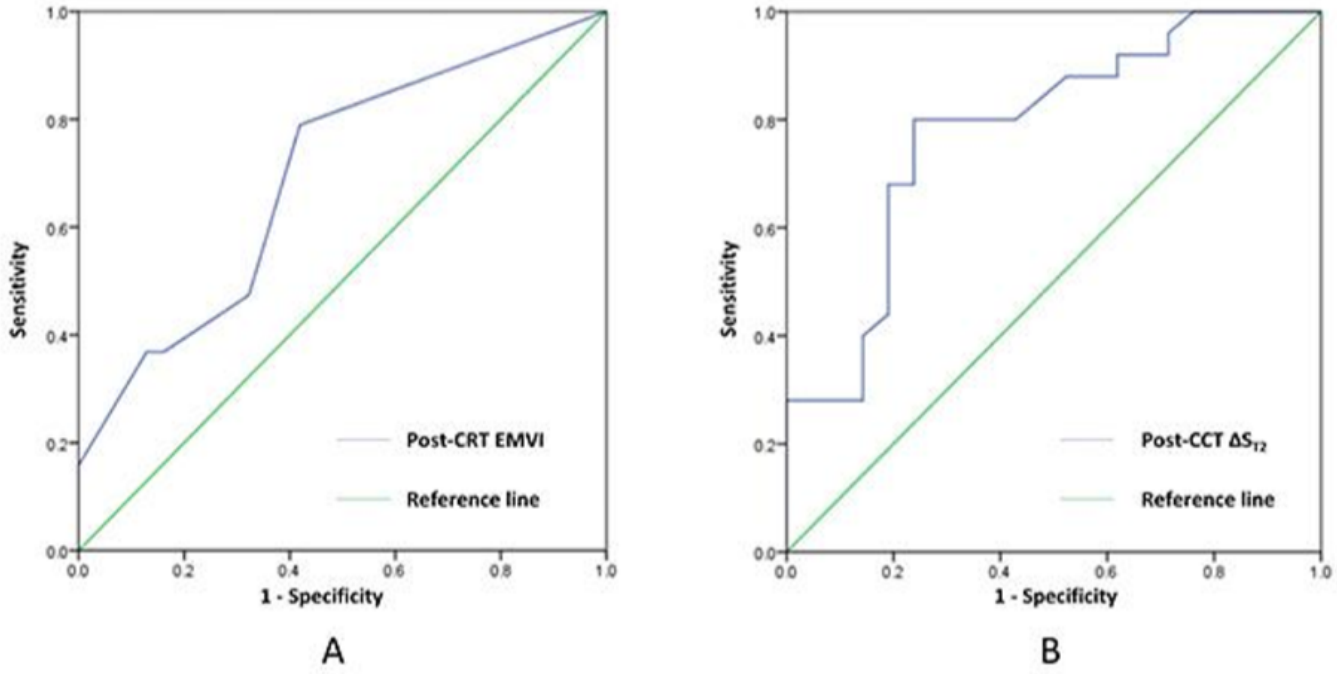

Figure 3

(A) ROC curves of predicting the high sensitive group (H group) in the post - CRT MRI cohorts. (B) ROC curves of predicting the high sensitive group (H group) in the post - CCT MRI cohorts.

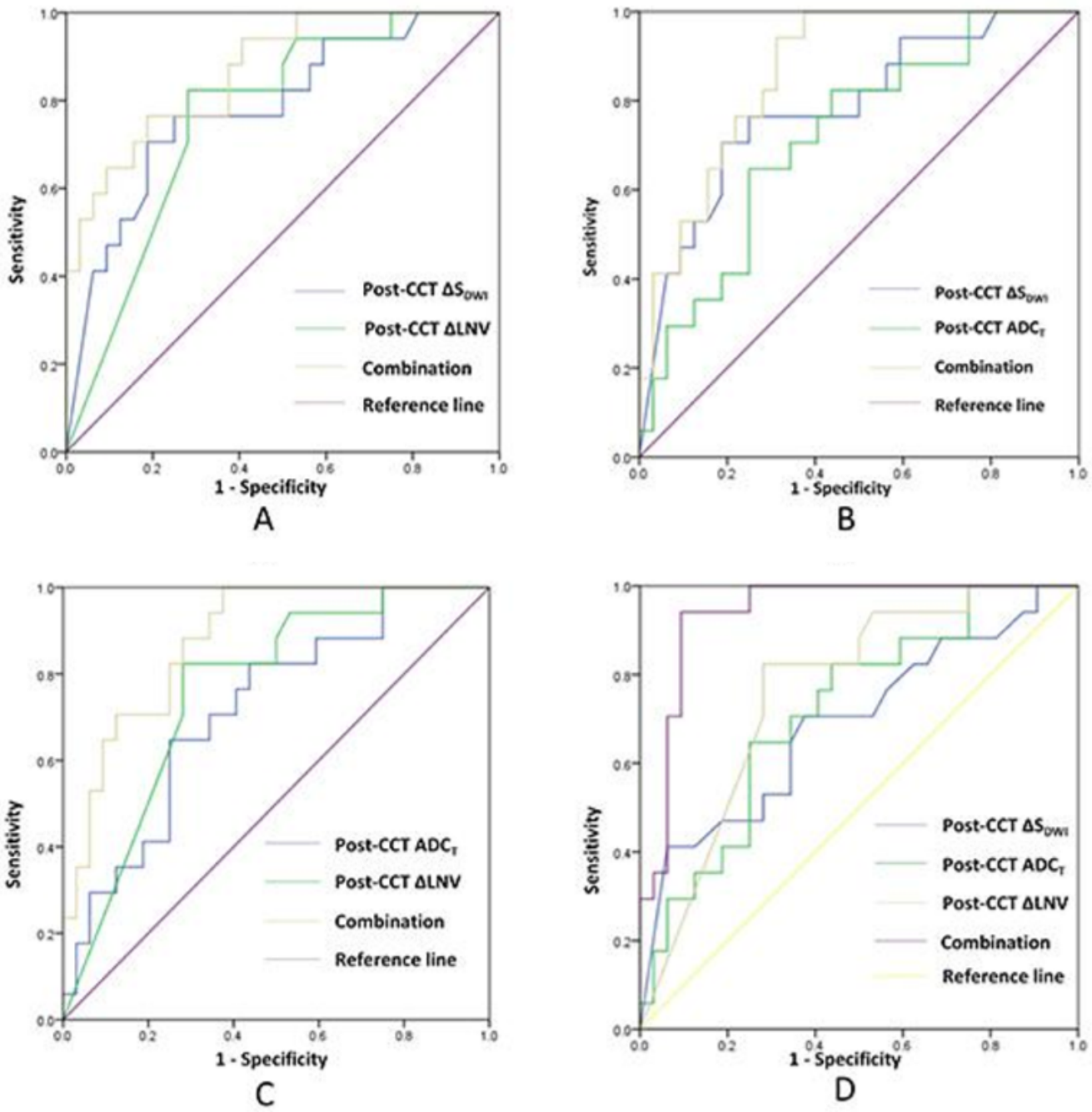

Figure 4

(A) ROC curves of predicting CR (combination of post – CCT ΔSDWI and post – CCT ΔLNV). (B) ROC curves of predicting CR (combination of post – CCT ΔSDWI and post – CCT ADCT). (C) ROC curves of predicting CR (combination of post – CCT ADCT and post – CCT ΔLNV). (D) ROC curves of predicting CR (combination of post – CCT ΔSDWI, post – CCT ADCT and post – CCT ΔLNV).

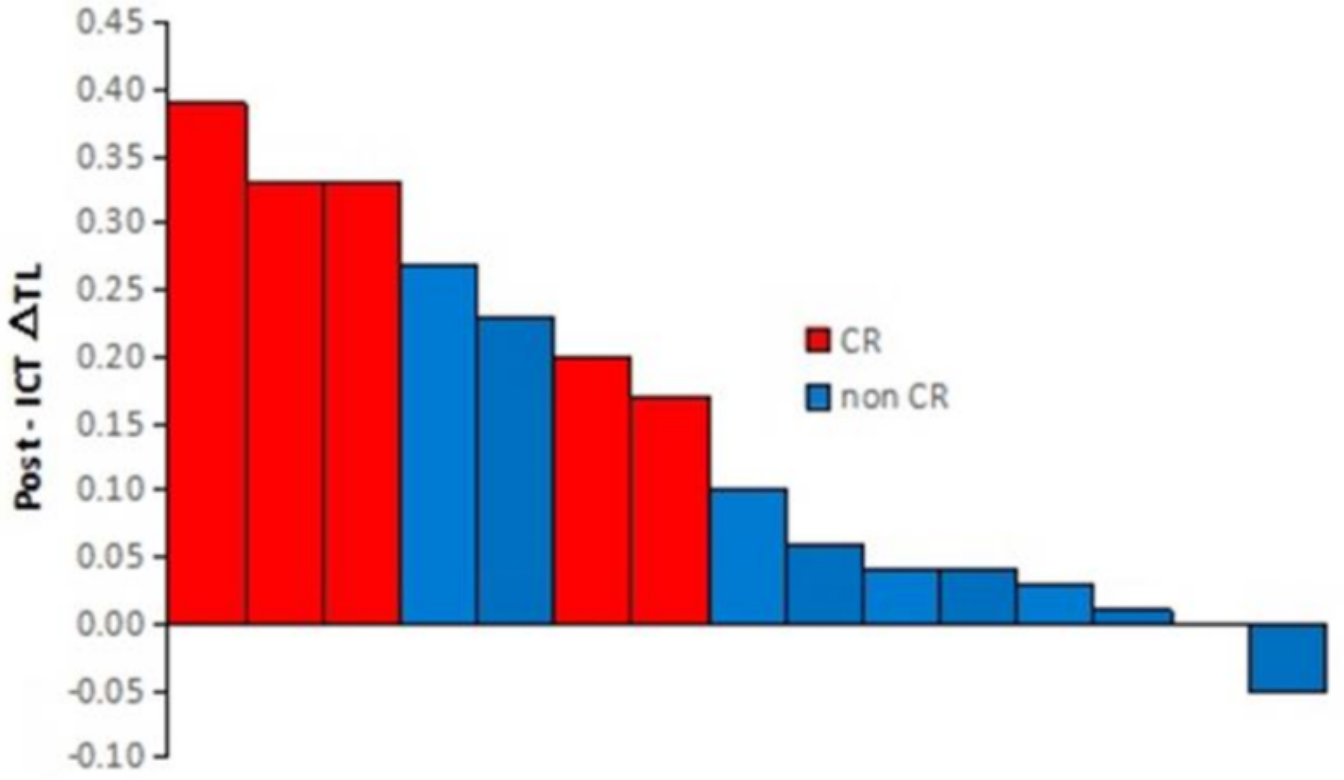

Figure 5

Post - ΔTL of CR vs non – CR for each patient.

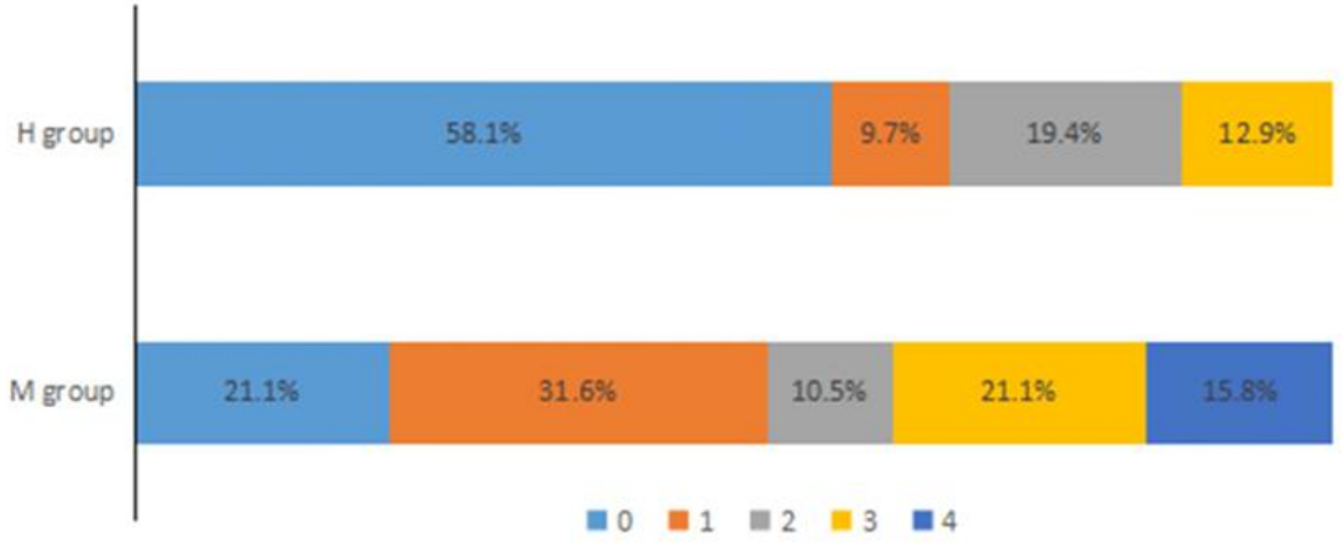

Figure 6

Post - CRT EMVI of H group vs M group for each patient.

Supplementary Files

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