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Beneficiaries of radical surgery among clinical complete responders to neoadjuvant chemoradiotherapy in rectal cancer

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Abstract

This study aimed to identify patients who benefit from radical surgery among those with rectal cancer who achieved clinical complete response (cCR). Patients with locally advanced rectal cancer (LARC; stage II/III) who achieved cCR after neoadjuvant chemoradiotherapy (nCRT) were included (n = 212). Univariate/multivariate Cox analysis was performed to validate predictors for distant metastasis-free survival (DMFS). A decision tree was generated using recursive partitioning analysis (RPA) to categorize patients into different risk stratifications. Total mesorectal excision (TME) was compared with the watch-and-wait (W&W) strategy in each risk group. Two molecular predicators of CEA and CA19-9 were selected to establish the RPA-based risk stratification, categorizing LARC patients into low-risk (n = 139; CA19-9 < 35 U/mL and CEA < 5 ng/mL) and high-risk (n = 73; CA19-9 ≥ 35 U/mL or CEA ≥5 ng/mL) groups. Superior 5-y DMFS was observed in the low-risk group vs. the high-risk group (92.9% vs. 76.2%, P = .002). Low-risk LARC patients who underwent TME had significantly improved 5-y DMFS compared with their counterparts receiving the W&W strategy (95.9% vs. 84.3%; P = .028). No significant survival difference was observed in high-risk patients receiving the 2 treatment modalities (77.9% vs. 94.1%; P = .143). LARC patients with cCR who had both baseline CA19-9 < 35 U/mL and CEA < 5 ng/mL may benefit from radical surgery.

KEYWORDS
clinical complete response, locally advanced rectal cancer, long-term survival, risk classification, watch-and-wait

1 | INTRODUCTION

Colorectal cancer is the third most commonly diagnosed cancer and the second most lethal cancer in both sexes.[1] With the cancer profile in China gradually shifting to the western distribution, an increase in colorectal cancer incidence has been observed, especially in urban areas.[2] According to the National Comprehensive Cancer Network clinical guidelines, preoperative chemoradiotherapy followed by total mesorectal excision (TME) plus adjuvant chemotherapy is the current standard therapeutic schedule for locally advanced rectal cancer (LARC). Approximately 15%-27% of patients with LARC treated with standard treatment will experience pathological complete response (pCR), with no residual tumor reported in histological findings, which indicates a favorable prognosis.[3] Evidently, these pCR patients do not need to receive radical surgery as no tumor cells exist in the original tumor site. Although the treatment strategy provides excellent oncologic control, it potentially brings about operation-related complications and severe social contact problems.[4,5] Up to 82.6% of the patients who underwent sphincter-sparing surgery suffered from a collection of bowel dysfunction syndromes called low anterior resection syndrome (LARS), which is characterized by frequent bowel movements, fecal incontinence and urgency.[6,7] Moreover, for patients with distal rectal cancer, permanent colostomy is the most disturbing problem. Therefore, surgery immensely impairs the quality of life of patients.

It was reported that approximately 30% of patients with LARC can achieve cCR after neoadjuvant chemoradiotherapy (nCRT).[8,9] Although many exploratory studies have focused on the application of TME for patients with LARC after cCR, the results were not in agreement and yielded controversial conclusions. The watch-and-wait (W&W) strategy, including both omission of TME and strict routine surveillance, is a practicable alternative option for LARC patients with cCR. On the one hand, past study results have indicated that the long-term overall survival of cCR patients undergoing the W&W strategy was equivalent to that of pCR patients.[10-13] Although patients undergoing the W&W strategy may have a significantly higher risk of local recurrence (LR), recurrence can be well managed with salvage surgery in 88%-97% of cases, as this treatment warrants effective tumor control.[8,9,13-18] Moreover, the W&W strategy has an obvious superiority over TME in saving medical cost and preserving physical and social function, such as avoiding surgery-related complications and maintaining a well-functioning anorectum.[19,20] On the other hand, although most instances of LR could be salvaged by surgery, these patients had a significantly higher rate of distant metastasis compared with patients without LR (36% vs. 1%, $P < .01$).[21] It seems that not all patients with LARC who have achieved cCR are suitable to undergo the W&W strategy. One way to address this issue is to determine which patients benefit from radical surgery among those with cCR after nCRT. Molecular factors, such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), have been proven to be associated with the prognosis of patients with colorectal cancer,[22-25] which may help to establish a risk stratification for precise treatment.

Therefore, this retrospective study established, validated, and applied decision trees that combine the 8th edition of the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) staging system, CEA, and CA19-9 for patients with LARC, with the aim of identifying the subgroups of clinical complete responders who had a relatively low risk of distant metastasis and can benefit most from radical surgery.

2 | MATERIALS AND METHODS

2.1 | Patients

Patients with LARC (ie, T_{any}N1-2M0 and T3-4N0M0) diagnosed by biopsy and imaging examinations who received nCRT in Sun Yat-sen University Cancer Center in the period of 2010 to 2018 were retrospectively reviewed. Patients with multiple primary colorectal tumors, inflammatory bowel disease, concurrent metastasis, concurrent other malignancies, prior history of malignant tumor, and those who had already received any antitumor treatment before admission were excluded.

Pretreatment staging was determined by electronic colonoscopy or endoscopic ultrasonography, pelvic magnetic resonance imaging (MRI), and thoracoabdominal computed tomography (CT). All patients underwent full colonoscopy to assess tumor morphology and the distance from the lower edge of the tumor to the anal verge. Primary staging was mainly based on pelvic MRI scans, including T2-weighted imaging and diffusion-weighted MRI, to confirm tumor infiltration depth and nodal status. Patients also underwent thoracoabdominal CT scans to exclude distant metastasis or any other synchronous primary tumor. Before treatment, baseline information, including serum CEA and CA19-9 concentrations, was collected. Assessment of cCR was consistent with the criteria published formerly by Maas Monique and Habr-Gama.[12,26,27] Clinical complete responders were fully informed of the expected goal and all risks of the W&W policy and decided to receive the W&W or standard TME according to their willingness.

2.2 | Treatment and evaluation of therapeutic efficacy

In total, 3 or 4 cycles of neoadjuvant chemotherapy were adopted before the evaluation of cCR. An optional cycle of chemotherapy based on the CapeOX regimen, which consisted of capecitabine alone (1000 mg/m^2, twice daily for 14 d every 3 wk) with or without oxaliplatin (130 mg/m^2, d 1), could be elected before radiotherapy. All patients were treated by intensity-modified radiotherapy (50 Gy in 25 fractions) plus 2 cycles of dose-modified concurrent chemotherapy (capecitabine alone [1000 mg/m^2, twice daily for 14 d every 3 wk] with or without oxaliplatin [100 mg/m^2, d 1]), followed by one cycle of CapeOX regimen-based chemotherapy.[28,29] Patients were scheduled for thorough re-examinations to evaluate the clinical response

4-12 wk after the completion of radiotherapy, including electronic colonoscopy, pelvic MRI, thoracoabdominal CT, and blood examination. The actual time interval from the end of radiotherapy to reexamination of the 212 patients was 28-120 d (average 42.7 d, IQR = 39-46 d).

As the standard definition of cCR is still under discussion, we evaluated the original tumor lesions according to previously published articles by authorities on this subject.[11,12,26,27] The assessment criteria adopted in this study are as follows: (a) tumor-related symptoms relieved to a great extent; (b) serum concentration of tumor biomarkers including CEA and CA19-9 reduced to normal levels; (c) no palpable tumor with digital rectal exam; (d) no residual tumor mass or ulceration, with or without telangiectasia or white flat scar at endoscopic assessment; (e) negative biopsies (only performed when necessary); (f) no residual tumor or lymph nodes on MRI; and (g) no new metastasis on MR or CT scan. Patients who chose surgery were scheduled to receive TME 4-12 wk after the completion of nCRT and to receive adjuvant chemotherapy thereafter. Patients in the W&W group started chemotherapy when they decided not to receive radical surgery. All patients planned to complete 6 mo of systematic chemotherapy. The actual completed cycles of chemotherapy and detailed baseline information are provided in Table 1.

2.3 | Follow-up and endpoint

Follow-up consisted of routine blood examination, serum concentration of CEA and CA19-9, colonoscopy, pelvis MRI, and thoracoabdominal CT. Patients were informed of routine surveillance every 3 mo during the first 3 y after the completion of treatment, then once semiannually, and then once per year after the 5th y post-treatment. The primary endpoint was metastasis-free survival (DMFS), measured from the day of diagnosis to the occurrence of distant metastasis. Secondary endpoints included overall survival (OS), disease-free survival (DFS) and local recurrence-free survival (LRFS). OS was recorded as the length of the time from day of diagnosis to death (any cause) or the latest known date alive; DFS was time from diagnosis to failure, death or last follow-up visit, whichever occurred first; and LRFS was the time from diagnosis to local recurrence.

2.4 | Statistical analyses

Assessment of clinical response and grouping of cases were performed as previously described. We included 9 potential indicators in this analysis. Continuous variables were converted into categorical variables using interquartile range (eg, age, distance from lower edge of tumor to anal verge) or clinical cut-off values (eg, CEA and CA19-9). Survival rates were determined by the Kaplan-Meier method and were compared by log-rank tests.[30] Univariate Cox regression analyses were performed to quantify the effect of predictors on DMFS, and predictors with P-values < .05 were put into the multivariate

analysis to validate their significance using the backward stepwise algorithm.[31,32]

A nomogram for DMFS was generated based on the multivariate Cox regression results, and concordance index (c-index) values were used to evaluate its performance by assessing the discrimination performance between the nomogram-predicted value and the Kaplan-Meier-calculated survival rate.[32] To allocate patients into groups according to the risk of distant metastasis (high vs. low), recursive partitioning analysis (RPA) was performed by incorporating the validated prognostic factors in the nomogram for DMFS using the *rpart* package in R software.[33] Hazard ratio (HR) was used as a summary statistic to quantitatively measure the risk of distant metastasis in different RPA-based stratifications. Comparison of the survival rates of patients who underwent the W&W strategy or TME was performed with the Kaplan-Meier method to identify patients who would benefit most from radical surgery. All statistical analyses were performed with SPSS 25.0 and the RMS package in R v.3.3.2 (http://www.r-project.org/). P-values were two-sided, and differences with P-values < .05 were considered significant.

3 | RESULTS

3.1 | Patient information

In total, 1463 patients with newly diagnosed LARC treated with nCRT were screened, of which 234 (16%) patients achieved cCR. We excluded 22 cases due to the lack of clinical information. As a result, 212 patients were retrospectively analyzed in this study, with 52 patients (24.5%) managed by the W&W strategy and 160 (75.5%) treated by TME. The median age of all included patients was 58 y old (IQR = 47-65 y), and the median follow-up time was 55.3 mo (IQR = 40.0-74.3 mo). Males and females accounted for 62.3% and 37.3% of all patients, respectively. Eight (3.8%) and 24 (11.3%) patients individually developed LR and distant metastasis, and 12 patients (5.7%) died based on the latest follow-up. Generally, the 5-y OS, DFS, LRFS and DMFS rates of the 212 patients were 94.8%, 87.4%, 96.2%, and 88.9%, respectively. Patients who developed distant metastasis had a 5-y OS of 61.8%, which was significantly lower than that of their counterparts without distant metastasis (98.7%; P < .001).

3.2 | RPA-generated risk stratification for DMFS

Baseline characteristics including age, sex, complications of systematic disease, serum concentration of CEA and CA19-9, T category, N category, histological grade, and the distance to anal verge were included in the univariate analysis. Predictors with P-values < .05 were selected for the multivariate analysis, which showed that histological grade, CEA, and CA19-9 had significant effects on DMFS (Table 1). Compared with patients with poorly differentiated adenocarcinoma, patients with moderately differentiated adenocarcinoma or high-grade neoplasia had lower HRs (0.58 and 0.45, respectively). We used 5 ng/mL and

TABLE 1 Clinicopathological characteristics of the 212 patients with LARC and univariate and multivariate analysis

Characteristic	Entire cohort (%)	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P	HR (95% CI)	P
Age, y					
27-47	55 (25.9%)	Reference	.590*	-	-
48-57	49 (23.1%)	1.15 (0.40-3.28)	.790	-	-
58-64	54 (25.5%)	0.99 (0.33-2.96)	.990	-	-
≥65	54 (25.5%)	0.45 (0.12-1.75)	.250	-	-
Sex					
Male	132 (62.3%)	Reference		-	-
Female	80 (37.7%)	1.66 (0.73-3.77)	.220	-	-
Systematic disease					
No	139 (65.6%)	Reference	.420*	-	-
Yes (1 type)	59 (27.8%)	0.50 (0.17-1.49)	.210	-	-
Yes (>1 type)	14 (6.6%)	0.57 (0.08-4.27)	.580	-	-
T category					
T2	15 (7.1%)	Reference	.590*	-	-
T3	146 (68.9%)	1.98 (0.26-14.83)	.510	-	-
T4	51 (24.1%)	1.23 (0.14-11.05)	.850	-	-
N category					
N0	54 (25.5%)	Reference	.280*	-	-
N1	102 (48.1%)	0.95 (0.32-2.83)	.930	-	-
N2	56 (26.4%)	1.92 (0.64-5.73)	.240	-	-
Baseline CEA					
<5 ng/mL	151 (71.2%)	Reference		Reference	
≥5 ng/mL	61 (28.8%)	3.14 (1.38-7.14)	0.006	2.71 (1.11-6.62)	.030
Baseline CA19-9					
<35 U/mL	183 (86.3%)	Reference		Reference	
≥35 U/mL	29 (13.7%)	3.73 (1.58-8.80)	.003	2.81 (1.12-7.04)	.030
Histological grade					
Poorly differentiated	25 (11.8%)	Reference	.013*	Reference	.020
Moderately differentiated	163 (76.9%)	0.61 (0.20-1.83)	.380	0.58 (0.19-1.76)	.330
Well differentiated	1 (0.5%)	18.85 (1.94-183.44)	.010	35.22 (3.46-358.43)	.030
High-grade neoplasia	23 (10.8%)	0.50 (0.09-2.72)	.420	0.45 (0.08-2.47)	.360
Distance to anal (cm)					
≤3.0	59 (27.8%)	Reference	.440*	-	-
≤5.0	76 (35.8%)	1.36 (0.46-4.08)	.580	-	-
≤6.5	24 (11.3%)	2.28 (0.66-7.88)	.190	-	-
>6.5	53 (25.0%)	0.84 (0.23-3.14)	.800	-	-
Total cycles of chemotherapy					
<8	109 (51.4%)	Reference	.897*	-	-
=8	97 (45.8%)	1.02 (0.45-2.31)	.962	-	-
>8	6 (2.8%)	1.62 (0.21-12.48)	.643	-	-

*P-values indicated the measurement of difference among all items of a variable.

35 U/mL as the cut-offs for CEA and CA19-9, respectively, according to actual clinical practice. Patients with baseline CEA ≥5 ng/mL had significantly worse DMFS compared with patients with CEA < 5 ng/mL (HR = 2.71, P = .03). The patients with baseline CA19-9 ≥ 35 U/mL had worse DMFS compared with patients with CA19-9 < 35 U/mL (HR = 2.81, P = .03). The detailed results of the univariate and

multivariate analyses are presented in Table 1. The nomogram for 3-y and 5-y DMFS in all included 212 patients with LARC is shown in Figure S1.

As distant metastasis significantly decreases patients' OS, we conducted RPA based on the validated predictors in the nomogram for DMFS to select the patients having a low risk of distant metastasis, who may benefit most from radical surgery favoring TME but not the W&W strategy. The RPA-based risk stratification was established with the values for CEA and CA19-9. As shown in Figure 1, the decision tree suggested that all included patients with LARC were categorized into a low-risk group (n = 139; CA19-9 < 35 U/mL and CEA < 5 ng/mL) and a high-risk group (n = 73; CA19-9 ≥ 35 U/mL or CEA ≥ 5 ng/mL). Patients with CA19-9 ≥ 35 U/mL had obviously high risk compared with patients with CA19-9 < 35 U/mL (HR = 2.329), and patients with CEA < 5ng/mL had obviously low risk compared with patients with CEA ≥5 ng/mL (HR = 0.5969).

Patients in the low-risk group had significantly better DMFS and DFS compared with those in the high-risk group, although no significant differences in OS and LRFS were found between the low-risk and high-risk groups (Figure 2). The 5-y DMFS rates of low-risk and high-risk patients were 92.9% vs. 76.2% (P = .002), and the 5-y DFS rates of the 2 groups of patients were 90.7% vs. 76.2% (P = .016), respectively.

3.3 | Selection of patients who may benefit from TME

As shown in Figure 3, patients in the low-risk group had significantly improved 5-y DMFS when treated with TME vs. the W&W

strategy (95.9% vs. 84.3%; P = .028). No difference in 5-y DMFS was observed between high-risk patients receiving TME and those undergoing the W&W strategy (77.9% vs. 94.1%; P = .143). Moreover, low-risk patients had significantly better 5-y OS (99.0% vs. 92.3%, P = .050), DFS (95.9% vs. 75.3%, P < .001), and LRFS (99.0% vs. 82.0%, P < .001) when they were treated with TME vs. the W&W strategy. High-risk patients acquired no such survival benefit from TME (Figure S2).

4 | DISCUSSION

Although there are some studies on the subject of the W&W strategy for rectal cancer, it is still unclear whether skipping radical surgery confers an increased risk of distant metastasis to patients receiving nonoperative management. We developed a nomogram based on single-centered retrospective data to predict 3-y and 5-y DMFS. Decision trees were generated based on predictors of baseline CEA and CA19-9 to divide patients into low-risk and high-risk groups, aiming to screen out patients who had relatively lower risk of distant metastasis and therefore may obtain survival benefits from radical surgery. As critical clinical molecules, CEA and CA19-9 have long been extensively used in the clinical practice of colorectal cancer,[25,34-36] gastric cancer[37] and pancreatic cancer,[38,39] including monitoring both the serum concentration and the changing pattern for their diagnostic and prognostic value in the whole course of treatment. Given that the examination of tumor biomarkers is a routine clinical test, it can guarantee an easy and repeatable application of this risk stratification method. Risk stratification using
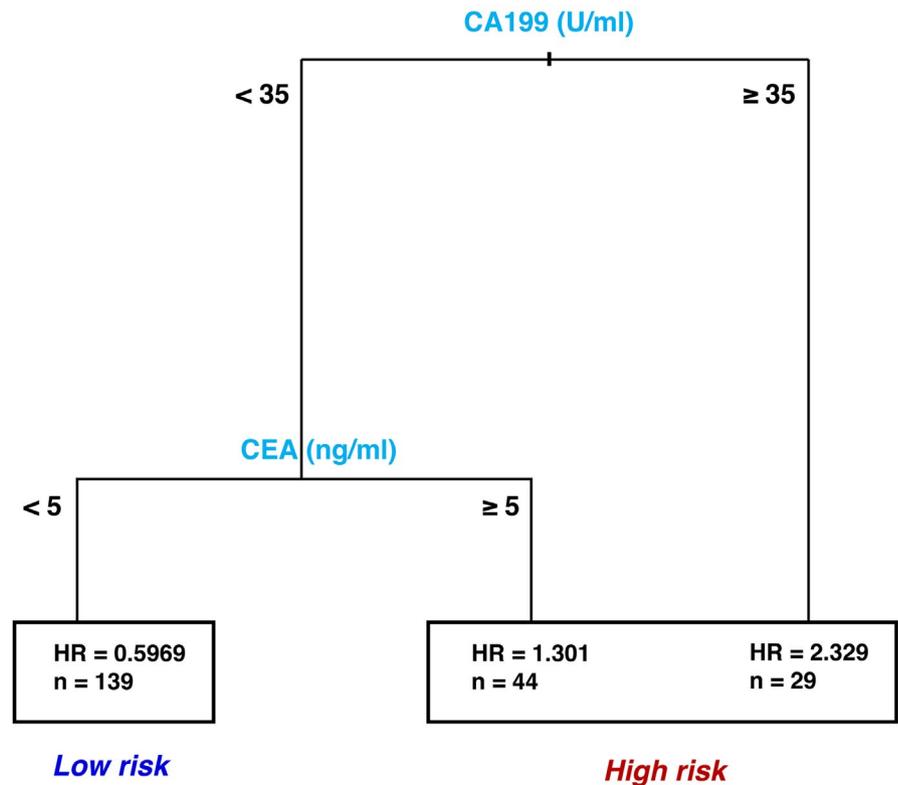

FIGURE 1 RPA-generated risk stratification of patients with LARC for predicting DMFS. LARC, locally advanced rectal cancer; RPA, recursive partitioning analysis
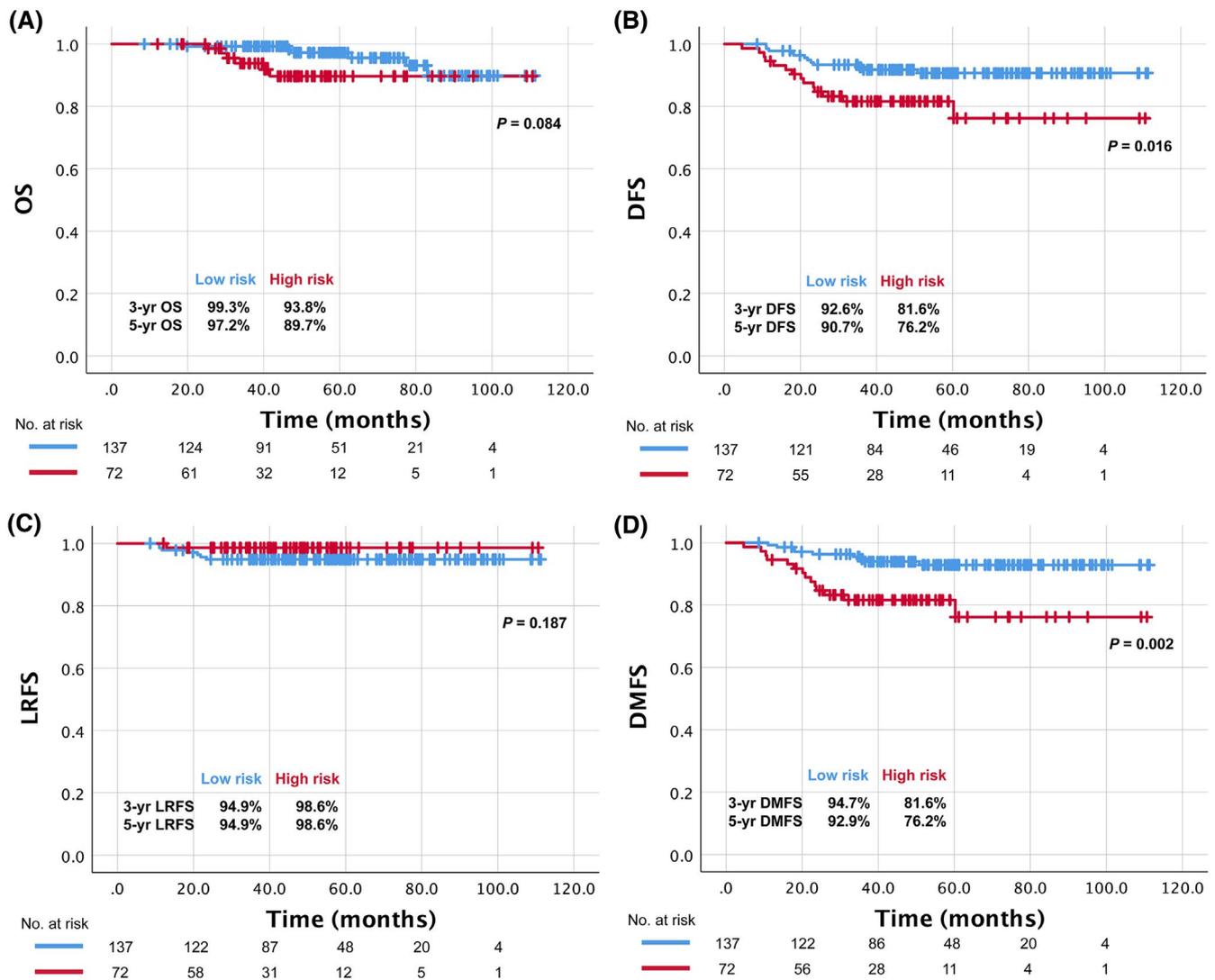
FIGURE 2 OS (A), DFS (B), LRFS (C), DMFS (D) for patients with low-risk and high-risk. DFS, disease-free survival; LRFS, local recurrence-free survival; OS, overall survival

non-invasive parameters has been widely applied in various tumor types for its efficient information provided in clinical decision making. A pretreatment plasma metabolite-based risk stratification for metastasis in stage II colorectal cancer prognosticated metastasis and non-metastasis, which provided important information for individualized treatment.[40] Similarly, a smaller sample study combined clinical characteristics and serum protein signatures showed satisfactory synergetic predictive value to group high-risk and low-risk patients with pancreatic intraductal papillary mucinous neoplasms.[41] In our study, patients with cCR with baseline CA19-9 < 35 U/mL and CEA < 5 ng/mL were classified as low-risk patients; otherwise, they were classified as high-risk patients. The key finding is that for low-risk patients, those who received TME had not only better 5-y DMFS but also better 5-y LRFS, DFS and OS compared with those who underwent the W&W strategy (Figures 3 and S2). However, high-risk patients shared an equal survival rate regardless of whether they accepted TME or W&W. This finding indicated that patients with cCR who were categorized as low-risk should be recommended TME

rather than the W&W strategy, while patients with high risk may not gain obvious survival benefit from radical surgery. Considering the potential morbidity and mortality brought by TME, the W&W strategy is a feasible alternative for high-risk patients for its outstanding preservation of patients' quality of life and its cost savings.[19,42,43]

It should be mentioned that based on our clinical data, the 5-y OS of the patients with cCR who underwent TME compared with that of those who underwent the W&W strategy was 95.9% and 90.9% (P = .240), respectively. In other words, no difference was seen between patients receiving the 2 different treatments, which is concordant with conclusions from previous studies. Habr-Gama et al[10] pioneered the W&W strategy by retrospectively comparing the long-term results of cCR patients who underwent the W&W strategy and TME. No difference in 5-y OS or DFS was seen between the observation group and resection group (100% vs. 88%, 92% vs. 83%).[10] A propensity score-matched cohort study revealed that patients managed by the W&W strategy and surgical resection had no difference in 3-y OS (96% vs. 87%); in contrast,
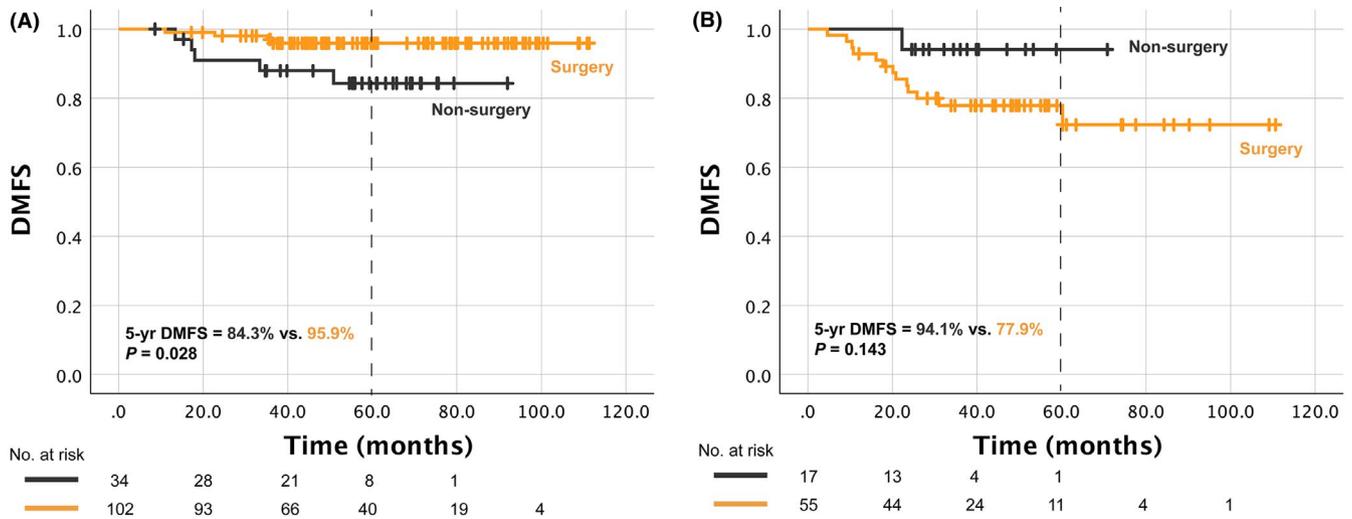
FIGURE 3 DMFS for patients with low-risk (A) and high-risk (B) who underwent radical surgery or the watch-and-wait strategy

patients managed non-operatively had significantly better 3-y colostomy-free survival than patients who underwent surgery (74% vs. 47%, P < .0001).[11] Other retrospective studies and meta-analyses showed a similar conclusion: no difference in long-term survival was observed between patients managed by the W&W strategy and those treated by TME.[8,12,13] LARC patients with cCR are a mixed population involving many subgroups with different prognoses. One way to identify target patients for individualized treatment is to establish a validated risk stratification and select the recipients who are most likely to benefit. This grouping method not only screens out patients who will benefit from TME, but also filters out patients who are more likely to develop metastasis, and these patients should strictly adhere to the surveillance schedule to ensure early metastasis detection. To the best of our knowledge, this study is the first attempt to investigate the stratification of distant metastasis risk and to determine which LARC patients with cCR could benefit from TME. According to European Society of Medical Oncology guidelines, prospective randomized trials are required for the validation of the W&W strategy.[44] Some problems remain to be solved with the awaited results from the international multi-center registry study that will be released by the International Watch & Wait Database (IWWD) consortium.[17]

Several limitations must be considered. First, this study included 212 eligible patients, which is a small sample size and conclusions in this article need to be further verified by large sample size date. Notably, only one patient's disease was pathologically diagnosed as *well differentiated* in the subgroup of *histological grade* (Table 1), which obviously brought significant bias into the statistical interpretation. Nonetheless, we have a greater sample size of patients with cCR than other previously published studies in rectal cancer (71,[10] 90,[14] 113,[21] 129,[11] 197[45]). Second, due to the small sample size, we did not include vital information, including extramural vascular invasion (EMVI) and circumferential margin (CRM), in the statistical analysis. It is reported that EMVI-positive stage II patients had similar clinical outcomes as stage III patients.[46] EMVI

is an independent predictor of poor prognosis, as it can indicate both local regrowth and distant metastasis.[46,47] CRM involvement is closely related to LR (95% CI, 1.53 to 8.00; P < .05).[48] These 2 factors have already been proven to be closely related to patient prognosis, indicating that enrolment of EMVI and CRM may further refine the decision trees. Improved risk stratification may help more precisely screen out patients who will benefit from TME, leading to fewer patients being recommended TME and more patients avoiding radical surgery. Therefore, the conclusions drawn from this study still need to be verified by prospective large cohort studies. Third, we used the term of "local recurrence" to describe local failure of patients with or without surgery, which was imprecise to some extent. Local failure of patients who never received surgery should be described as "local regrowth", while local failure of patients who had surgery should be described as "local recurrence". We used the general term because we needed the equal measurable event to compare among patients in different groups. Despite these abovementioned limitations, the results of this study provide new insights into the nonoperative regimen of rectal cancer and indicate that risk stratification may become a necessary step in the evaluation of appropriate candidates for the W&W strategy in the near future.

DISCLOSURE

The authors have no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.