ORIGINAL ARTICLE

Effects of neoadjuvant chemotherapy with or without intensity-modulated radiotherapy for patients with rectal cancer

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Abstract

Neoadjuvant chemoradiotherapy (nCRT) followed by total mesorectal excision and adjuvant chemotherapy is the standard regimen for patients with locally advanced rectal cancer (LARC). However, whether and to which extent neoadjuvant radiotherapy could be removed from nCRT for patients with LARC is still unclear. This was a multicenter, retrospectively recruited, prospectively maintained cohort study. A propensity score matching model was employed to minimize potential confounding factors between subgroup patients treated with neoadjuvant chemotherapy (nCT) or nCRT. Overall survival (OS), disease-free survival (DFS), local recurrence-free survival (LRFS), and distant metastasis-free survival (DMFS) were assessed between subgroup patients by Kaplan-Meier analysis, log-rank test, and Cox regression model. In total, 3233 consecutive patients, consist of 571 nCT and 2662 nCRT-treated cases, were included. After propensity score matching (1:4), 565 nCT-treated patients were matched to 1852 nCRT-treated patients. Compared with nCT, nCRT treatment indeed decreased 3-y local recurrence (10.0% vs 6.6%, $P = .026$), but had no impact on OS, DFS and DMFS (all $P > .05$) for LARC. Stratified analysis further confirmed that nCRT treatment was associated with higher 3-y LRFS and 3-y DFS than nCT treatment for baseline high-risk subgroup (cT4, cN+, and cIII stage) patients (all $P < .05$). Conversely, for the baseline low-risk subgroup patients (cT3, cN0, and cII stage), nCRT and nCT treatment had similar 3-y OS, LRFS, DFS, and DMFS (all $P > .05$). The administration of neoadjuvant radiotherapy for LARC patients might be determined by baseline risk classification, the high-risk individuals could be delivered while low-risk patients might be omitted.

1 | INTRODUCTION

Currently, nCRT followed by TME surgery and postoperative chemotherapy is the standard regimen for patients with LARC.[1,2] Previously, the Swedish Rectal Cancer Trial confirmed that, compared with surgery alone, neoadjuvant radiotherapy significantly decreased the local recurrence for LARC (26.9% vs 11.4%).[3] Similarly, the Dutch Colorectal Cancer Group Trial, the largest phase III trial in the TME era, reported that their 10-y cumulative local recurrence rate was 11.0% in the TME operation subgroup alone and 5.0% in the short-term radiotherapy (5 × 5 Gy) subgroup.[4] Furthermore, CAO/ARO/AIO-94[1] and NSABP R-03[5] trials found that, although it did not have OS benefit, concurrent nCRT treatment resulted in lower recurrence within the pelvic area for patients compared with those given adjuvant chemotherapy alone (6.0%-13.0%% vs 23.9%-27.5%). Hence, the benefit of neoadjuvant radiotherapy mainly lies in reducing local recurrence for patients with LARC.

Supported by the development of a standard TME surgery protocol and en bloc removal of a gross tumor mass, clearance of local micrometastatic deposits as well as lymph nodes is guaranteed. Given the overlapping function of TME surgery and preoperative radiotherapy in local control, a strategy of removing neoadjuvant radiotherapy by intensified neoadjuvant chemotherapy (nCT) was raised for LARC, aiming to achieve both favorable local control and a high quality of life. Prospective trials, such as STAR-01,[6] NSABP R-04,[7] the German CAO/ARO/AIO-04,[8,9] and FORWAC,[10] have enlightened us to the fact that the combination of more powerful nCT treatment with or without target therapy might be a promising way to reduce distant metastasis and improve oncological outcomes for LARC.[11,12] Taking the German CAO/ARO/AIO-04 study for example, adding oxaliplatin to fluorouracil-based nCRT and adjuvant chemotherapy significantly improved DFS for cT3-4 or cN1-2 LARC patients.[9] In contrast, several trails also confirmed that aggressive nCT only increased acute toxicity, however it failed to increase the proportion of pathologic complete responses (pCR) or to improve survival.[7,10] Therefore, the efficacy of nCT and nCRT treatment remained controversial in patients with LARC.

Here, based on a retrospectively recruited, prospectively maintained, multicenter LARC patient cohort, the survival outcomes (OS, DFS, LRFS and DMFS) between subgroup patients given neoadjuvant radiochemotherapy or systemic neoadjuvant chemotherapy were compared using a propensity score matching approach.

2 | MATERIAL AND METHODS

2.1 | Patients

This study recruited patients with LARC (clinically T3-T4 and/or N-positive) within 15 cm of anal verge from January 2010 through December 2018. Patients were all histologically confirmed as having rectal adenocarcinoma. Prior to neoadjuvant treatment, contrast-enhanced pelvic magnetic resonance imaging, transrectal ultrasound, and enteroscopy were performed to evaluate the tumor invasion area. The clinical stage of each LARC patient was defined based on the American Joint Committee on Cancer TNM classification system (8th edition), by retrospectively reviewing contrast-enhanced pelvic magnetic resonance imaging.[13] The exclusion criteria consisted of patients with non-adenocarcinoma, distant metastasis at diagnosis, stage I or IV, R1 or R2 resection, prior history of malignancy, Eastern Cooperative Oncology Group Performance Status ≥ 2, or without TME surgery. This study was approved by the Clinical Ethics Review Committee of the Sixth Affiliated Hospital of Sun Yat-sen University (No. 2019ZSLYEC-137).

2.2 | Treatment

All LARC patients received nCRT or nCT, followed by TME surgery with or without adjuvant chemotherapy subsequently. Briefly, neoadjuvant radiotherapy was delivered by direct beam radiation of 50.0 Gy in 25 fractions, and patients were concurrently given fluoropyrimidine-based chemotherapy.[10] After a 6-8 wk waiting time, the concurrent nCRT-treated patients received the standard TME surgery under the protocol we previously described.[10] nCT was administrated with a fluorouracil-based FOLFOX or CAPOX regimen, while the regimen and cycles delivered were determined at the multidiscipline team (MDT)'s discretion. At 2 wk after completion of nCT, patients received a standard TME operation. The TME surgery specimen was pathologically evaluated by the American Joint Committee on Cancer and College of American Pathologists tumor regression grade (AJCC/CAP TRG) system.[14] At 2-4 wk later, the

fluoropyrimidine-based adjuvant chemotherapy was administered. The adjuvant chemotherapeutic regimen and cycles to be given were at the institutional MDT's discretion.

2.3 | Follow-up

After TME surgery, all patients were followed up at 3-mo intervals during the first 3 y and at 6-mo intervals thereafter. At each follow-up, physical examination, complete biochemistry, and tumor biomarkers test were regularly monitored. Contrast-enhanced pelvic magnetic resonance imaging and colonoscopy was performed annually at the first 3 y. The latest date of each patient being followed up was August 1, 2019. Specifically, OS was defined as time to death, or when censored at the latest date if patients were still alive. DFS was defined as time to the date of disease relapse, or the date of death or when censored at the latest date. LRFS and DMFS were defined as time to the date of local recurrence or distant metastases, respectively, or date of death or when censored at the latest date.

2.4 | Propensity score matching

The propensity scores model was employed to match the potential bias of confounding covariates between nCRT and nCT subgroup patients. Firstly, a multivariable logistic regression model was constructed to generate propensity scores. The propensity score model was performed by matching the potential confounding clinicopathological factors, including of age (≤55 y vs >55 y) at diagnosis, sex (male vs female), clinical stage (II vs III), clinical T stage (T3 vs T4), clinical N stage (N0 vs N+), histologic grade (well, moderately, poorly differentiated), tumor distance from anus (≤ 5, 6-10, >10 cm), nCT (with vs without), nCT cycles (0, 1-4, > 4), CRM (negative vs positive), ypT, ypN, ypTNM stage, adjuvant chemotherapy (with vs without), and cycle of adjuvant chemotherapy (0, 1-4, >4). The nCT and nCRT-treated subgroup patients were matched at 1:4 ratio, using a greedy, nearest neighbor matching algorithm with no replacement. A caliper width equal to 0.2 of the standard deviation was utilized as the logit of the propensity score. Patient characteristics between the propensity score-matched subgroups were compared using the *P*-value.

2.5 | Statistical analysis

Kaplan-Meier survival curves were used to compare OS, DFS, DMFS, and LRFS between the subgroup patients. Statistical differences between curves were calculated using the log-rank test. The chi-square test was performed to compare each clinicopathological variable. The multivariate Cox proportional hazards model was used to estimate the HR and 95% CI for patient outcome. All *P*-values quoted were two-sided. A *P*-value less than .05 was considered as statistically different. Statistical analysis was performed using SPSS (version 24.0; SPSS, Inc).

3 | RESULTS

3.1 | Patient characteristics

In total, 3233 consecutively enrolled patients with LARC were included in this study (median age, 55.0 y; 67.7% of male). Of these, 571 (17.7%) patients were given nCT solely (range, 1-12 cycles; median, 4 cycles), and the remaining 2662 (82.3%) patients were treated with concurrent nCRT (range, 1-12 cycles; median, 3 cycles). Specifically, tumor located at 0-5 cm from anal verge, clinical III (cIII) stage, cT3, cT4, cN0, cN1 and cN2 stages were noted at 40.2%, 73.9%, 75.8%, 21.4%, 26.1%, 73.9%, and 0.0% in nCT subgroup patients, and at 55.1%, 79.6%, 62.4%, 33.7%, 20.4%, 79.0%, and 0.6% in nCRT subgroup patients, respectively. Moreover, pCR was observed in 17.3% (99/571) of nCT subgroup patients, and in 27.3% (728/2662) of nCRT subgroup patients (*P* < .001). Significantly, compared with patients who received nCT treatment, nCRT-treated patients always had a favorable ypT, ypN and AJCC/CAP TRG category (all *P* < .05) (Table 1).

At 1:4 propensity score matching, 565 nCT-treated patients were matched to 1852 patients who received nCRT treatment. As shown in Table 1, after propensity score matching, the standardized differences of included covariates between these 2 subset patients were all less than 0.1 (Figure S1), suggesting a well balanced covariates distribution.

3.2 | Survival analyses

The median follow-up time of the entire cohort was 40.0 mo (range, 3.0 to 148.0 mo). At 1:4 matching, the 3-y OS ratio between these 2 subgroup patients did not reach a significant difference (Figure 1A): the 3-y OS rate was 93.9% for the nCT subgroup patients, and 90.6% for the nCRT subgroup patients (*P* = .062). Moreover, patients treated with or without neoadjuvant radiotherapy had a comparable 3-y DFS (Figure 1B): the 3-y DFS rate was 73.5% for the nCT subgroup patients, and 77.3% for the nCRT subgroup patients (*P* = .057). Additionally, these 2 subgroup patients had a similar 3-y DMFS (nCT vs nCRT, 78.3% vs 80.6%, *P* = .26; Figure 1C). Significantly, compared with nCT, nCRT treatment was correlated with an improved 3-y LRFS (nCRT vs NCT, 93.4% vs 90.0%, *P* = .026. HR, 1.450; 95% CI, 1.044-2.013; Figure 1D).

3.3 | Stratified survival analyses

In light of baseline cIII, cT4 and cN+ stage, subgroup patients had a high risk of developing disease progression;[9,15-17] stratified survival analyses (all at 1:4 propensity score matching) were

TABLE 1 Patients baseline characteristics before and after propensity score matching

Characteristics	Before Matching			After Matching (1:4)		
	nCT No. (%) (n = 571)	nCRT No. (%) (n = 2662)	*P*-value	nCT No. (%) (n = 565)	nCRT No. (%) (n = 1852)	*P*-value
Age, median 55 y						
≤55	276 (48.3)	1271 (47.7)	.798	273 (48.3)	883 (47.7)	.790
>55	296 (51.7)	1391 (52.3)		292 (51.7)	969 (52.3)	
Gender						
Male	391 (68.5)	1797 (67.5)	.653	388 (68.7)	1255 (67.8)	.596
Female	180 (31.5)	865 (32.5)		177 (31.3)	597 (32.2)	
Clinical T stage						
cT1	1 (0.2)	7 (0.3)	<.001	1 (0.2)	6 (0.3)	.292
cT2	15 (2.6)	97 (3.6)		14 (2.5)	87 (4.7)	
cT3	433 (75.8)	1660 (62.4)		430 (76.1)	1271 (68.7)	
cT4	122 (21.4)	898 (33.7)		120 (21.2)	488 (26.3)	
Clinical N stage						
cN0	149 (26.1)	542 (20.4)	.001	147 (26.0)	428 (23.1)	.136
cN1	422 (73.9)	2104 (79.0)		418 (74.0)	1421 (76.7)	
cN2	0 (0.0)	16 (0.6)		0 (0.0)	3 (0.2)	
Clinical TNM stage						
II	149 (26.1)	542 (20.4)	.002	147 (26.0)	428 (23.1)	.155
III	422 (73.9)	2120 (79.6)		418 (74.0)	1361 (76.9)	
Location from anal verge, cm						
0-5	230 (40.2)	1468 (55.1)	<.001	230 (40.7)	907 (49.0)	.024
5-10	279 (48.9)	1028 (38.6)		276 (48.8)	795 (42.9)	
>10	52 (9.1)	87 (3.3)		52 (9.2)	77 (4.2)	
Unknown/missing	10 (1.8)	79 (3.0)		7 (1.3)	73 (3.9)	
Tumor differentiation						
High-differentiated	154 (27.0)	386 (14.5)	<.001	150 (26.5)	340 (18.4)	.005
Median-differentiated	348 (60.9)	1819 (68.3)		346 (61.3)	1297 (70.0)	
Low-differentiated	69 (12.1)	457 (17.2)		69 (12.2)	215 (11.6)	
nCT or not						
NO NCT	0 (0.0)	55 (2.1)	.001	—	—	—
NCT	571 (10.0)	2607 (97.9)		565 (100.0)	1852 (100.0)	
nCT cycle, median 4 cycles						
0	0 (0.0)	55 (2.0)	.009	—	—	
1-4	418 (73.2)	2028 (76.2)		413 (73.1)	1393 (75.2)	.311
≥5	153 (26.8)	579 (21.8)		152 (26.9)	459 (24.8)	
Pathological T stage						
ypT0	99 (17.3)	728 (27.3)	.001	99 (17.5)	412 (22.2)	.226
ypT1	38 (6.7)	143 (5.4)		37 (6.5)	99 (5.3)	
ypT2	125 (21.9)	572 (21.5)		123 (21.8)	426 (23.0)	
ypT3	269 (47.1)	916 (34.4)		266 (47.1)	696 (37.7)	
ypT4	40 (7.0)	303 (11.4)		40 (7.1)	219 (11.8)	
Pathological N stage						
ypN0	435 (76.2)	2090 (78.5)	.063	433 (76.6)	1448 (78.1)	.395
ypN1	97 (17.0)	452 (17.0)		97 (17.2)	303 (16.4)	

(Continues)

TABLE 1 (Continued)

Characteristics	Before Matching			After Matching (1:4)		
	nCT No. (%) (n = 571)	nCRT No. (%) (n = 2662)	P-value	nCT No. (%) (n = 565)	nCRT No. (%) (n = 1852)	P-value
ypN2	39 (6.8)	120 (4.5)		35 (6.2)	101 (5.5)	
Pathological TNM stage						
ypT0N0	99 (17.3)	728 (27.3)	.001	99 (17.5)	412 (22.2)	.126
I	150 (26.3)	606 (22.8)		149 (26.4)	454 (24.6)	
II	203 (35.6)	798 (30.0)		200 (35.4)	612 (33.0)	
III	119 (20.8)	530 (19.9)		117 (20.7)	374 (20.2)	
Vessel carcinoma embolus						
Positive	541 (94.7)	2600 (97.7)	<.001	535 (94.7)	1807 (97.6)	.001
Negative	30 (5.3)	62 (2.3)		30 (5.3)	45 (2.4)	
Tumor neural invasion						
Positive	527 (92.3)	2535 (95.2)	.004	522 (92.4)	1753 (94.7)	045
Negative	44 (7.7)	127 (4.8)		43 (7.6)	99 (5.3)	
Surgical margin						
Positive	567 (99.3)	2650 (99.5)	.440	561 (99.3)	1847 (99.7)	.135
Negative	4 (0.7)	12 (0.5)		4 (0.7)	5 (0.3)	
Circumferential resection margin, mm						
≤1	567 (99.3)	2632 (98.9)	.365	561 (99.3)	1842 (99.5)	.645
>1	4 (0.7)	30 (1.1)		4 (0.7)	10 (0.5)	
AJCC/CAP TRG						
0	99 (17.3)	728 (27.3)	<.001	99 (17.5)	412 (22.2)	<.001
1	91 (15.9)	677 (25.4)		90 (15.9)	497 (26.8)	
2	217 (38.0)	1040 (39.1)		215 (38.1)	778 (42.0)	
3	164 (28.8)	217 (8.2)		161 (28.5)	165 (9.0)	
ACT or not						
No ACT	80 (14.0)	585 (22.0)	<.001	80 (14.2)	307 (16.6)	.170
ACT	491 (86.0)	2077 (78.0)		485 (85.8)	1545 (83.4)	
ACT cycle，median 4 cycle						
0	80 (14.0)	585 (21.9)	<.001	78 (13.8)	304 (16.4)	.003
1-4	178 (31.2)	1104 (41.5)		180 (31.9)	686 (37.0)	
≥5	313 (54.8)	973 (36.6)		307 (54.3)	862 (46.6)	

Abbreviations:: ACT, adjuvant chemotherapy; AJCC/CAP TRG, the American Joint Committee on Cancer and College of American Pathologists tumor regression grade; nCRT, neoadjuvant chemoradiotherapy; nCT, neoadjuvant chemotherapy.

conducted to identify the subgroup that would benefit most from neoadjuvant radiotherapy. Compared with nCT treatment, concurrent nCRT treatment was correlated with a prolonged 3-y DFS (72.3% vs 77.2%, P = .034; HR, 0.784; 95% CI, 0.626-0.983; Figure 2B) and 3-y LRFS (88.8% vs 93.3%, P = .020; HR, 0.645; 95% CI, 0.444-0.936; Figure 2D) for patients with baseline cIII stage. However, a comparable 3-y OS (P = .173; HR, 1.293; 95% CI, 0.892-1.874; Figure 2A) and 3-y DMFS (P = .270; HR, 0.870; 95% CI, 0.679-1.115; Figure 2C) was observed between baseline cIII stage subgroup patients treated with nCT and nCRT. For the baseline cII stage patients, nCT or nCRT treatment was

associated with similar survival outcome (3-y OS, 3-y DFS, 3-y LRFS, and 3-y DMFS) (all P > .05; Figure S2).

As expected, for baseline cT4 stage patients, nCRT treatment was correlated with a favorable 3-y DFS (78.1% vs 68.0%, P = .028; HR, 0.648; 95% CI, 0.438-0.959; Figure 3B) and 3-y LRFS (92.1% vs 84.4%, P = .022; HR, 0.512; 95% CI, 0.285-0.917; Figure 3D) than nCT treatment. However, this difference was not observed at 3-y OS (P = .476; HR, 1.272; 95% CI, 0.655-2.470; Figure 3A) and 3-y DMFS (P = .050; HR, 0.657; 95% CI, 0.430-1.004; Figure 3C) for baseline cT4 stage patients given nCT or nCRT. Also, for baseline cT3 stage patients, nCT or nCRT
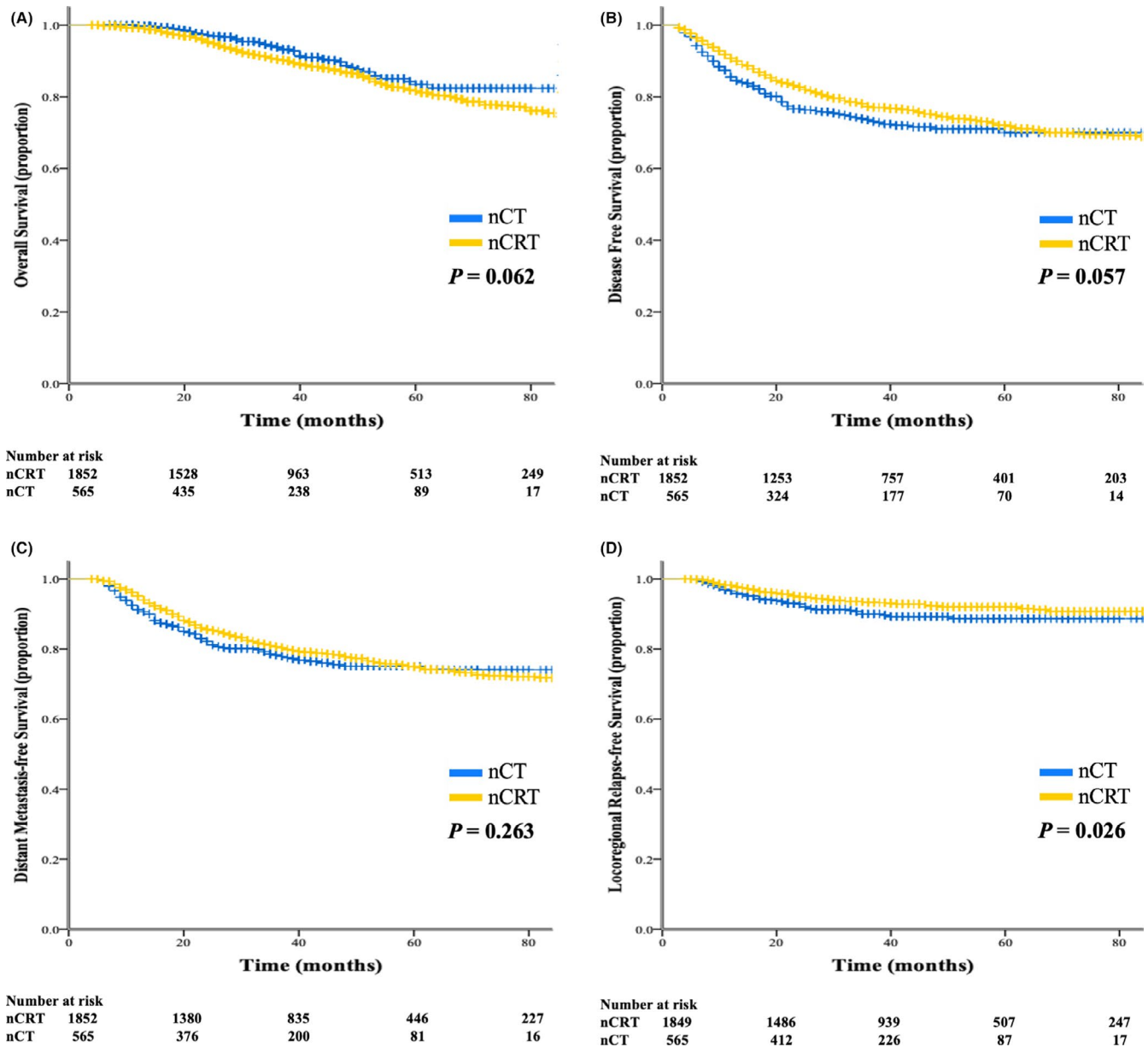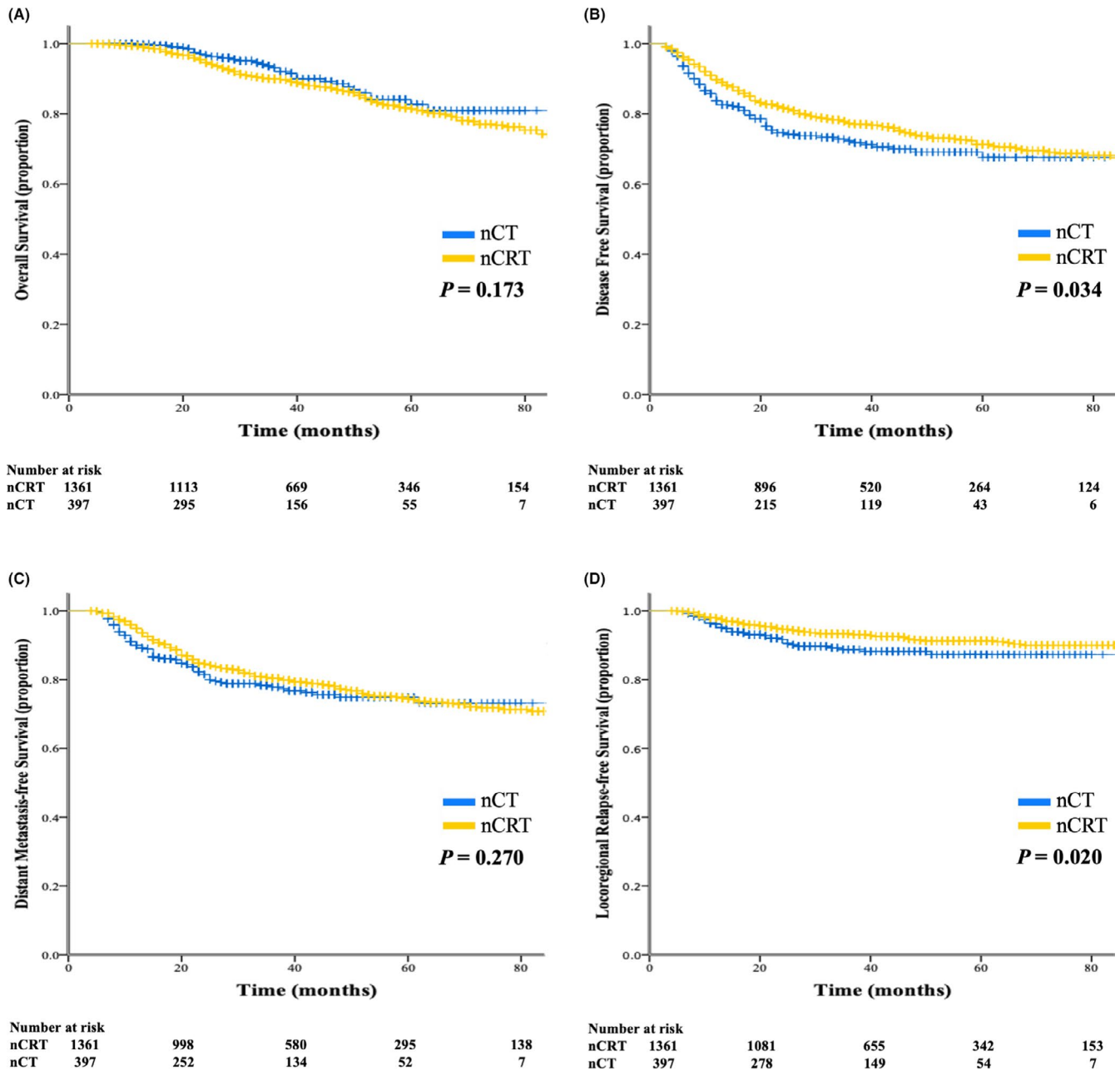
FIGURE 1 Kaplan-Meier curve analysis of overall survival (A), disease-free survival (B), distant metastasis-free survival (C) and locoregional relapse-free survival (D) for the locally advanced rectal cancer patients treated with or without neoadjuvant radiotherapy after propensity score matching (1:4). nCRT, neoadjuvant chemoradiotherapy; nCT, neoadjuvant chemotherapy

treatment had a comparable 3-y survival outcome (OS, DFS, LRFS, and DMFS, all $P > .05$; Figure S3).

Similarly, for baseline cN+ stage patients, nCRT treatment was correlated with a prolonged 3-y DFS (77.0% vs 71.7%, $P = .024$; HR, 0.779; 95% CI, 0.626-0.969; Figure 4B) and 3-y LRFS (93.2% vs 88.7%, $P = .013$; HR, 0.635; 95% CI, 0.443-0.910; Figure 4D) than nCT treatment. By contrast, nCT and nCRT treatment achieved a comparable 3-y OS ($P = .262$; HR, 1.220; 95% CI, 0.861-1.728; Figure 4A) and 3-y DMFS ($P = .181$; HR, 0.851; 95% CI, 0.671-1.079; Figure 4C) for baseline cN+ stage patients. Moreover, for baseline cN0 stage patients, nCT or nCRT treatment correlated with similar survival outcomes (3-y OS, 3-y DFS, 3-y LRFS, and 3-y DMFS) (all $P > .05$; Figure S4).

3.4 | Multivariate analysis

All clinicopathological factors that displayed significance in univariate analysis were subjected to the Cox regression multivariate analysis (Figure S5). As shown in Table 2, AJCC/CAP TRG system, tumor location, tumor differentiation status, neoadjuvant treatment regimen, ypT stage, and ypN stage were the independent factors to predict LRFS. Specifically, individuals had inferior AJCC/CAP TRG categories, low-differentiated differentiation, ypT3-4, or ypN+ stage and displayed a high propensity to poor LRFS (all $P < .001$). Importantly, patients who did not receive neoadjuvant radiotherapy were more likely to develop local relapse ($P = .027$). Also, subgroup patients with tumors located at 5-10 cm from anal verge tended to
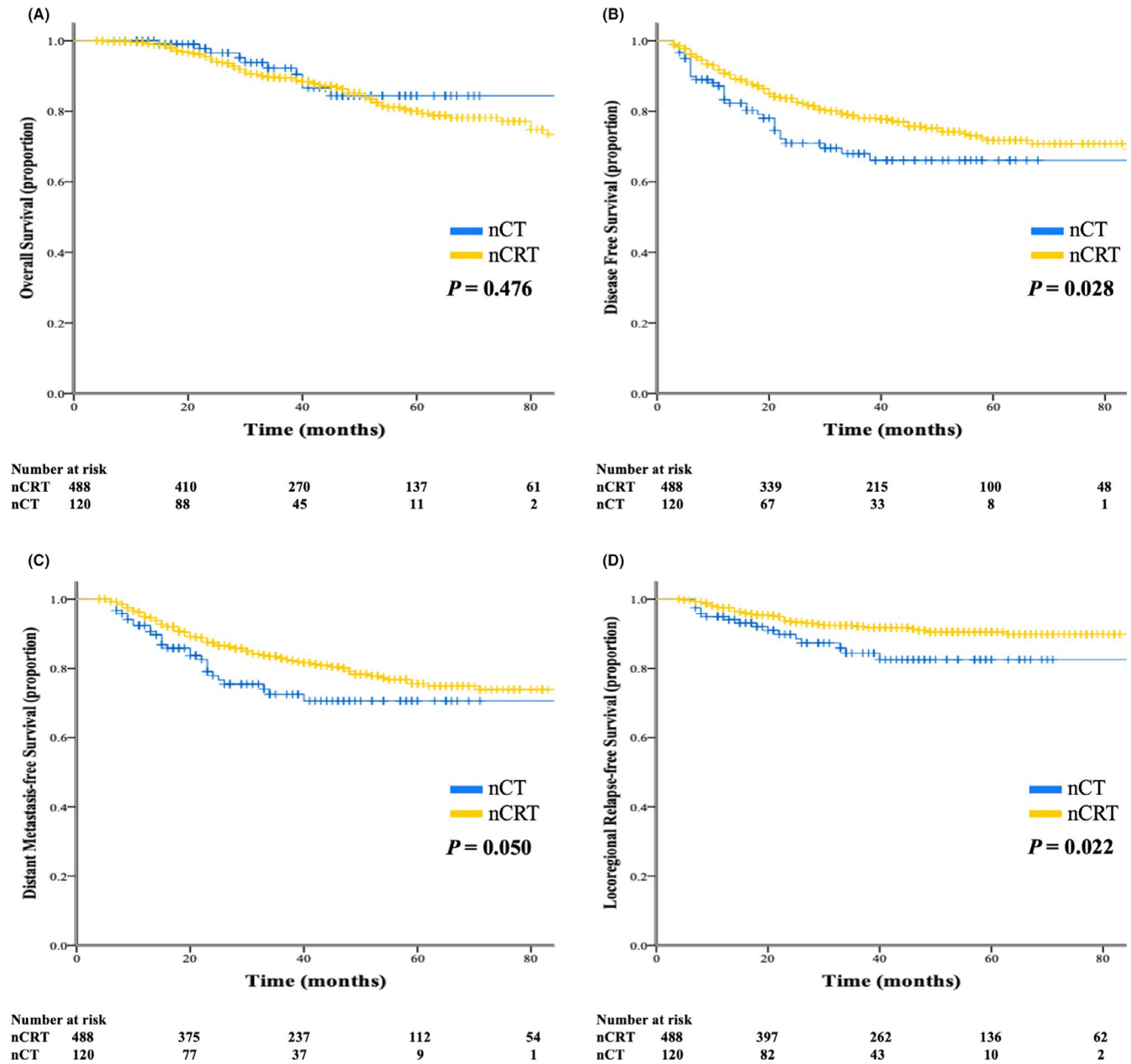
FIGURE 2 Kaplan-Meier curve analysis of overall survival (A), disease-free survival (B), distant metastasis-free survival (C) and locoregional relapse-free survival (D), comparing clinical III stage rectal cancer subgroup patients with or without neoadjuvant radiotherapy after propensity matching (1:4). nCRT, neoadjuvant chemoradiotherapy; nCT, neoadjuvant chemotherapy

obtain a better LRFS, whereas those with tumors at 0-5 cm or > 10 cm were prone to have an inferior LRFS ($P = .004$).

4 | DISCUSSION

In the function-preserving strategy era, the concept of replacing neoadjuvant radiochemotherapy by systemic neoadjuvant chemotherapy was raised for LARC, as neoadjuvant radiotherapy only helps to control local recurrence in patients who are at risk of acute and long-term radiation-related toxicity. Moreover, the

high quality of TME surgery also makes the pelvic recurrence rate low. However, whether and to what extent nCRT could be replaced by nCT has not yet been addressed. Here, by summarizing consecutive large size patient groups and using the propensity score matching method, the survival outcomes for the subgroup patients treated with nCRT and nCT were compared. Compared with previous studies,[3,4,18-21] we found that although 3-y OS and DMFS were not improved, adding radiotherapy to nCT still minimized the pelvic recurrence for patients with LARC. Stratified analysis further confirmed that the neoadjuvant radiotherapy-improved LRFS was mainly observed in baseline cIII, cT4, and cN+
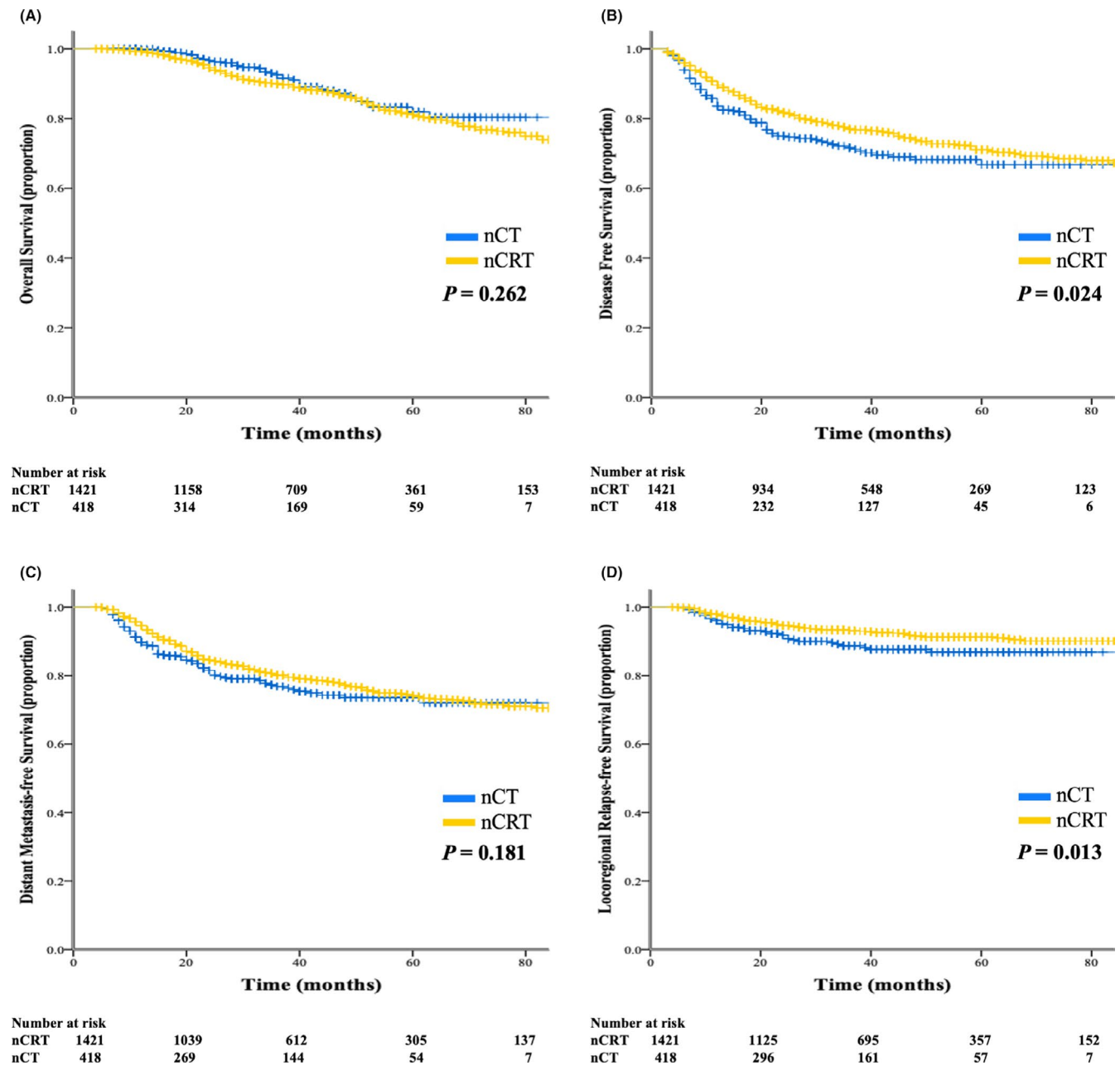
FIGURE 3 Kaplan-Meier curve analysis of overall survival (A), disease-free survival (B), distant metastasis-free survival (C) and locoregional relapse-free survival (D), comparing the clinical T4 stage rectal cancer subgroup patients with or without neoadjuvant radiotherapy after propensity matching (1:4). nCRT, neoadjuvant chemoradiotherapy; nCT, neoadjuvant chemotherapy

stage subgroup patients. Importantly, this prolonged 3-y LRFS was consequently translated into a higher 3-y DFS. Therefore, even in the TME surgery era, neoadjuvant radiotherapy is still important to control pelvic relapse and could not be replaced by systemic nCT for baseline high-risk LARC patients.

Previously, side effects caused by neoadjuvant radiotherapy, such as fecal incontinence, sexual dysfunction, bowel dysfunction, and secondary malignancy, have been the major concern of physician and patients, due to the resulting impairment in quality of life.[4,22-26] Actually, our recently phase III FOWARC trial confirmed that neoadjuvant radiotherapy-induced side effects were acceptable.[10] Compared with the mFOLFOX6 subset, a slightly

higher grade 3-4 hematologic, diarrhea, radiation dermatitis and proctitis toxicity were observed in the nCRT subgroup. Although higher grade 3 to 4 levels of leukopenia (19.0% vs 5.7%) and neutropenia (16.6% vs 9.0%) occurred in the mFOLFOX6-radiotherapy subgroup patients compared with the mFOLFOX6 subgroup patients, leukopenia and neutropenia were easily managed by G-CSF treatment. Significantly, neoadjuvant radiotherapy-induced postoperative complications, particularly anastomotic leakage, clinical fistula, and perineal infection, which were also well tolerated and associated with high treatment compliance. Moreover, treatment-related deaths did not occur, even in the nCRT subgroup that had a higher ratio of cT4b patients. Therefore, neoadjuvant

FIGURE 4 Kaplan-Meier curve analysis of overall survival (A), disease-free survival (B), distant metastasis-free survival (C) and locoregional relapse-free survival (D), comparing the clinical N + stage rectal cancer subgroup patients with or without neoadjuvant radiotherapy after propensity matching (1:4). nCRT, neoadjuvant chemoradiotherapy; nCT, neoadjuvant chemotherapy

radiotherapy-caused side effects might be overestimated for LARC.

In line with previous studies,[18,19,27] here we confirmed that, compared with systemic nCT, nCRT treatment correlated with a favorable LRFS for LARC patients. Particularly, we identified that individuals at the cIII stage, cT4, or cN+ stage would most benefit from nCRT treatment. Importantly, adding neoadjuvant radiotherapy to nCT increased local control (Figure 1) and pCR ratio (17.3% vs 27.3%), which finally translated into favorable DFS. In our recent FOWARC trial, although high-risk cT4b and cN+ patients were more likely to be placed in the nCRT treatment arm, the

nCRT subset still had an evidently higher pCR ratio than the systemic nCT subset (27.5% vs 6.6%, P = .005). However, this sound pCR ratio difference was not translated into varied local control and DFS ratio.[28] The underlying reason might be attributed to the limited patient size in each arm. As shown in the methods section of the FOWARC trial, the primary endpoint was 3-y DFS, which was estimated as 60.0% in the fluorouracil-radiotherapy group, while it was 75.0% in either the mFOLFOX6 or the mFOLFOX6-radiotherapy arms. This 15.0% 3-y DFS gap included 165 patients per arm that would be enough to meet the study design. Actually, even in the present study with a large patient size (3233 cases),

TABLE 2 Univariate and multivariate analysis of accumulative recurrence

| | Univariate analysis | | | Multivariate analysis | | |
| | 3-y LRFS | | | 3-y LRFS | | |
Parameter	HR	95% CI	P-value	HR	95% CI	P-value
AJCC/CAP TRG						
0	0.163	0.084 to 0.317	<.001	0.149	0.075 to 0.297	<.001
1	0.405	0.257 to 0.639	<.001	0.409	0.258 to 0.648	<.001
2	0.693	0.480 to 0.999	.050	0.669	0.463 to 0.968	.033
3	1		–	1		–
Age, year						
≤55	1.480	1.098 to 1.996	.010	1.314	0.968 to 1.784	.158
>55	1		–	1		–
Gender						
Female	1		–	–		–
Male	1.152	0.833 to 1.592	.393	–		–
Clinical T stage						
cT1	<0.001	0.000 to 8.916E + 10^9	945	–		–
cT2	0.215	0.052 to 0.882	.033	–		–
cT3	0.772	0.561 to 1.063	.113	–		–
cT4	1		–	–		–
Clinical N stage						
cN0	302.531	0.000 to 1.410E + 44	.907	–		–
cN1	442.869	0.000 to 2.064E + 44	.901	–		–
cN2	1		–	–		–
Clinical TNM stage						
II	0.732	0.515 to 1.042	.084	–		–
III	1			–		–
Location from anal verge, cm						
0-5	0.857	0.471 to 1.558	.612	0.891	0.490 to 1.620	.705
5-10	0.513	0.275 to 0.957	.036	0.528	0.283 to 0.986	.045
>10	1		–	1		–
Tumor differentiation						
High-differentiated	0.421	0.266 to 0.667	<.001	0.596	0.366 to 0.972	.038
Median-differentiated	0.390	0.272 to 0.558	<.001	0.523	0.355 to 0.770	.001
Low-differentiated	1		–	1		–
Neoadjuvant RT or not						
No RT	1.450	1.044 to 2.013	.027	1.413	1.007 to 1.983	.046
RT	1		–	1		–
nCT cycle						
1-4	0.894	0.638 to 1.251	.513	–		–
≥5	1			–		–
Pathological T stage						
ypT0	0.176	0.089 to 0.349	<.001	0.220	0.106 to 0.457	<.001
ypT1	0.231	0.082 to 0.653	0.06	0.298	0.105 to 0.851	.024
ypT2	0.255	0.143 to 0.455	<.001	0.347	0.192 to 0.627	<.001
ypT3	0.799	0.641 to 1.408	.799	0.993	0.663 to 1.489	.974

(Continues)

TABLE 2 (Continued)

Parameter	Univariate analysis 3-y LRFS			Multivariate analysis 3-y LRFS		
	HR	95% CI	P-value	HR	95% CI	P-value
ypT4	1		–	1		–
Pathological N stage						
ypN0	0.249	0.160 to 0.388	<.001	0.561	0.344 to 0.916	.021
ypN1	0.761	0.476 to 1.218	.256	1.132	0.691 to 1.853	.624
ypN2	1		–	1		–
Pathological TNM stage						
ypT0N0	0.123	0.064 to 0.237	<.001	–		–
I	0.162	0.096 to 0.274	<.001	–		–
II	0.503	0.364 to 0.694	<.001	–		–
III	1		–	–		–
Vessel carcinoma embolus						
Positive	1		–	1		–
Negative	0.366	0.208 to 0.645	<.001	0.659	0.356 to 1.220	.185
Surgical margin						
Positive	3.373	0.837 to 13.596	.087	–		–
Negative	1		–	–		–
Tumor neural invasion						
Positive	1		–	1		–
Negative	0.504	0.305 to 0.831	.007	1.187	0.697 to 2.021	.528
ACT or not						
No ACT	1.054	0.699 to 1.588	.802	–		–
ACT	1		–	–		–
ACT cycle, median 4 cycle						
0	0.950	0.605 to 1.492	.823	–		–
1-4	1.069	0.774 to 1.475	.686	–		–
≥5	1		–	–		–
Circumferential resection margin, mm						
>1	1		–	1		–
≤1	0.213	0.079 to 0.574	.002	0.657	0.234 to 1.848	.426

Abbreviations:: 95% CI, 95% confidence interval; ACT, adjuvant chemotherapy; HR, hazard ratio; nCT, neoadjuvant chemotherapy; RT, radiotherapy.

the largest 3-y DFS difference was 10.1% (nCRT vs nCT, 78.1% vs 68.0%), which was only observed in the cT4 stage subgroup patients. Thus, neoadjuvant radiotherapy would confer survival benefit to baseline high-risk (cT4, cN+ and cIII stage) subgroup patients. By contrast, survival analysis revealed that neoadjuvant radiotherapy could be omitted for the baseline low-risk LARC subgroup patients (cT3, cN0, and cII stage). Together, the option to deliver neoadjuvant radiotherapy or not could be determined by their baseline risk category for patients with LARC.

We realize that our study had limitations. First, this was a retrospective study, and potential bias might be induced by confounding variables such as cTNM stage, chemotherapy regimen, and cycles. To minimize the potential bias, we recruited a consecutive and large size cohort patient. Using the propensity score matching model, the bias caused by confounding factors was minimized to the most extent. Significantly, our study did not include the neoadjuvant treatment complication information. As known, chemotherapy toxicities may increase the side effects of radiotherapy, which would affect the survival outcome.

In conclusion, using a propensity score matching model in large size LARC patients, our study confirmed that neoadjuvant radiotherapy might be omitted from nCRT for baseline low-risk LARC patients. Conversely, neoadjuvant radiotherapy is important to control pelvic recurrence and disease relapse for baseline high-risk LARC patients. This finding would be relevant for prospective PROSPECT (NCT01515787) and BACCHUS (NCT01650428) trials.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

WXB and HF designed the study. HF performed contouring, treatment planning and the statistical analysis. YL, DY, WJ, ZJ, LS, PXL, CHY, JA and LZH reviewed the data. All authors discussed the data. WXB and HF drafted the manuscript. All co-authors read and approved the manuscript. All authors read and approved the final manuscript.

CONSENT FOR PUBLICATION

Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The protocol was approved by the ethics committee of the Sixth Affiliated Hospital, Sun Yat-sen University (No. 2019ZSLYEC-137).

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

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