Impact of neoadjuvant chemoradiotherapy on the local recurrence and distant metastasis pattern of locally advanced rectal cancer: a propensity score-matched analysis

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Abstract

Background: Previous studies have demonstrated different predominant sites of distant metastasis between patients with and without neoadjuvant chemoradiotherapy (NCRT). This study aimed to explore whether NCRT could influence the metastasis pattern of rectal cancer through a propensity score-matched analysis.

Methods: In total, 1296 patients with NCRT or post-operative chemoradiotherapy (PCRT) were enrolled in this study between January 2008 and December 2015. Propensity score matching was used to correct for differences in baseline characteristics between the two groups. After propensity score matching, the metastasis pattern, including metastasis sites and timing, was compared and analyzed.

Results: After propensity score matching, there were 408 patients in the PCRT group and 245 patients in the NCRT group. NCRT significantly reduced local recurrence (4.1% *vs.* 10.3%, $P = 0.004$), but not distant metastases (28.2% *vs.* 27.9%, $P = 0.924$) compared with PCRT. In both the NCRT and PCRT groups, the most common metastasis site was the lung, followed by the liver. The NCRT group developed local recurrence and distant metastases later than the PCRT group (median time: 29.2 [18.8, 52.0] months *vs.* 18.7 [13.3, 30.0] months, $Z = -2.342$, $P = 0.019$; and 21.2 [12.2, 33.8] *vs.* 16.4 [9.3, 27.9] months, $Z = -1.765$, $P = 0.035$, respectively). The distant metastases occurred mainly in the 2nd year after surgery in both the PCRT group (39/114, 34.2%) and NCRT group (21/69, 30.4%). However, 20.3% (14/69) of the distant metastases appeared in the 3rd year in the NCRT group, while this number was only 13.2% (15/114) in the PCRT group.

Conclusions: The predominant site of distant metastases was the lung, followed by the liver, for both the NCRT group and PCRT group. NCRT did not influence the predominant site of distant metastases, but the NCRT group developed local recurrence and distant metastases later than the PCRT group. The follow-up strategy for patients with NCRT should be adjusted and a longer intensive follow-up is needed.

Keywords: Locally advanced rectal cancer; Metastases pattern; Neoadjuvant chemoradiotherapy; Propensity score matching

Introduction

Currently, neoadjuvant chemoradiotherapy (NCRT) followed by total mesorectal excision (TME) has become the standard treatment for locally advanced (stage II to III) mid-low rectal cancer.[1] NCRT has been proven to remarkably reduce local recurrence, and most studies have demonstrated that the local recurrence rates are below 10%.[2] However, NCRT is less effective in preventing distant metastases, and the incidence of distant metastases remains in the range of 20% to 30%.[3,4] Therefore, the major threat to long term survival after radical surgery is distant metastases for rectal cancer patients treated with NCRT.

The most common site of distant metastases in colorectal cancer is the liver, followed by the lung.[5-7] The proportion

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of lung metastases is higher in rectal cancer than in colon cancer, but the liver is still the predominant site of distant metastases in rectal cancer according to previous reports.[6] However, a retrospective study that enrolled 735 rectal cancer patients with NCRT indicated that the lung was the most common site of metastases, followed by the liver (9.6% *vs.* 5.9%).[8] Another study that included 593 patients also showed a preponderance of lung metastases in rectal cancer patients with NCRT.[9] These studies indicated that the predominant site of distant metastasis was quite different between rectal cancer patients with and without NCRT. One explanation for this difference was that NCRT changed the pattern of distant metastases.[9]

However, the baseline characteristics of the patients in the previous studies, such as the clinical tumor-node-metastasis (TNM) stage before treatment, the tumor location, and the treatment regimen, were not comparable between those with and without NCRT. The different metastasis patterns between patients with and without NCRT may be partly due to the different disease stages or different tumor locations before receiving treatment. The patients who received NCRT usually had more advanced disease and lower tumor locations than the patients who received surgery directly. A lower tumor location is considered an independent risk factor for pulmonary metastases in rectal cancer.[10]

This study aimed to explore whether NCRT impacts the metastasis pattern of rectal cancer, including the sites and occurring time of metastases, by using a propensity score-matched analysis. By conducting propensity score matching for the baseline factors, especially tumor stage, tumor location, and adjuvant treatment regimen, we could more accurately evaluate the correlation between NCRT and the metastasis pattern.

Methods

Ethical approval

This study was approved by the institutional review board of the Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (No. NCC2018B-029) and the requirement to obtain the informed consent was waived.

Patients

This retrospective cohort study was carried out by using an institutional database. A total of 4383 consecutive rectal cancer patients at our institution between January 2008 and December 2015 were reviewed, and 1296 patients who met the inclusion criteria were enrolled in the study.

Patients who met the following criteria were included in the study: (1) rectal cancer patients with biopsy-proven adenocarcinoma; (2) the inferior edge of the primary tumor was located less than 10 cm from the anal verge; and (3) patients who received long-course radiotherapy (40–50 Gy) and concurrent chemotherapy before or after radical resection. Patients were excluded from the present study if they met any of the following criteria: (1) had multiple adenocarcinomas of the colon and rectum; (2) had metastatic diseases; (3) had synchronous or metachronous second primary tumors; (4) had familial adenomatous polyposis or Lynch syndrome; (5) post-operatively died within 30 days of surgery; (6) developed distant metastases within 6 months after being diagnosed with rectal cancer; and (7) had incomplete clinicopathological data.

Treatment

The pre-treatment clinical stage was determined based on abdominopelvic computed tomography (CT) scans, pelvic magnetic resonance imaging (MRI) or endorectal ultrasonography (EUS), and chest radiography/CT. The treatment decision regarding whether surgery or NCRT should be the first treatment was based on the clinical stage of the disease, the decision of a multidisciplinary team, and the preference of the patient. All of the included patients received long-course radiotherapy (40–50 Gy) either before or after the operation, and concurrent chemotherapy was administered with a 5-fluorouracil-based regimen with or without oxaliplatin. For patients who received NCRT, radical resections were performed according to the TME principle at a median interval of 7 weeks after NCRT. The control group received post-operative chemoradiotherapy (PCRT) at a median interval of 4 weeks after surgery.

Follow-up

The follow-up evaluations were performed every 3 months for the first 2 years, then every 6 months for the next 3 years, and annually thereafter. The post-operative follow-up included a physical examination, serum carcinoembryonic antigen test, chest and abdominal CT, pelvic CT or MRI, and colonoscopy. The patients' characteristics, recurrence status, and metastasis information were collected from their medical records or through a telephone follow-up. All patients were followed up until death or until August 31, 2019.

Pathological evaluation and definitions

The original hematoxylin and eosin tissue slides were retrieved and independently reviewed by two gastrointestinal tumor pathologists. If a discrepancy occurred between the two pathologists, they reviewed the slides again and reached a consensus. All patients were staged according to the eighth edition of the American Joint Committee on Cancer TNM staging system.

Currently, for patients with NCRT, T stage is determined by the depth of residual cancer cells, and N stage is determined by the absolute number of metastatic lymph nodes that still have residual cancer cells, which are defined as pathological tumor stage after neoadjuvant chemoradiotherapy (ypT) and pathological node stage after neoadjuvant chemoradiotherapy (ypN), respectively.

NCRT can lead to tumor regression and result in downstaging of T and N stage, and the presence of the fibrosis or mucinous lakes was considered to be the evidence of tumor regression. The tumor regression grade

(TRG) was evaluated according to the ratio of the area of the tumor cell to the area of fibrosis or mucinous lakes, which was first proposed by Mandard et al.[11] The area of the fibrosis or mucinous lakes after NCRT was considered to be the tumor region before NCRT. Subsequently, several similar classifications of TRG were developed based on the Mandard's TRG system.[12-15] Nowadays, the TRG is routinely reported in the pathological reports for tumors that received NCRT. On the basis of the method of assessing the TRG, in this study, we developed a novel method to evaluate the initial true pathological tumor (ipT) stage and initial true pathological lymph node (ipN) stage before receiving treatment for rectal cancer with NCRT. In our study, the ipT stage was determined by the deepest depth of the residual cancer cells, fibrosis or mucous lakes, which can truly represent the initial T stage pre-NCRT. For example, if the residual cancer cells are located in the submucosa layer but the deepest fibrosis or mucous lakes are located in the muscle layer, then the tumor stages are ypT1 and ipT2.

The lymph node regression grade was evaluated with the same protocol as the primary tumor.[16] The presence of fibrosis or mucinous lakes in the lymph nodes was also considered to be the evidence of cancer cell regression. The ipN stage was determined by the absolute number of lymph nodes with any residual cancer cells, fibrosis or mucous lakes. The presence of fibrosis or mucinous lakes with no residual tumor cells in the lymph node was considered to be evidence of complete tumor regression and indicated that the lymph node was metastatic prior to NCRT.

Propensity score matching process

Propensity score matching was used to balance the distribution of the baseline characteristics and to compare the metastasis pattern between patients with NCRT and patients with PCRT. Two groups of patients were matched by age, sex, tumor distance from the anal verge, treatment period, adjuvant chemotherapy, and pathological T, N, and TNM stage before radiotherapy (staging by pathological evaluation; pT, pN, and pTNM for patients with PCRT; ipT, ipN, and ipTNM for patients with NCRT). Since CT and MRI have been reported to have low accuracy for clinical staging, we used pTNM and ipTNM in the propensity score matching process.

The matching process was based on the nearest neighbor matching principle and 1:2 matching with a caliper of 0.01.

Statistical analysis

The matching process was calculated using the package "MatchIt" in R version 3.6.1 for Mac OS X (R Foundation for Statistical Computing, http://www.R-project.org). The statistical analyses were performed with SPSS 25.0 for MAC (SPSS Inc., Chicago, IL, USA). Disease-free survival (DFS) was defined as the time interval from the date of surgery to the date of first local recurrence, distant metastases, death, or the last follow-up. Overall survival (OS) was defined as the time from the date of surgery to the date of death or the last follow-up. Survival analysis was performed using the Kaplan-Meier method and log-rank test. The clinicopathological features of the two groups were presented as numbers (percentages) for categorical variables or median (Q_1, Q_3) for non-normally distributed continuous variables, and evaluated using the Chi-square test or Mann-Whitney *U* test as appropriate. A two-tailed P value < 0.05 was considered statistically significant.

Results

Baseline clinicopathological characteristics

A total of 1296 rectal cancer patients were enrolled in our study, including 335 patients with NCRT and 961 patients with PCRT. The baseline clinicopathological characteristics of the two groups are shown in Table 1. There were significant differences in the (i)pT stage ($\chi^2 = 71.1$, $P < 0.001$), (i)pN stage ($\chi^2 = 30.0$, $P < 0.001$), (i)pTNM stage ($\chi^2 = 54.4$, $P < 0.001$), distance from the anal verge ($\chi^2 = 37.7$, $P < 0.001$), and treatment period ($\chi^2 = 46.2$, $P < 0.001$) between the NCRT group and PCRT group before propensity scoring matching. The 961 patients who received PCRT were matched with the 335 patients who received NCRT at a 2:1 ratio. The remaining 653 patients were included for analysis, which included 408 patients in the PCRT group and 245 patients in the NCRT group [Figure 1]. After matching, no significant differences were found between the two groups in terms of age, sex, (i)pT stage, (i)pN stage, (i)pTNM stage, tumor location, treatment period or adjuvant chemotherapy (all $P > 0.05$) [Table 1].

Survival and recurrence

The median follow-up time was 56.9 (36.6, 75.9) months for all of the patients. There were no significant differences in OS or DFS at 5 years between the PCRT group and NCRT group (80.6% *vs.* 80.4%, $P = 0.612$; 60.7% *vs.* 67.7%, $P = 0.079$, respectively) [Figure 2]. During the follow-up period, 230 of the 653 (35.2%) patients developed recurrence, including local recurrence and distant metastases: 151 (23.1%) patients in the PCRT group and 79 (12.1%) patients in the NCRT group. The median recurrence time for the PCRT group was 16.8 (10.7, 30.0) months and that for the NCRT group was 23.8 (12.7, 37.1) months. Of all patients with recurrence in the PCRT group, 66.2% (100/151) experienced recurrence within the first 2 years, 81.5% (123/151) within the first 3 years, and only 4.0% (6/151) beyond 5 years after surgery. In the NCRT group, 51.9% (41/79) of recurrence occurred within the first 2 years, 73.4% (58/79) within the first 3 years, and 6.3% (5/79) beyond 5 years after resection. Recurrence most commonly occurred in the 2nd year (57/151, 37.7%), followed by the 1st year (43/151, 28.5%) and the 3rd year (23/151, 15.2%) after surgery in the PCRT group [Table 2]. In the NCRT group, recurrence most commonly appeared in the 2nd year (23/79, 29.1%), followed by the 1st year (18/79, 22.8%) and the 3rd year (17/79, 21.5%) after surgery. Nonetheless, 20.3% (16/79) of recurrences still occurred in the 4th to the 5th year after surgery in the NCRT group, while only 14.6% (22/151) of recurrences occurred within the same period in the PCRT group [Table 2].

Table 1: Characteristics of patients with locally advanced rectal cancer receiving PCRT and NCRT before and after propensity score matching.

Variables	Before matching				After matching			
	PCRT group ($n=961$)	NCRT group ($n=335$)	χ^2	*P* values	PCRT group ($n=408$)	NCRT group ($n=245$)	χ^2	*P* values
Age			0.1	0.836			0.7	0.421
≥65 years	674 (70.1)	233 (69.6)			296 (72.5)	170 (69.4)		
<65 years	287 (29.9)	102 (30.4)			112 (27.5)	75 (30.6)		
Sex			3.2	0.079			0.6	0.494
Male	575 (59.8)	219 (65.4)			275 (67.4)	158 (64.5)		
Female	386 (40.2)	116 (34.6)			133 (32.6)	87 (35.5)		
(i)pT*			71.1	<0.001			1.9	0.387
T1	8 (0.8)	0 (0)			0 (0)	0 (0)		
T2	97 (10.1)	21 (6.3)			12 (2.9)	10 (4.1)		
T3	780 (81.2)	230 (68.6)			354 (86.8)	203 (82.8)		
T4	76 (7.9)	84 (25.1)			42 (10.3)	32 (13.1)		
(i)pN			30.0	<0.001			3.6	0.165
N0	331 (34.4)	171 (51.1)			171 (41.9)	113 (46.1)		
N1	370 (38.5)	104 (31.0)			125 (30.6)	81 (33.1)		
N2	260 (27.1)	60 (17.9)			112 (27.5)	51 (20.8)		
(i)pTNM			54.4	<0.001			1.3	0.532
1	14 (1.5)	21 (6.3)			6 (1.5)	5 (2.0)		
2	317 (32.9)	150 (44.8)			165 (40.4)	108 (44.1)		
3	630 (65.6)	164 (48.9)			237 (58.1)	132 (53.9)		
Distance from anal verge			37.7	<0.001			0.5	0.506
≤5 cm	441 (45.9)	219 (65.4)			248 (60.8)	156 (63.7)		
>5 cm	520 (54.1)	116 (34.6)			160 (39.2)	89 (36.3)		
Treatment period†			46.2	<0.001			0.1	0.764
<2011	387 (40.3)	66 (19.7)			89 (21.8)	51 (20.8)		
≥2011	574 (59.7)	269 (80.3)			319 (78.2)	194 (79.2)		
Adjuvant chemotherapy			1.2	0.295			0.1	1.000
Yes	606 (63.1)	200 (59.7)			253 (62.0)	152 (62.0)		
No	355 (36.9)	135 (40.3)			155 (38.0)	93 (38.0)		

Data were presented as *n* (%). *(i)pN: Initial pathological lymph node stage (ipN) for patients in the NCRT group and pathological lymph node stage (pN) for those in the PCRT group; (i)pT: Initial pathological tumor stage (ipT) for patients in the NCRT group and pathological tumor stage (pT) for those in the PCRT group; (i)pTNM: Initial pathological tumor-node-metastasis stage (ipTNM) for patients in the NCRT group and pathological tumor-node-metastasis stage (pTNM) for those in the PCRT group. †The time when the patients were diagnosed with rectal cancer and received therapy. NCRT: Neoadjuvant chemoradiotherapy; PCRT: Post-operative chemoradiotherapy; TNM: Tumor-node-metastasis.

Local recurrence

During the follow-up period, there were 42 (10.3%) patients in the PCRT group and ten (4.1%) patients in the NCRT group with local recurrence. There was a significant reduction in the local recurrence rate in the NCRT group compared with that in the PCRT group (4.1% *vs.* 10.3%, $P=0.004$) [Figure 3A]. The median local recurrence time was 18.7 (13.3, 30.0) months in the PCRT group and 29.2 (18.8, 52.0) months in the NCRT group, showing a significant difference ($Z=-2.342$, $P=0.019$). Of all patients with local recurrence, 54.8% (23/42) of patients in the PCRT group and 30.0% (3/10) in the NCRT group experienced local recurrence within the first 2 years after resection. Local recurrences occurred in 81.0% (34/42) of the PCRT group and 60.0% (6/10) of the NCRT group in the first 3 years. Local recurrences occurred mainly in the 2nd year (18/42, 42.9%) for the PCRT group and in the 3rd year (3/10, 30%) for the NCRT group [Table 2].

Distant metastases

There was no significant difference in the cumulative incidence of distant metastases between the two groups (27.9% in the PCRT group *vs.* 28.2% in the NCRT group, $P=0.924$) [Figure 3B]. In the PCRT group, 114 (27.9%, 114/408) patients developed distant metastases during the follow-up period. The most common site of metastases was the lung (55/408, 13.5%), followed by the liver ($n=28$, 6.9%) and multiorgan metastases (17/408, 4.2%) [Figure 4A]. There were 69 (28.2%, 69/245) patients who developed distant metastases in the NCRT group, and the most common site of metastases was also the lung (30/245, 12.2%), followed by the liver (16/245, 6.5%) and peritoneum (9/245, 3.7%) [Figure 4B]. Overall, the predominant site of distant metastases was the lung, followed by the liver, in both groups.

The median time to develop metastases was 16.4 (9.3, 27.9) months in the PCRT group and 21.2 (12.2, 33.8)

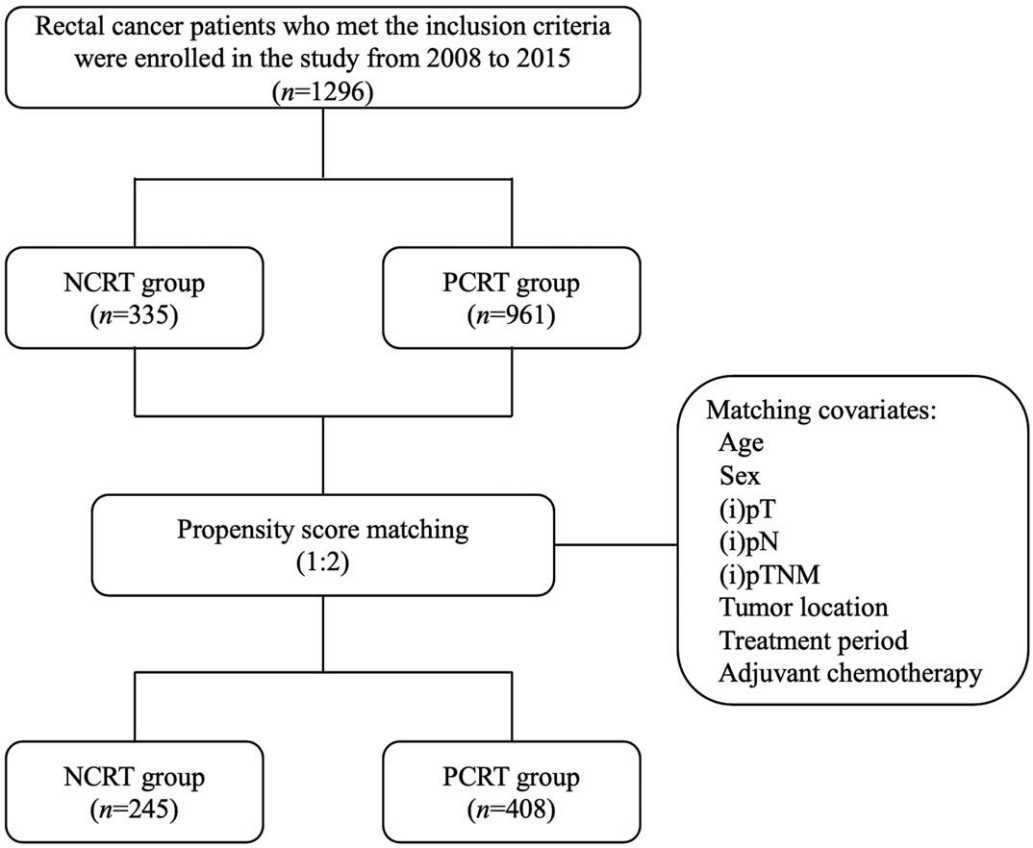

Figure 1: Study flow chart of patient enrollment. (i)pN: Initial pathological lymph node stage (ipN) for patients in the NCRT group and pathological lymph node stage (pN) for those in the PCRT group; (i)pT: Initial pathological tumor stage (ipT) for patients in the NCRT group and pathological tumor stage (pT) for those in the PCRT group; (i)pTNM: Initial pathological tumor-node-metastasis stage (ipTNM) for patients in the NCRT group and pathological tumor-node-metastasis stage (pTNM) for those in the PCRT group; NCRT: Neoadjuvant chemoradiotherapy; PCRT: Post-operative chemoradiotherapy.

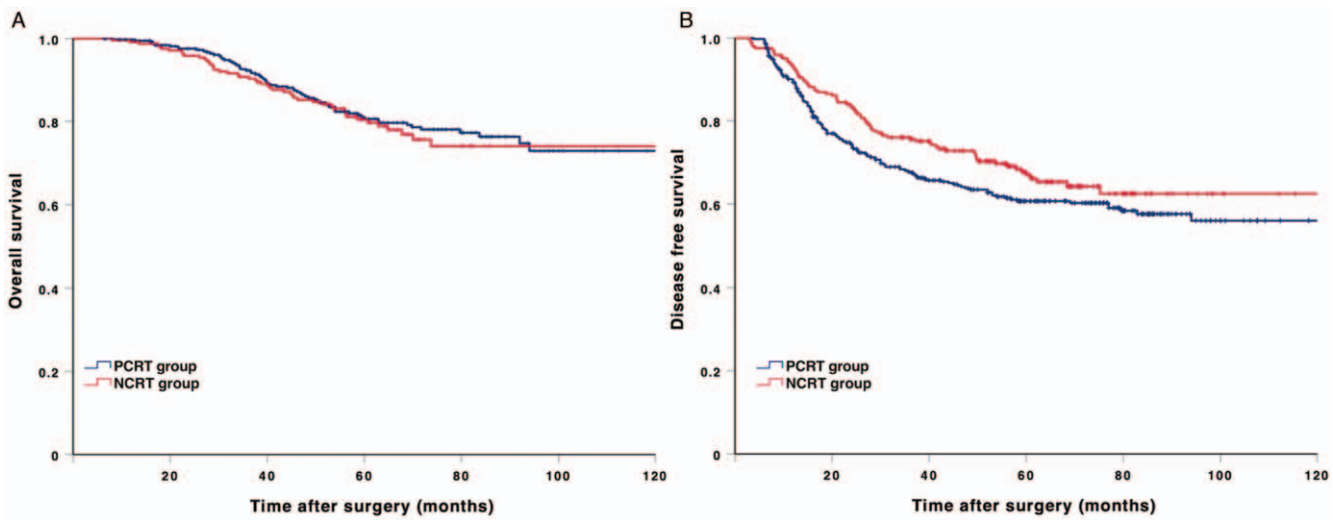

Figure 2: Overall survival (A) and disease free survival (B) for the PCRT and NCRT groups. NCRT: Neoadjuvant chemoradiotherapy; PCRT: Post-operative chemoradiotherapy.

months in the NCRT group, indicating a significant difference ($Z = -1.765$, $P = 0.035$). In the PCRT group, 67.5% (77/114) of all metastases occurred in the first 2 years, 80.7% (92/114) in the first 3 years and 95.6% (109/114) in the first 5 years after surgery. In the NCRT group, 55.1% (38/69) of the metastases occurred in the first 2 years after resection, 75.4% (52/69) in the first 3 years after resection and 95.7% (66/69) in the first 5 years after resection [Table 2]. The distant metastases occurred mainly in the 2nd year after surgery in both the

Table 2: Number and rate of local recurrences and distant metastases in patients with locally advanced rectal cancer receiving PCRT and NCRT according to the number of years after surgery.

	Local recurrence				Distant metastases				Total recurrence			
	PCRT group ($n=42$)		NCRT group ($n=10$)		PCRT group ($n=114$)		NCRT group ($n=69$)		PCRT group ($n=151$)		NCRT group ($n=79$)	
Time after surgery (years)	No. of LR (%)	Accu no. of LR (%)	No. of LR (%)	Accu no. of LR (%)	No. of DM (%)	Accu no. of DM (%)	No. of DM (%)	Accu no. of DM (%)	No. of TR (%)	Accu no. of TR (%)	No. of TR (%)	Accu no. of TR (%)
1	5 (11.9)	5 (11.9)	1 (10.0)	1 (10.0)	38 (33.3)	38 (33.3)	17 (24.6)	17 (24.6)	43 (28.5)	43 (28.5)	18 (22.8)	18 (22.8)
2	18 (42.9)	23 (54.8)	2 (20.0)	3 (30.0)	39 (34.2)	77 (67.5)	21 (30.4)	38 (55.1)	57 (37.7)	100 (66.2)	23 (29.1)	41 (51.9)
3	11 (26.2)	34 (81.0)	3 (30.0)	6 (60.0)	15 (13.2)	92 (80.7)	14 (20.3)	52 (75.4)	23 (15.2)	123 (81.5)	17 (21.5)	58 (73.4)
4	3 (7.1)	37 (88.1)	1 (10.0)	7 (70.0)	11 (9.6)	103 (90.4)	6 (8.7)	58 (84.1)	13 (8.6)	136 (90.1)	7 (8.9)	65 (82.3)
5	4 (9.5)	41 (97.6)	1 (10.0)	8 (80.0)	6 (5.3)	109 (95.6)	8 (11.6)	66 (95.7)	9 (6.0)	145 (96.0)	9 (11.4)	74 (93.7)
6	1 (2.4)	42 (100.0)	2 (20.0)	10 (100.0)	3 (2.6)	112 (98.2)	2 (2.9)	68 (98.6)	4 (2.6)	149 (98.7)	4 (5.1)	78 (98.7)
7	0 (0)	42 (100.0)	0 (0)	10 (100.0)	1 (0.9)	113 (99.1)	1 (1.4)	69 (100.0)	1 (0.7)	150 (99.3)	1 (1.3)	79 (100.0)
>7	0 (0)	42 (100.0)	0 (0)	10 (100.0)	1 (0.9)	114 (100.0)	0 (0)	69 (100.0)	1 (0.7)	151 (100.0)	0 (0)	79 (100.0)

Accu no. of: Accumulative number of; DM: Distant metastases; LR: Local recurrence; NCRT: Neoadjuvant chemoradiotherapy; PCRT: Post-operative chemoradiotherapy; TR: Total recurrence, including local recurrences and distant metastases.

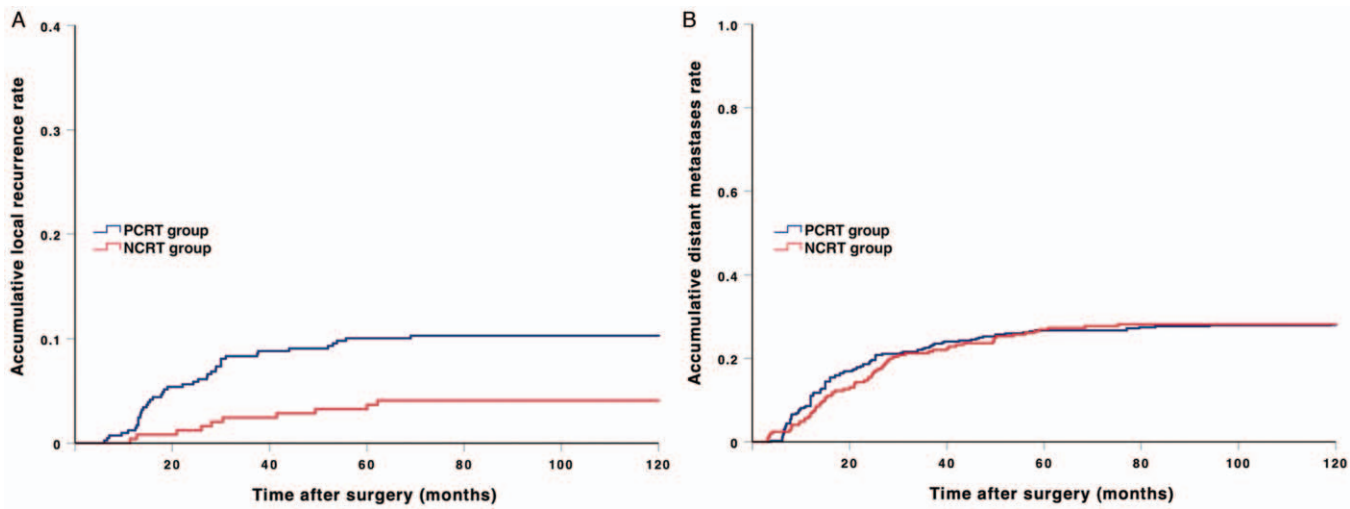

Figure 3: Accumulative local recurrence rate (A) and distant metastases rate (B) for the PCRT and NCRT groups. NCRT: Neoadjuvant chemoradiotherapy; PCRT: Post-operative chemoradiotherapy.

PCRT group and NCRT group (34.2% [39/114] and 30.4% [21/69]). However, 20.3% (14/69) of the distant metastases still appeared in the 3rd year in the NCRT group, while only 13.2% (15/114) were observed in the 3rd year in the PCRT group [Table 2]. In total, 20.3% (14/69) of distant metastases occurred in the 4th to 5th year after surgery in the NCRT group, while only 14.9% (17/114) occurred in the PCRT group [Table 2]. There were still sporadic distant metastases beyond the 5th year after surgery in both groups [Table 2].

Discussion

NCRT has been proven to reduce local recurrence but not distant metastases for locally advanced rectal cancer.[17] Some studies had shown that the lung is the predominant site of metastases in rectal cancer patients treated with NCRT,[18,19] and the liver is the most common site of metastases for rectal cancer patients without NCRT.[20] However, previous studies did not consider the differences in baseline clinicopathological characteristics and treatment regimens when comparing metastasis pattern between patients with and without NCRT. The rectal cancer patients who received NCRT and those who directly underwent surgery always had different baseline clinicopathological characteristics and adjuvant treatment, which might influence the metastasis pattern, and the patients who received NCRT usually had more advanced disease and a lower tumor location than the patients who underwent surgery directly. Evaluating the differences in metastasis pattern between patients who have heterogeneous baseline clinicopathological characteristics and treatment regimens is unreliable.

Our results showed that there were significant differences in baseline characteristics such as the primary stage, distance from the anal verge and treatment period between the NCRT group and PCRT group in our consecutive cohort, and the wrong conclusion may be drawn if the

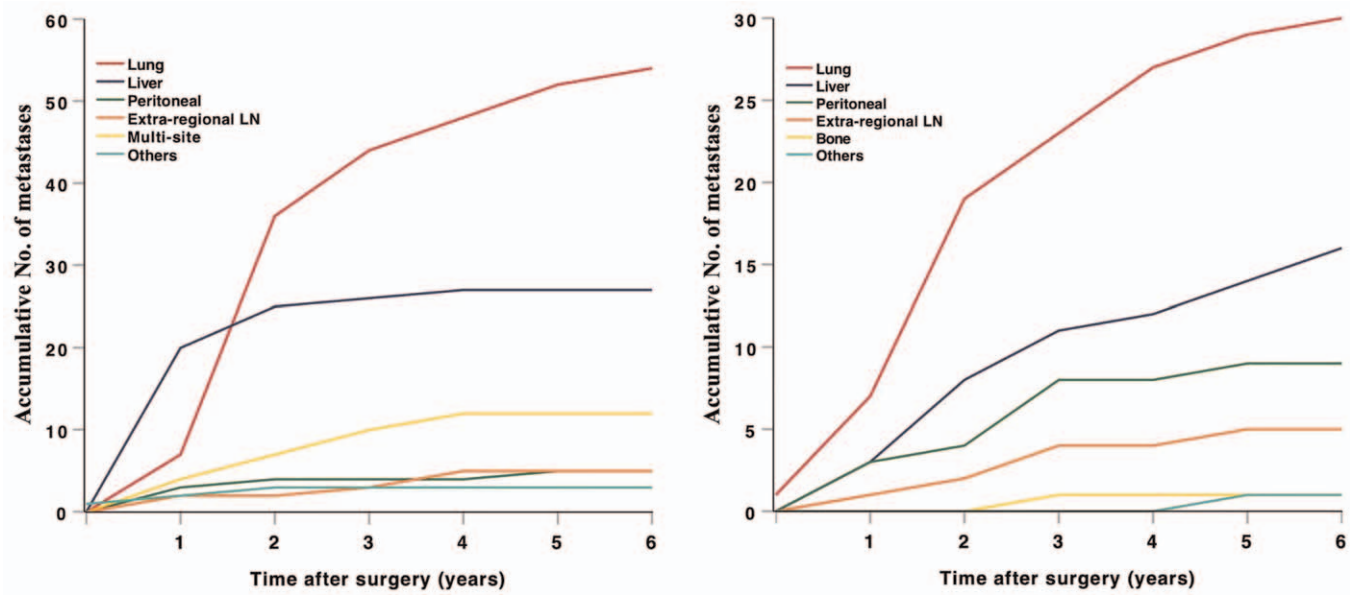

Figure 4: Accumulative number of distant metastases by site for the PCRT group (A) and NCRT group (B). LN: Lymph node; NCRT: Neoadjuvant chemoradiotherapy; PCRT: Post-operative chemoradiotherapy.

distant metastasis patterns are directly compared between the two groups. Therefore, we employed propensity score matching to minimize the differences in baseline characteristics and treatment between the PCRT group and NCRT group. Furthermore, on the basis of the method of TRG assessment, we originally proposed a new method to accurately evaluate the initial tumor stage and initial lymph node stage before NCRT for rectal cancer patients. This method depends on the pathological evaluation of residual cancer cells, fibrosis, and mucous lakes and can more accurately classify the initial stage because fibrosis and mucous lakes can be regarded as tumor shrinkage and tumor regression. We think this staging method can reflect the true tumor stage before NCRT. Previous related studies were mainly based on the clinical stage and ypTNM stage. However, the clinical stage, which depends on CT, MRI, or EUS, cannot accurately reflect the true tumor stage. The accuracies of CT, MRI, and EUS for evaluating the T stage are 53.0%, 66.0%, and 75%, respectively, while the corresponding accuracies for evaluating lymph node involvement are 57.7%, 72.0%, and 56.8%, respectively.[21-23] The ypTNM stage is affected by the downstaging effect of NCRT. Therefore, the initial tumor stages of patients with and without NCRT were heterogeneous in the previous related studies. In this study, after propensity score matching, the variabilities in the initial tumor stage and other selection biases between the two groups were minimized.

Our study showed that NCRT significantly decreased local recurrence compared with PCRT (4.1% *vs.* 10.3%, $P = 0.004$), which was consistent with previous studies.[4,17] Moreover, NCRT not only reduced local recurrence but also delayed recurrence after radical resection. A meta-analysis comprising 25 studies indicated that the mean time to local recurrence was 31 months in patients with NCRT and 15 months in patients with PCRT.[24] We found that the median time to local recurrence in the NCRT group was 10.5 months later than that in the PCRT group (median recurrence time: 29.2 *vs.* 18.7 months). The local recurrences mainly occurred in the third year (3/10, 30.0%) after surgery for the NCRT group and in the second year (18/42, 42.9%) for the PCRT group, and 40.0% (4/10) of the local recurrences in the NCRT group and 19.0% (8/42) in the PCRT group occurred beyond the third year after surgery. Therefore, NCRT changed the local recurrence rate and the timing of local recurrence.

Randomized controlled clinical trials (RCTs) have proven that NCRT does not reduce distant metastases compared with PCRT.[4,17] Consistent with the RCTs, our study indicated that there was no significant difference in the distant metastasis rate between the NCRT group and PCRT group (28.2% *vs.* 27.9%, $P = 0.924$). More importantly, our results showed that the lung was the most common site of metastases in both the NCRT and PCRT groups, followed by the liver. Some previous studies considered that NCRT could lead to changes in the predominant metastases site from the liver to lung.[3,9,25] However, after propensity score matching, our study showed that the lung was still the most common site of metastases in the PCRT group, which indicated that lung-predominant metastases were not caused by NCRT. Patients who received NCRT usually had more advanced tumors, more lymph node metastases, and lower tumor locations than the patients who underwent surgery directly. Therefore, the change may be associated with the low tumor location or other histopathologic factors. Lower rectal cancer has a higher rate of lung metastases than upper rectal cancer, which is considered to be associated with the anatomical features of the venous drainage system of the rectum.[26,27] The cancer cells of

lower rectal cancer could potentially directly spread to the lungs via the vena cava from the inferior and middle rectal veins.[10]

Furthermore, similar to the local recurrence results, metastases developed later in the NCRT group than in the PCRT group (median time: 21.2 *vs*. 16.4 months), and 55.1% of the metastases in the NCRT group and 67.5% in the PCRT group occurred in the first 2 years. Still, 20.3% of the distant metastases appeared in the 3rd year after surgery in the NCRT group while distant metastases in the 3rd year accounted for only 13.2% in the PCRT group, which indicated that NCRT delayed the occurrence of metastases.

The National Comprehensive Cancer Network guidelines for rectal cancer recommend that follow-up evaluations should be conducted every 3 to 6 months for the first 2 years, then every 6 months for the next 3 years, and annually thereafter.[1] The same follow-up strategy is used for patients with or without NCRT, and the follow-up strategy strictly focuses on recurrence or metastases in the first 2 years after surgery. However, our results showed that the recurrence time for the NCRT group was later than that for the PCRT group. Additionally, 20.3% of the distant metastases and 30.0% of the local recurrences occurred in the 3rd year after surgery for the NCRT group, which means that the patients with NCRT required a longer intensive follow-up period than patients with PCRT. Thus, the follow-up strategy should be adjusted for patients with NCRT.

Therefore, we advise that the follow-up assessments should be performed every 3 months for the first 3 years and every 6 months for the next 2 years and annually thereafter for patients with NCRT.

To the best of our knowledge, this is the first study to compare recurrence patterns using propensity score matching between patients treated with NCRT and those treated with PCRT. This study is also the first to present the ipT and ipN stages before receiving treatment, which were determined by an accurate pathologic evaluation, for rectal cancer patients with NCRT. With these two methods, the bias in the baseline clinicopathological characteristics between the NCRT group and PCRT group was minimized. Therefore, a solid conclusion could be reached that the predominant site of distant metastases was the lung, followed by the liver, for both the NCRT group and PCRT group, and the recurrence time of the NCRT group was delayed, indicating that intensive follow-up evaluations should continue until at least the 3rd year after surgery.

Our study had certain inherent limitations since it is a single-center retrospective analysis. Selection bias still existed, although we tried to minimize this by using propensity score matching. The data were obtained from patients treated between 2008 and 2015; therefore, the adjuvant chemotherapy regimens were not homogeneous and some patients had short follow-up periods.

In conclusion, our study indicated that the predominant site of distant metastases was the lung, followed by the liver, for both the NCRT group and PCRT group. NCRT did not change the predominant metastasis organ. However, the time to develop local recurrence and distant metastases was later in the NCRT group than in the PCRT group. The follow-up strategy for patients with NCRT should be adjusted, and these patients need a longer intensive follow-up than those with PCRT.

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Conflicts of interest

None.

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