Total neoadjuvant chemoradiotherapy (consolidation chemotherapy during the interval after chemoradiotherapy) for distal rectal cancer increases the rates of complete response

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Research

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Abstract

Objective

To compare the safety and efficacy between neoadjuvant concurrent chemoradiotherapy (CRT) and total neoadjuvant chemoradiotherapy (TNT) in patients with locally advanced rectal cancer.

Methods

Patients with cT3/T4 or TxN+M0 rectal cancer were randomized to receive CRT/TNT. In CRT group, we planned pelvic radiotherapy (50.0Gy in 25 fractions) with two cycles of concurrent CAPOX followed by total mesorectal excision (TME). In TNT group, 3 cycles of CAPOX were administered 2 weeks after the completion of CRT before TME. The primary endpoints of my study were pathological complete response (pCR) rates in the two cohorts.

Results

A total of 197 patients were included in our study. Eighty-one patients received CRT while one hundred and sixteen patients received TNT (consolidation chemotherapy). Nine patients did not undergo surgery because of the distant metastases (1 patient (1.2%) in CRT group, 2 patients (1.7%) in TNT group) or clinical complete response (cCR) (2 patients in CRT group, 4 patients in TNT group). The rate of pathological complete response in TNT was significantly higher than the rate in CRT (32.7% vs12.8%, P =0.002). No grade 4 or serious adverse events were observed. There was no statistically significant difference in the grade 3 acute toxicities of neoadjuvant treatment and surgical complications between the two groups (all P >0.05).

Conclusions

Our data suggests that total neoadjuvant chemoradiotherapy (consolidation chemotherapy) is effective and safe for patients with locally advanced rectal cancer and is associated with high rates of pathological complete response. The long-term follow-up and survival outcomes for patients are necessary to be evaluated in future prospective randomized trial.

Introduction

The standard therapeutic approach for locally advanced rectal cancer (LARC) (T3/T4N0, or TanyN1/N2) is neoadjuvant concurrent chemoradiotherapy (CRT) followed by total mesorectal excision (TME) and postoperative adjuvant chemotherapy. This multidisciplinary treatment has significant improvements in reducing the risk of local recurrence [1–2]. However, distant metastasis now exceeds the rate of local failure, which is the primary cause of cancer death in rectal cancer [3]. The data for adjuvant chemotherapy for rectal cancer does not show clear benefit in improving overall survival, disease-free survival, or distant recurrences [4–6]. In one meta-analysis of over 6000 patients suggested that patients with a pathologic complete response after chemoradiotherapy may not benefit from adjuvant

chemotherapy, whereas patients with residual tumor showed superior outcomes when adjuvant chemotherapy was given [6]. In addition, patient's compliance with adjuvant chemotherapy was poor [7–8]. Nearly 30% of eligible patients had never started adjuvant chemotherapy [9] and less than half of them had received the full chemotherapy or initiated treatment after a significant delay [7, 10]. Therefore, there is controversial about the efficacy of adjuvant chemotherapy in LARC.

Total neoadjuvant chemoradiotherapy (TNT), which means to move the adjuvant chemotherapy to the preoperative setting, has been reported by several researchers [11–16]. It has the promise to better address microscopic metastatic disease early and increase treatment compliance. The current study defined TNT as induction chemotherapy followed by CRT or consolidation chemotherapy (delivering systemic chemotherapy after CRT). There were many studies on induction chemotherapy but few on consolidation chemotherapy [17]. It has been previously reported that in patients undergoing CRT with consolidation chemotherapy, tumors are less likely to regain metabolic activity between 6 and 12 weeks [18].

The aim of this retrospectively study was to compare the safety and efficacy in two cohorts: TNT (consolidation chemotherapy) vs CRT.

Materials And Methods

Patients

We included 197 patients with LACR who underwent CRT or TNT during September 1, 2017 to September 1,2019 based on hospital coding at the Department of General Surgery, Beijing Chao-Yang Hospital. Patients aged at least 18 years, with diagnosis of rectal adenocarcinoma by biopsy and clinical stage Ⅱ(T3-4,N0) or Ⅲ(any T, N1-2) who had a distal tumor border within 12 cm from the anal verge by coloscopy were eligible for inclusion. Clinical staging was done by endorectal ultrasonography, pelvic magnetic resonance imaging (MRI), or computed tomography (CT). Eligible patients were required to have an Eastern Collaborative Oncology Group performance status score of 0 or 1and normal bone marrow /liver/kidney function. Patients with the following characteristics were excluded: (1) presence of distant metastases; (2) presence of unresectable cancer; (3) previous chemotherapy or pelvic radiation; (4) previous history (within 5 years) of malignant tumor.

Informed consent was obtained from all participants before treatment. The study was approved by the ethics committee of Beijing Chao-Yang Hospital, Capital Medical University.

Procedures

Patients were randomly included in the TNT or CRT group. All the patients received pelvic intensity-modulated radiotherapy (IMRT) and two cycles of concurrent CAPOX. Patients in TNT group received three cycles of consolidation CAPOX two weeks after chemoradiation. Then, A radical surgery was done

two weeks after completion of consolidation chemotherapy. Patients in CRT group had surgery 6–8 weeks rest after chemoradiation. Patients underwent IMRT receiving 2.0 Gy / fraction per day, 5 days per week, for a total dose of 50.0 Gy in 25 fractions. Concurrent CAPOX consisted of oxaliplatin 100 mg/m^2 on day 1 and 22, capecitabine 825 mg/m^2 twice a day, 5 days per week for 25–28 days. Consolidation CAPOX consisted of oxaliplatin 130 mg/m^2 on day 1, capecitabine 1000 mg/m^2 twice a day on day 1–14, every 3 weeks.

Both groups all underwent repeat coloscopy, endorectal ultrasonography, CT and pelvic MRI restaging at one week before surgery. Tumor response was assessed by Response Evaluation Criteria in Solid Tumors (RECIST) guidelines in solid tumors [19] during the neoadjuvant treatment course. Patients who developed distant metastasis during the neoadjuvant treatment course did not receive the surgery and received systemic therapy according to the decision of Multiple Disciplinary Team (MDT). Patients with clinical and radiological evidence of complete clinical response (cCR) were still recommended to receive radical surgery. Only when patients rejected a radical surgery, watch-and-wait approach would be conducted. Surgery was done according to the principles of TME. The surgeon decided the surgical procedure: abdominoperineal resection (APR), low anterior resection (LAR) or Hartmann procedure (Hartmann).

Pathologic Examination

The 7th edition of the American Joint Committee on Cancer (AJCC)TNM system was used for staging. After TME, ypTNM stages were evaluated by two experienced pathologists. The system used to grade tumor response as recommended by the AJCC cancer Staging Manual modified from Ryan R [20]. The pathological complete response (pCR) was defined as no residual cancer cells in the resection specimen [21].

Outcomes

The primary endpoints of my study were pCR rates in the two cohorts. The second endpoints were to compare the safety and efficacy in two cohorts. Adverse events during total neoadjuvant setting were measured using the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE5.0). Postoperative complications were defined as any medical or surgical complication occurred within 30 postoperative days according to Clavien-Dindo scale [22–23].

Statistical analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences software, version 20(SPSS Inc, Chicago, IL). Continuous variables are expressed as mean ± standard deviation (SD). Student's t test, Chi-square test and Wilcoxon test were used for statistical analysis. P values < 0.05 were considered to be statistically significant.

Results

Patients Characteristics

Of these 197 patients, 81 patients were treated with CRT and 116 patients were treated with TNT. Nine patients did not undergo surgery because of the distant metastases (1 patient (1.2%) in CRT group, 2 patients (1.7%) in TNT group) or refusal of resection (2 patients in CRT group, 4 patients in TNT group). A flow chart of the treatment approach for patients is shown in the Fig. 1.Table 1 shows the patients characteristics. Age, sex ECOG performance status, clinical stage and distance from anal verge were similar between the two groups.

Table 1
Patients characteristics

Characteristics	Patients, No. (%)		
	CRT(n = 81)	TNT(n = 116)	P value
Age(years)	60.2 ± 11.4	59.7 ± 11.8	0.859
Sex			
Male	47(58.0)	73(62.9)	0.487
Female	34(42.0)	43(37.1)	
Tumor height from anal verge(cm)			
<5	41(50.6)	63(54.3)	0.799
5–10	31(38.3)	43(37.1)	
>10	9(11.1)	10(8.6)	
ECOG			
0	71(87.7)	106(91.4)	0.394
1	10(12.3)	10(8.6)	
cT stage			
T2	4(4.9)	9(7.8)	0.721
T3	64(79.0)	84(72.4)	
T4a	10(12.3)	19(16.4)	
T4b	3(3.8)	4(3.4)	
cN stage			
cN0	23(28.4)	24(20.7)	0.212
cN positive	58(71.6)	92(79.3)	
Clinical stage			
	15(18.5)	28(24.1)	0.347
	66(81.5)	88(75.9)	
metastasis	1(1.2)	2(1.7)	1.000
ECOG, Eastern Collaborative Oncology Group			

Neoadjuvant Administration And Toxicities

In CRT group, all of the patients received a full 2-cycle course of CAPOX. In TNT group, 111(95.7%) received a full 5-cycle course of CAPOX. There were 5 patients (4.3%) who received 4 cycles of CAPOX for the reason of grade 3 neutropenia. The mean number of CAPOX cycles were 5 cycles (SD 0.2). The most common grade 3 acute adverse events associated with the neoadjuvant administration were neutropenia in 18 patients (9.1%; six in CRT group and twelve in TNT group), thrombocytopenia in 13 patients (6.6%; four in CRT group and nine in TNT group), diarrhea in 11 patients(5.6%; three in CRT group and eight in TNT group) and rectal pain in 11 patients(5.6%; four in CRT group and seven in TNT group). Grade 3 anemia and radiation dermatitis were observed in 9 patients (4.6%; three in CRT group and six in TNT group), respectively. Only one patient had grade 3 vomiting in TNT group. The proportion of patients of CRT group experiencing adverse events during the neoadjuvant treatment was lower than patients of TNT group. But there was no statistically significant difference in the acute adverse events between the two groups. Table 2 summarizes grade 3 acute toxicities of neoadjuvant treatment. No grade 4 or serious adverse events were observed. No deaths occurred during chemoradiation.

Table 2 sever acute toxicity of neoadjuvant treatment

Grade 3 acute toxicities of neoadjuvant treatment	CRT(n=81)	TNT(n=116)	*P* value
Neutropenia	6（7.4）	12（10.3）	0.481
Anemia	3（3.7）	6（5.2）	0.889
Thrombocytopenia	4（4.9）	9（7.8）	0.433
Diarrhea	3（3.7）	8（6.7）	0.519
Vomiting	0	1（0.9）	
Radiation dermatitis	3（3.7）	6（5.2）	0.889
Rectal pain	4（4.9）	7（6.0）	0.989

Pathologic Response

All pathologic findings are described in Table 3. In the CRT group 10(12.8%) of 78 patients who underwent surgery achieved a pCR, whereas 36(32.7%) of 110 patients had surgery and a pCR in TNT group. The primary end point (pCR) was significant difference between the two groups (12.8% vs 32.7%, P = 0.002). Patients of CRT group had similar ypTNM classification(stage 29.5% vs 23.6%, P = 0.368; stage 30.8% vs 28.2%, P = 0.701;stage 26.9% vs 15.5, P = 0.054) and TRG scale(TRG1 34.6% vs 26.4, P = 0.223; TRG2 30.8% vs 28.2%, P = 0.701; TRG3 21.8% vs 12.7%, P = 0.099). There was no statistically significant difference in venous invasion (26.9% vs 21.8%, P = 0.419) and perineural invasion (28.2% vs 23.6%, P = 0.479) between patients in the CRT group compared with those in the TNT group.

Table 3 pathologic examination of resected specimens

tumor characteristic	CRT（n=78）	TNT（n=110）	*P* value
pathological complete response	10(12.8)	36(32.7)	0.002
ypTNM classification			
Ⅰ	23(29.5)	26(23.6)	0.368
Ⅱ	24(30.8)	31(28.2)	0.701
Ⅲ	21(26.9)	17(15.5)	0.054
tumor circumferential margin<1mm	0	1(0.09)	
TRG scale			
0	10(12.8)	36(32.7)	0.002
1	27(34.6)	29(26.4)	0.223
2	24(30.8)	31(28.2)	0.701
3	17(21.8)	14(12.7)	0.099
Venous invasion	21(26.9)	24(21.8)	0.419
perineural invasion	22(28.2)	26(23.6)	0.479

TRG,tumor regression grade

Surgery And Surgical Morbidity

Clinical complete responses were observed in 13.2% of patients. Six patients (two in CRT group and four in TNT group) refused to undergo further surgery, thus 188 oncological rectal resections with TME were available for complete pathologic examination and morbidity comparisons.

Table 4 illustrates the surgical results in our study. In total, 70.2% (132/188) and 23.4% (44/188) of patients underwent low anterior resection and abdominoperineal resection, while the other 12 (6.4%) patients underwent a Hartmann procedure. The rate of APR was higher in the TNT group. (31.8 vs 11.5%, P = 0.002). The mean operative time and blood loss was longer and more in the TNT group(195.1 ± 11.3minutes vs 180.5 ± 12.3minutes, P = 0.132; 122.1 ± 20.2 milliliters vs 102.1 ± 15.2 milliliters, P = 0.343), respectively. There was no statistically significant difference in pelvic infection, anastomotic leakage, bowel obstruction, wound infection and pulmonary infection (all P > 0.05). Only 2(1.8%) patients had anastomotic bleeding in TNT group. The mean length of hospital stay was similar across the two groups(P = 0.869).

Table 4 surgical results

Items	CRT(n=78)	TNT(n=110)	*P* value
Type of surgery			
LAR	60(77.0)	72(65.5)	0.002
APR	9(11.5)	35(31.8)	
Hartmann	9(11.5)	3(2.7)	
Pelvic infection	2(2.6)	6(5.5)	0.548
Anastomotic leakage	4(5.1)	8(7.3)	0.772
Anastomotic bleeding	0	2(1.8)	
Bowel obstruction	2(2.6)	5(4.5)	0.752
Wound infection	3(3.8)	6(5.5)	0.871
Pulmonary infection	1(1.3)	3(2.7)	0.87
Operation time(minutes)	180.5±12.3	195.1±11.3	0.132
Blood loss(milliliters)	102.1±15.2	122.1±20.2	0.343
Hospital stay(days)	7.8±3.2	6.9±3.8	0.869

LAR, low anterior resection
APR, abdominoperineal resection

Discussion

The therapeutic approach of LACR primarily aims to improve the disease-free survival, local or distant recurrence rates. Recently, TNT is attracting more and more interests [11–16]. In these studies, the authors discovered the following advantage: moving systemic therapy earlier than CRT to address possible microscopic metastatic disease, increased treatment compliance, assessed the sensitivity of chemotherapy in vivo, avoided the discomfort of patents undergoing chemotherapy with a stoma. Currently, there are more studies on the model of induction chemotherapy followed by CRT than the model of consolidation chemotherapy. However, which is the most reasonable TNT model are still unknown. There have been series of published studies suggesting that a critical decrease in tumor metabolism from CRT completion is associated with improved rates of CR and overall outcomes [24–26]. So, we chose the consolidation chemotherapy regiment in our study and compared it with CRT in safety and efficacy.

In our study, we show that total neoadjuvant treatment that consists of 5 cycles of neoadjuvant CAPOX (concurrent 2 cycles followed by 3 cycles) and radiotherapy of 50.0 Gy in 25 fractions, is effective and safe for patients with locally advanced rectal cancer. Lengthening the neoadjuvant treatment time by delivering CAPOX before operation did not increase the risk of disease progression. The rates of distant metastasis diagnosed during neoadjuvant treatment were equivalent between the two groups. No grade 4 or serious adverse events were observed in our study. Although TNT group had higher grade 3 toxicity rate than CRT group, there was no statistically significant difference between them. Our results were consistent with previously published evidence [12, 27]. In a phase 2 trial performed by Fernandez-Martos [12], the addition of induced chemotherapy did not increase the incidence of grade 3–4 adverse events in the neoadjuvant treatment. In another study [27], a similar conclusion was reached that consolidation chemotherapy did not increase the incidence of complications after chemoradiotherapy.

As to the safety of surgery, our data showed that the mean operative time and blood loss was longer and more in TNT group(195.1 ± 11.3minutes vs 180.5 ± 12.3minutes, P = 0.132; 122.1 ± 20.2 milliliters vs 102.1 ± 15.2 milliliters, P = 0.343), which may be related to more APR patients in TNT group (31.6% vs 13%, P < 0.05). The other specific complications, such as pelvic infection, anastomotic leakage, bowel obstruction, wound infection and pulmonary infection did not differ between study groups. Garcia-Aguilar et al conducted a multicenter study [28] and they found that delivering systemic chemotherapy after chemoradiation did not increase the risk of surgical complication.

We showed in our study that our 32.7% pCR rate in TNT was significantly higher than the 12.8% rate in CRT (P = 0.002). These results were comparable with those of previously published studies about induction chemotherapy [11, 13–14]. In a recnet study published by Cercek et al [13], which examined 308 patients received TNT (introduction fluorouracil-and oxaliplatin-based chemotherapy followed by chemoRT), the pCR rate was 35.7% in the TNT cohort compared with 21.3% in the chemoRT with planned adjuvant chemotherapy cohort. However, in a large phase □ Polish trail, patients with consolidation chemotherapy only had 16% pCR rate [16]. In this trail, patients were randomly assigned to two treatment groups: one with short-course radiotherapy (5 × 5 Gy) followed by 3 cycles of chemotherapy with fluorouracil and oxaliplatin and the other with standard CRT. In fact, a recent systematic review of factors affecting tumor response to neoadjuvant therapy in over 4,700 patients undergoing Phase II and Phase III trials has shown that a dose of □45Gy was significantly associated with increased rates of complete tumor response [29]. In our study, all patients underwent IMRT received a total dose of 50.0 Gy in the two groups, which may be one of the factors leading to a higher rate of pCR after neoadjuvant therapy in rectal cancer. TNT includes different strategies, the most reasonable sequence of the induction chemotherapy, concurrent CRT and consolidation chemotherapy are still unknown. The pathologic complete response following neoadjuvant chemoradiotherapy and interval proctectomy, in patients with rectal cancer, was associated with excellent long-term survival and low rates of local recurrence and distant disease [30]. Park et al reported that tumor response (complete v intermediate v poor) to neoadjuvant chemoradiotherapy among patients with locally advanced rectal cancer undergoing radical resection was associated with 5-year RFS(Recurrence-free survival) (90.5% vs 78.7% vs 58.5%; P□0.001), 5-year DM(distant metastasis) rates (7.0% vs 10.1% vs 26.5%; P□0.001), and 5-year LR(local recurrence) rates (0% vs 1.4% vs 4.4%; P = 0.002) [31].

The chemoradiation-to-surgery interval was prolonged in the TNT group. Although the optimal interval between completion of neoadjuvant chemoradiotherapy and surgery in rectal cancer is controversial [32–34], more and more evidences showed that operating 12 weeks after radiotherapy is safe with improved treatment response [35–36]. In our study, the interval between radiotherapy and surgery in TNT group was 12 weeks, which did not increase the surgical complications. Habr-Gama et al found that patients undergoing surgery 12 weeks or more from CRT completion was safe and did not negatively affect survival [35]. Time from completing neoadjuvant therapy to surgery was almost at 12 weeks in Cercek et al.' s study [13].

We did not routinely evaluate cCR to neoadjuvant therapy in two groups. Six patients (2 patients in CRT group, 4 patients in TNT group) refused operation because of cCR and underwent observational management. In 2004, Habr-Gama et al. published that the overall survival (OS) and disease-free survival (DFS) at 5 years ended up being higher in the observation group than resection group [37]. OnCoRe et al. from the UK performed a prospectively study supporting watch-and-wait approach [38]. They demonstrated that there was no statistical difference between watch and wait and surgical resection in 3-year DFS and OS. In addition, the colostomy-free survival was significantly better in the observational group (47% vs 74%, P□0.001). Evaluation of clinic complete response according to current adopted criteria has low sensitivity [39], so how to identify the patients with a cCR who may potentially benefit from the nonoperative management is still a problem.

Several limitations of our trail deserve mention. First, this study was a retrospective study, which might have selection bias. Although our findings lend support to the TNT mode (consolidation chemotherapy), they should still be regards as exploratory and in need of confirmation in a prospective randomized trial. Second, our study used pCR rate as the primary endpoint, and it was revealed that TNT strategy used in this study achieved a pCR rate of 32.7%. Although pCR is associated with improved the long-term outcomes [30–31], further investigation with mature follow-up and survival data are warranted. Third, we did not routinely assess cCR to neoadjuvant therapy in all patients. The watch-and-wait approach to the management of cCR in rectal cancer is often the first concern of a patient and we as clinicians are obliged to discuss these options with our patients.

Conclusions

Our data suggests that total neoadjuvant chemoradiotherapy (consolidation chemotherapy) is effective and safe for patients with locally advanced rectal cancer. It is associated with high rates of pathological complete response and makes it possible to treat patients with nonoperative watch-and-wait approach. The long-term follow-up and survival outcomes for patients are necessary to be evaluated in future prospective randomized trial.

Declarations

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Author's contributions

ZWZ and ZJW designed the study. ZWZ and KNZ acquired data of the patients with locally advanced rectal cancer and drafted the manuscript. CW analyzed and interpreted the patient data. JGH, TZ, LXW and JNY were the members of the Multiple Disciplinary Team and supervised the study. All authors read and approved the final manuscript.

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Availability of data and materials

Not applicable

Ethics approval and consent to participate

Informed consent was obtained from all participants before treatment. The study was approved by the ethics committee of Beijing Chao-Yang Hospital, Capital Medical University. (Number:2016-350)

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Figures

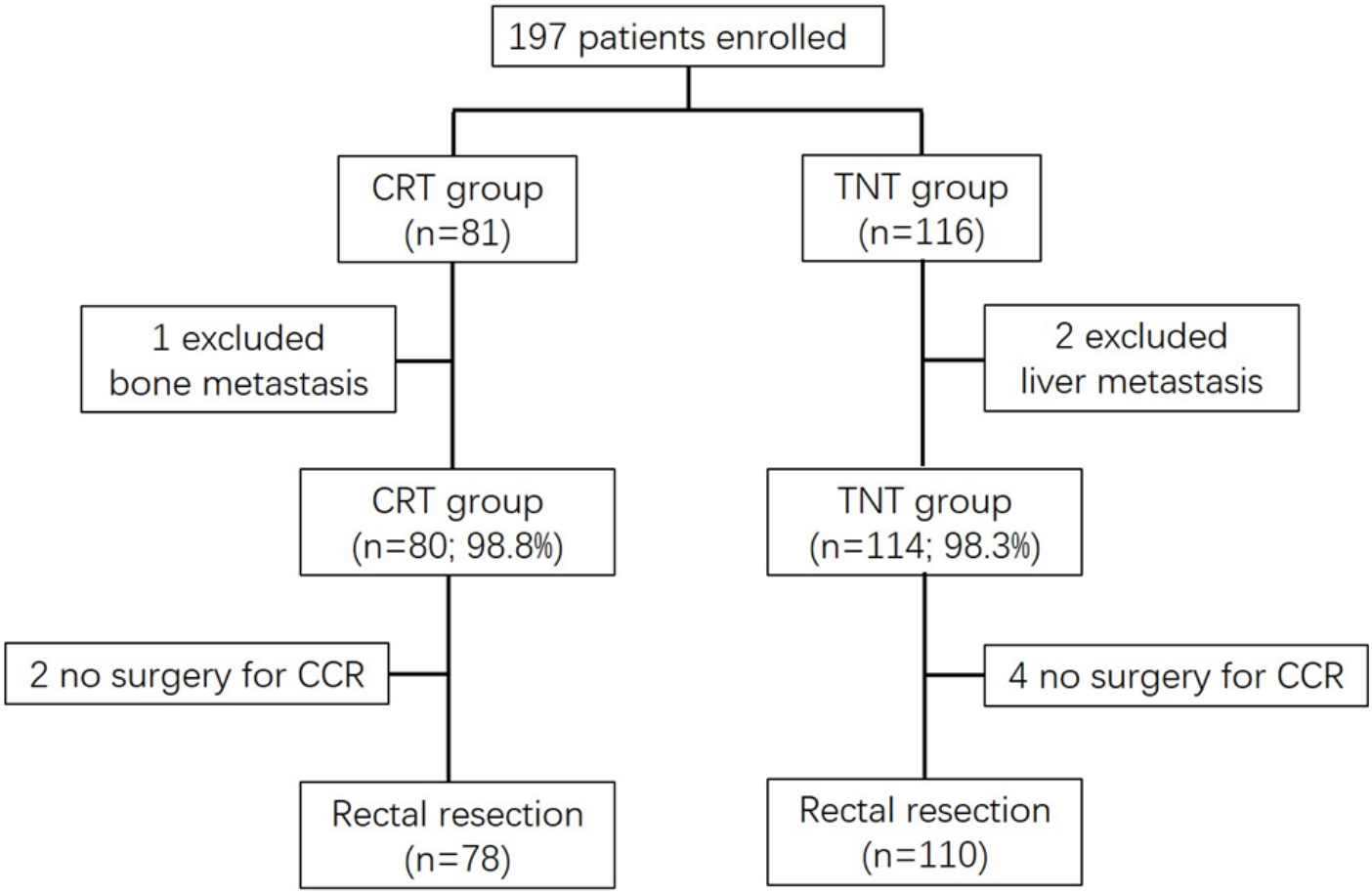

Figure 1

Treatment approach. CCR, complete clinical response