Oncologic Outcomes of ypT1-3N0 mid-Low Rectal Cancer Compared with pT1-3N0 Disease After Radical Resection

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Research article

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Abstract

**Background:** Neoadjuvant chemoradiotherapy (CRT) can downstage rectal carcinoma, resulting in superior resectability, better local control and survival benefits. However, it is unclear whether patients treated with CRT and those who did not have similar outcomes at the same pathological stage. This study aimed to investigate the long-term outcomes of ypT1-3N0 mid-low rectal cancer who received neoadjuvant CRT followed by total mesorectal excision (TME) compared with pT1-3N0 rectal cancer immediately managed with surgery.

**Methods:** We retrospectively enrolled 180 patients with pT1-3N0 or ypT1-3N0 rectal cancer located within 10 cm from the anal edge who underwent TME between 2009 and 2015. Of these patients, 63 received neoadjuvant CRT, while 117 underwent radical proctectomy without preoperative therapy. The disease-free survival (DFS) and cancer-specific survival (CSS) were compared between the two groups.

**Results:** Within a median follow-up time of 65 months, the 5-year DFS was lower in the CRT group than the non-CRT group (74.9% vs. 92.6%, P=0.001), and the 5-year CSS presented a similar trend as well (89.6% vs. 97.1%, P=0.054). By subgroup analysis, the difference in DFS and CSS was mainly caused by the difference between ypT3N0 and pT3N0 disease (71.1% vs. 96.1%, P<0.001 and 90.9% vs. 100%, P=0.029, respectively). However, patients with ypT1-2N0 had an analogous prognosis to those with pT1-2N0 disease (77.9% vs. 89.0%, P=0.225 and 88.1% vs. 94.2%, P=0.292, respectively). Multivariate analysis indicated that neoadjuvant CRT was not an independent predictor of DFS.

**Conclusion:** After neoadjuvant CRT followed by TME, patients with ypT1-2N0 rectal cancer had an analogous prognosis to those with initial pT1-2N0 disease, whereas patients with ypT3N0 rectal cancer had worse prognosis compared with that of pT3N0 disease.

**Background**

Neoadjuvant chemoradiotherapy (CRT) followed by total mesorectal excision (TME) is considered to be the standard of care for patients with locally advanced mid-low rectal cancer (clinically T3/T4 or N+) because of superior sphincter preservation rates, increased local tumor control, and preferable disease-free survival [1–4]. Many studies have shown that in patients with rectal cancer treated with CRT, pathologic staging is a better predictor of tumor prognosis than clinical staging [5–7]. Tumor response to neoadjuvant CRT varies from complete response to progression. As is well-known, pathologic complete response (pCR) to neoadjuvant CRT has something to do with a better survival, but most patients have partial or no response to neoadjuvant CRT [5, 8, 9]. It has been demonstrated that patients with lymph-node negative (ypN0) rectal cancer have a superior prognosis compared with those with lymph node metastases (ypN+) after neoadjuvant CRT [7, 10, 11]. However, it is still unknown whether the prognosis of patients with ypN0 rectal cancer is as good as that of patients with pN0 disease without neoadjuvant CRT. Several studies have indicated that a good response (ypT1-2N0) after neoadjuvant CRT for locally advanced rectal cancer is related to good local control and improved disease-free survival [6, 12, 13].
Controversially, some study has even shown that patients with ypT1-2N0 rectal cancer after neoadjuvant CRT have similar oncologic outcomes compared with patients with initially early rectal cancer (pT1-2N0) [14]. However, few studies have specifically compared the prognostic difference between ypT3N0 and pT3N0 disease. Although in patients with ypT3N0 rectal cancer who received neoadjuvant CRT, the tumor was also confined to the rectal wall without lymph node metastasis due to downstaging, the prognosis is not well known.

Therefore, the aim of the present study was to compare the oncologic outcomes of patients with ypT1-3N0 rectal cancer who received radical resection after neoadjuvant CRT with those with pT1-3N0 disease undergoing surgery immediately. By performing subgroup analysis, we hope to learn more about the prognosis of patients with lymph node pathologically negative after neoadjuvant CRT.

**Material And Methods**

**Patients**

We retrospectively analyzed clinicopathological parameters of patients with mid-low rectal cancer who underwent resection with curative intent at the Department of Gastrointestinal Surgery IV, Peking University Cancer Hospital between 2009 and 2015. Patients enrolled in this study satisfied the following criteria: (1) pathologically diagnosed as rectal adenocarcinoma with endoscopic biopsy; (2) tumor located within 10 cm from the anal edge; (3) underwent TME surgery; (4) pathologically classified as stage I (pT1-2N0 or ypT1-2N0) or stage IIA (pT3N0 or ypT3N0) after surgery. Patients with distant metastases at the time of diagnosis, concurrent malignancies or a history of other malignancies within 5 years were not included. Patients undergoing palliative resection, emergent surgery and multivisceral resection were also excluded. According to the above criteria, a total of 180 consecutive patients were ultimately included in this study. Of these patients, 63 received neoadjuvant CRT (the CRT group), while 117 had no preoperative therapy (the non-CRT group). The oncologic outcomes of the two groups were compared. A flowchart of the patients’ accrual is depicted in Fig. 1. This study was approved by the Research Ethics Committee of Peking University Cancer Hospital & Institute.

Clinical assessment was conducted by means of digital rectal examination, tumor marker levels (CEA and CA19-9), colonoscopy biopsy, chest radiography, abdominal and pelvic computed tomography (CT) and pelvic magnetic resonance imaging (MRI). In addition, endorectal ultrasonography (US) was used in patients with low rectal cancer. Low rectal cancer was defined as tumors within 5 cm from the anal verge, while middle rectal cancer was defined as tumors between 5 and 10 cm from the anal verge, which was assessed by colonoscopy at initial diagnosis.

**Interventions**

Patients who received neoadjuvant CRT underwent long-course radiotherapy (50.6 Gy in 22 fractions). Capecitabine (825 mg/m$^2$ per day) was administered synchronously with radiotherapy. Surgery based on
the principle of TME was recommended within 6 to 10 weeks of the completion of radiotherapy, whereas patients without neoadjuvant CRT underwent an immediate radical resection. Each patient receiving neoadjuvant CRT was reevaluated by chest and abdominal CT and pelvic MRI before surgery. All the operations were performed by the same surgical team. Surgical procedures included low anterior resection (LAR), abdominoperineal resection (APR), extralevator abdominoperineal excision (ELAPE), and Hartmann's procedure. The choice of procedure was mainly based on the location and stage of tumors as well as the surgeon's judgment during operation.

Pathologic evaluation was independently performed by 2 pathologists according to the American Joint Committee on Cancer TNM staging system (the seventh edition) [15]. Positive circumferential resection margin (CRM) was defined as tumor within 1 mm from the transected margin. Tumor regression grade (TRG) was classified according to the grading system recommended by National Comprehensive Cancer Network (NCCN) [16], including four tiers: complete response (TRG 0), moderate response (TRG 1), minimal response (TRG 2) and poor response (TRG 3). About 4 weeks after surgery, patients with stage II disease with risk factors were recommended to receive 5-fluorouracil-based adjuvant chemotherapy (AC) for 6 months. AC was also recommended for patients who received neoadjuvant CRT.

Follow-up

Patients were followed every three months for the first two years after surgery, every six months for the next three years, and yearly thereafter. Follow-up examinations included a physical examination, complete blood cell count, blood biochemistry and serum CEA and CA 19 – 9 levels. Chest x-rays and abdominopelvic CT were performed every six months, and a colonoscopy was performed annually after the surgery. Disease-free survival (DFS) was measured from the date of surgery to that of any type of recurrence. Cancer-specific survival (CSS) was defined as the time from the date of surgery to that of death from the same cancer.

Statistical analysis

Categorical variables were described as numbers with percentages and compared with either a chi-square or Fisher's exact test. Continuous variables were expressed by median and range and analyzed using Mann-Whitney U test. DFS and CSS were estimated using a Kaplan–Meier model, and comparisons were analyzed with the log-rank test. Parameters found to be associated with survival by the univariate analysis (based on a P-value <0.05) were entered into a multivariate Cox regression analysis. Statistical analyses were performed with the IBM SPSS Statistic 22.0 software package. A P-value of <0.05 was considered statistically significant.

Results

Clinicopathologic characteristics
The clinicopathologic characteristics of the total cohort are shown in Table 1. Patients in the non-CRT group were older than those in the CRT group (\( P = 0.016 \)). Pretreatment clinical staging was significantly different in terms of \( T \) (\( P = 0.007 \)) and \( N \) categories (\( P<0.001 \)) between the two groups. The CRT group had more patients with low rectal cancer and more non-restorative surgery performed than the non-CRT group (\( P<0.001 \)). All patients in the non-CRT group underwent laparoscopic surgery, whereas a proportion of patients in the CRT group underwent open surgery (\( P<0.001 \)). The rate of CRM involvement was higher and fewer lymph nodes (LN) were dissected in the CRT group (\( P = 0.005 \) and \( P<0.001 \), respectively). However, there was no significant difference in the aspect of tumor differentiation, lymphovascular invasion, perineural invasion, distal resection margin (DRM) and initial levels of CEA and CA19-9 between the two groups. Furthermore, more patients received AC in the CRT group compared with the non-CRT group (\( P<0.001 \)).
## Table 1
Clinicopathologic characteristics of CRT and Non-CRT patients

| Variable                      | CRT (n = 63) | Non-CRT (n = 117) | P value |
|-------------------------------|--------------|-------------------|---------|
| Sex                           |              |                   |         |
| Male                          | 40 (63.5)    | 65 (55.6)         | 0.303   |
| Female                        | 23 (36.5)    | 52 (44.4)         | 0.016   |
| Median age (range) (y)        | 58 (43–76)   | 61 (31–85)        | 0.702   |
| ASA I                         |              |                   |         |
| II–III                        |              |                   |         |
| Location                      |              |                   |         |
| Mid                           | 62 (96.8)    | 97 (82.9)         | <0.001  |
| Lower                         | 61 (31–85)   | 61 (31–85)        | 0.502   |
| Tumor differentiation         |              |                   |         |
| Well + moderate               | 57 (90.5)    | 106 (90.6)        | 1.000   |
| Poor                          | 2 (3.2)      | 20 (17.1)         | 1.000   |
| Initial clinical T category   |              |                   |         |
| cT1–2                         | 62 (96.8)    | 97 (82.9)         | <0.001  |
| cT3–4                         | 61 (31–85)   | 61 (31–85)        | 0.133   |
| Initial clinical N category   |              |                   |         |
| cN0                           | 62 (98.4)    | 116 (99.1)        | <0.001  |
| cN+                           | 1 (1.6)      | 1 (0.9)           |         |
| Pathological T category       |              |                   |         |
| pT1–2                         | 55 (87.3)    | 117 (100.0)       |         |
| pT3                           | 17 (27.0)    | 97 (82.9)         |         |
| Lymphovascular invasion       |              |                   |         |
| Negative                      | 34 (54.0)    | 2 (1.7)           |         |
| Positive                      | 1 (1.6)      | 1 (0.9)           |         |

ASA = American Society of Anesthesiologists; APR = Abdominoperineal resection; LAR = Low anterior resection; ELAPE = extralevator abdominoperineal excision; DRM = Distal resection margin; CRM = circumferential resection margin; LNs = lymph nodes; CEA = Carcinoembryonic antigen; CRT = chemoradiotherapy.
| Variable                      | CRT (n = 63) | Non-CRT (n = 117) | P value |
|-------------------------------|--------------|-------------------|---------|
| Perineural invasion          | 2 (3.2)      | 6 (5.1)           |         |
| Negative                      | 61 (96.8)    | 111 (94.9)        |         |
| Positive                      | 5 (7.9)      | 0                 |         |
| Surgical approach            | 58 (92.1)    | 117 (100.0)       |         |
| Open                          | 40 (63.5)    | 25 (21.4)         |         |
| Laparoscopic                  | 23 (36.5)    | 92 (78.6)         |         |
| Type of operation            | 53 (84.1)    | 87 (74.4)         |         |
| LAR                           | 10 (15.9)    | 30 (25.6)         |         |
| APR                           | 2 (3.2)      | 3 (2.6)           |         |
| ELAPE                         | 61 (96.8)    | 114 (97.4)        |         |
| Hartmann                      | 17 (27.0)    | 100 (85.5)        |         |
| DRM (cm)                      | 46 (73.0)    | 17 (14.5)         |         |
| ≤ 1                           |              |                   |         |
| > 1                           |              |                   |         |
| CRM (mm)                      |              |                   |         |
| ≤ 1                           |              |                   |         |
| > 1                           |              |                   |         |
| Retrieved LNs                |              |                   |         |
| < 12                          |              |                   |         |
| ≥ 12                          |              |                   |         |
| Initial CEA (ng/ml)           |              |                   |         |
| ≤ 5                           |              |                   |         |
| > 5                           |              |                   |         |
| Initial CA199 (U/ml)          |              |                   |         |
| ≤ 37                          |              |                   |         |
| > 37                          |              |                   |         |
| Adjuvant chemotherapy         |              |                   |         |

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Subgroup analysis showed that patients with ypT1-2N0 disease included more low rectal cancer and underwent non-restorative surgery more often as well compared with those with pT1-2N0 disease (P<0.001). The initial clinical T and N stages were more advanced in ypT1-2N0 patients (P = 0.002 and P = 0.001, respectively). Moreover, higher of CRM involvement was observed and fewer LNs were harvested in ypT1-2N0 patients (P = 0.049 and P = 0.017, respectively). Most of the ypT1-2N0 patients received AC, whereas none received AC in pT1-2N0 patients (P<0.001) (Table 2). Similarly, the difference in the mentioned clinicopathologic features was also found between patients with ypT3N0 and pT3N0 disease, except for initial clinical T stage and CRM involvement (Table 3).
Table 2
Clinicopathologic characteristics of ypT1-2N0 and pT1-2N0 patients

| Variable                        | ypT1-2N0 (n = 34) | pT1-2N0 (n = 57) | P value |
|---------------------------------|-------------------|------------------|---------|
| Sex                             | 20 (58.8)         | 34 (59.6)        | 0.938   |
| Male                            | 14 (41.2)         | 23 (40.4)        | 0.147   |
| Female                          | 58 (45–76)        | 61 (37–82)       | 0.421   |
| Median age (range) (y)          | 12 (35.3)         | 25 (43.9)        | < 0.001 |
| ASA                             | 22 (64.7)         | 32 (56.1)        | 0.708   |
| l                               | 10 (29.4)         | 44 (77.2)        | 0.002   |
| ll-III                          | 24 (70.6)         | 13 (22.8)        | 0.001   |
| Location                        | 32 (94.1)         | 52 (91.2)        | 0.527   |
| Mid                             | 2 (5.9)           | 5 (8.8)          | 1.000   |
| Lower                           | 2 (5.9)           | 20 (35.1)        | 0.006   |
| Tumor differentiation           | 32 (94.1)         | 37 (64.9)        | < 0.001 |
| Well + moderate                 | 9 (26.5)          | 36 (63.2)        | 0.628   |
| Poor                            | 25 (73.5)         | 21 (36.8)        | 0.049   |
| Initial Clinical T category     | 34 (100.0)        | 55 (96.5)        | 0.017   |
| cT1-2                           | 0                 | 2 (3.5)          | 0.558   |
| cT3-4                           | 34 (100.0)        | 57 (100.0)       | 1.000   |
| Initial Clinical N category     | 0                 | 0                | < 0.001 |
| cN0                             | 5 (14.7)          | 0                |         |
| cN+                             | 29 (85.3)         | 57 (100.0)       |         |
| Lymphovascular invasion         | 7 (20.6)          | 43 (75.4)        |         |
| Negative                        | 5 (14.7)          | 12 (21.1)        |         |
| Positive                        | 22 (64.7)         | 1 (1.8)          |         |
| Perineural invasion             | 0                 | 1 (1.8)          |         |
| Negative                        | 2 (5.9)           | 2 (3.5)          |         |
| Positive                        | 32 (94.1)         | 55 (96.5)        |         |

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| Variable                          | ypT1-2N0 (n = 34) | pT1-2 N0(n = 57) | P value |
|----------------------------------|-------------------|------------------|---------|
| Surgical approach                |                   |                  |         |
| Open                             | 30 (88.2)         | 47 (82.5)        |         |
| Laparoscopic                     | 4 (11.8)          | 10 (17.5)        |         |
| Type of operation                | 33 (97.1)         | 56 (98.2)        |         |
| LAR                             | 12 (35.3)         | 57 (100.0)       |         |
| APR                             | 22 (64.7)         | 0                |         |
| ELAPE                            |                   |                  |         |
| Hartmann                         |                   |                  |         |
| DRM (cm)                         |                   |                  |         |
| ≤ 1                              |                   |                  |         |
| > 1                              |                   |                  |         |
| CRM (mm)                         |                   |                  |         |
| ≤ 1                              |                   |                  |         |
| > 1                              |                   |                  |         |
| Retrieved LNs                    |                   |                  |         |
| < 12                             |                   |                  |         |
| ≥ 12                             |                   |                  |         |
| Initial CEA (ng/ml)              |                   |                  |         |
| ≤ 5                              |                   |                  |         |
| > 5                              |                   |                  |         |
| Initial CA199 (U/ml)             |                   |                  |         |
| ≤ 37                             |                   |                  |         |
| > 37                             |                   |                  |         |
| Adjuvant chemotherapy            |                   |                  |         |
| No                               |                   |                  |         |
| Yes                              |                   |                  |         |

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Table 3
Clinicopathologic characteristics of ypT3N0 and pT3N0 patients

| Variable                        | ypT3N0 (n = 29) | pT3N0 (n = 60) | P value |
|---------------------------------|----------------|----------------|---------|
| Sex                             |                |                |         |
| Male                            | 20 (69.0)      | 31 (51.7)      | 0.122   |
| Female                          | 9 (31.0)       | 29 (48.3)      | 0.067   |
| Median age (range) (y)          | 58 (43–71)     | 61.5 (31–85)   | 0.783   |
| ASA l                           | 12 (41.4)      | 23 (38.3)      | 0.001   |
| ASA ll-lll                      | 17 (58.6)      | 37 (61.7)      | 0.722   |
| Incisional TJ category          | 17 (58.6)      | 53 (88.3)      | 1.000   |
| Location                        | 12 (41.4)      | 7 (11.7)       | <0.001  |
| Mid                             | 25 (86.2)      | 54 (90.0)      | 0.326   |
| Lower                           | 4 (13.8)       | 6 (10.0)       | 0.548   |
| Tumor differentiation           | 29 (100.0)     | 60 (100.0)     | <0.001  |
| Well + moderate                 | 2 (6.9)        | 26 (43.3)      | 0.299   |
| Poor                            | 27 (93.1)      | 34 (56.7)      | 0.104   |
| Initial Clinical T category     | 28 (96.6)      | 60 (100.0)     | <0.001  |
| cT1-2                           | 1 (3.4)        | 0              | 0.320   |
| cT3-4                           | 28 (96.6)      | 59 (98.3)      | 1.000   |
| Initial Clinical N category     | 1 (3.4)        | 1 (1.7)        | <0.001  |
| cN0                             | 3 (10.3)       | 0              |         |
| cN+                             | 26 (89.7)      | 60 (100.0)     |         |
| Lymphovascular invasion         | 10 (34.5)      | 54 (90.0)      |         |
| Negative                        | 6 (20.7)       | 5 (8.3)        |         |
| Positive                        | 12 (41.4)      | 1 (1.7)        |         |
| Perineural invasion             | 1 (3.4)        | 0              |         |
| Negative                        | 0              | 4 (6.7)        |         |
| Positive                        | 29 (100.0)     | 56 (93.3)      |         |

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| Variable                  | \( \text{ypT3N0} (n = 29) \) | \( \text{pT3N0} (n = 60) \) | \( P \) value |
|--------------------------|-------------------------------|-----------------------------|--------------|
| Surgical approach       | 2 (6.9)                       | 0                           |              |
| Open                     | 27 (93.1)                     | 60 (100.0)                  |              |
| Laparoscopic             | 20 (69.0)                     | 6 (10.0)                    |              |
| Type of operation        | 9 (31.0)                      | 54 (90.0)                   |              |
| LAR                      | 23 (79.3)                     | 40 (66.7)                   |              |
| APR                      | 6 (20.7)                      | 20 (33.3)                   |              |
| ELAPE                    | 28 (96.6)                     | 58 (96.7)                   |              |
| Hartmann                 | 1 (3.4)                       | 2 (3.3)                     |              |
| DRM (cm)                 | 5 (17.2)                      | 43 (71.7)                   |              |
| \( \leq 1 \)            | 24 (82.8)                     | 17 (28.3)                   |              |
| \( >1 \) CRM (mm)       |                               |                             |              |
| \( \leq 1 \)            |                               |                             |              |
| \( >1 \)                |                               |                             |              |
| Retrieved LNs            |                               |                             |              |
| \( <12 \)               |                               |                             |              |
| \( \geq 12 \)           |                               |                             |              |
| Initial CEA (ng/ml)      |                               |                             |              |
| \( \leq 5 \)            |                               |                             |              |
| \( >5 \)                |                               |                             |              |
| Initial CA199 (U/ml)     |                               |                             |              |
| \( \leq 37 \)           |                               |                             |              |
| \( >37 \)               |                               |                             |              |
| Adjuvant chemotherapy    |                               |                             |              |
| No                       |                               |                             |              |
| Yes                      |                               |                             |              |

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Survival Analyses

The median follow-up period was 65 months (range, 34–125 months). Recurrences were observed in 25 patients (13.9%): 4 had local recurrence, while 21 had systemic recurrence. Ten patients died due to tumor recurrence, 2 died of heart disease, 1 died of stroke and 1 died of suicide.

The 5-year DFS was lower in patients who underwent neoadjuvant CRT compared with those who did not (74.9% vs. 92.6%, P = 0.001, Fig. 2a). Besides, patients in the CRT group were inclined to have inferior 5-year CSS than the non-CRT group (89.6% vs. 97.1%, P = 0.054, Fig. 2b). Pathologic T stage analysis indicated that the difference in DFS and CSS were mainly caused by the difference between ypT3N0 and pT3N0 patients (71.1% vs. 96.1%, P<0.001, Fig. 3a; 90.9% vs. 100%, P = 0.029, Fig. 3b). However, there was no significant difference in the 5-year DFS and CSS between ypT1-2N0 and pT1-2N0 patients (77.9% vs. 89.0%, P = 0.225, Fig. 4a; 88.1% vs. 94.2%, P = 0.292, Fig. 4b).

Based on the univariate analysis, neoadjuvant CRT (P = 0.001), ASA score (P = 0.007), type of operation (P<0.001), CRM status (P = 0.020) and number of retrieved LNs (P = 0.015) were significantly associated with DFS (Table 4). By multivariate analysis, only ASA score (HR, 4.216; 95% CI, 1.383–12.850; P = 0.011) and type of operation (HR, 2.920; 95% CI, 1.080–7.898; P = 0.035) were independent factors that affected DFS (Table 5). Considering the CSS, the univariate analysis demonstrated that only the type of operation was associated with CSS (P = 0.003) (Table 4), hence no multivariate analysis was conducted.
Table 4
Univariate analysis of prognostic factors for disease-free survival (DFS) and cancer-specific survival (CSS)

| Variable                        | N  | 5-year DFS (%) | P value | 5-year CSS (%) | P value |
|--------------------------------|----|----------------|---------|----------------|---------|
| Sex                            |    |                |         |                |         |
| Male                           | 75 | 82.7           | 0.376   | 92.4           | 0.881   |
| Female                         | 88 | 89.7           | 0.007   | 94.3           | 0.175   |
| Age(y)                         |    |                |         |                |         |
| ≤ 60                           | 72 | 95.8           | 0.799   | 97.2           | 0.217   |
| > 60                           | 108| 80.1           | 0.226   | 92.6           | 0.087   |
| ASA                            |    |                |         |                |         |
| I                              | 56 | 80.2           | 0.344   | 90.9           | 0.059   |
| II-III                         | 163| 86.3           | 0.496   | 95.2           | 0.670   |
| Location                       |    |                |         |                |         |
| Mid                            | 22 | 81.8           | 0.313   | 86.4           | 0.326   |
| Low                            | 158| 87.0           | < 0.001 | 95.6           | 0.003   |
| Tumor differentiation          |    |                |         |                |         |
| Well + moderate                | 107| 86.8           | 0.020   | 93.7           | 0.604   |
| Poor                           | 91 | 85.0           | 0.015   | 91.8           | 0.298   |
| Initial clinical T category    |    |                |         |                |         |
| cT1-2                          | 177| 86.2           | 0.781   | 94.4           | 0.176   |
| cT3-4                          | 3  | 100.0          | 0.001   | 100.0          | 0.054   |
| Initial clinical N category    |    |                |         |                |         |
| cN0                            | 2  | -              | -       | -              | -       |
| cN+                            | 8  | 75.0           |         | 87.5           |         |
| Pathological T category        |    |                |         |                |         |
| pT1-2                          | 114| 93.1           |         | 98.8           |         |
| pT3                            | 66 | 75.1           |         | 87.3           |         |
| Lymphovascular invasion        | 8  | 87.5           |         | 100.0          |         |

ASA = American Society of Anesthesiologists; APR = Abdominoperineal resection; LAR = Low anterior resection; ELAPE = extralevator abdominoperineal excision; DRM = Distal resection margin; CRM = circumferential resection margin; LNs = lymph nodes; CEA = Carcinoembryonic antigen; CRT = chemoradiotherapy.
| Variable                        | N  | 5-year DFS (%) | P value | 5-year CSS (%) | P value |
|--------------------------------|----|----------------|---------|----------------|---------|
| Negative                       | 65 | 78.9           |         | 91.6           |         |
| Positive                       | 115| 90.7           |         | 96.1           |         |
| Perineural invasion Negative   | 140| 89.0           |         | 92.9           |         |
| Negative                       | 40 | 78.3           |         | 100.0          |         |
| Positive                       | 175| 86.7           |         | 95.0           |         |
| Surgical approach              | 5  | 80.0           |         | 80.0           |         |
| Open                           | 63 | 74.9           |         | 89.6           |         |
| Laparoscopic                   | 117| 92.6           |         | 97.1           |         |
| Type of operation              | 63 | 83.5           |         | 94.8           |         |
| Restorative                    | 117| 88.2           |         | 94.4           |         |
| Non-restorative                |    |                |         |                |         |
| DRM (cm)                       |    |                |         |                |         |
| ≤ 1                            |    |                |         |                |         |
| > 1                            |    |                |         |                |         |
| CRM (mm)                       |    |                |         |                |         |
| ≤ 1                            |    |                |         |                |         |
| > 1                            |    |                |         |                |         |
| Retrieved LNs                  |    |                |         |                |         |
| < 12                           |    |                |         |                |         |
| ≥ 12                           |    |                |         |                |         |
| Initial CEA (ng/ml)            |    |                |         |                |         |
| ≤ 5                            |    |                |         |                |         |
| > 5                            |    |                |         |                |         |
| Initial CA199 (U/ml)           |    |                |         |                |         |
| ≤ 37                           |    |                |         |                |         |
| > 37                           |    |                |         |                |         |

Neoadjuvant CRT

ASA = American Society of Anesthesiologists; APR = Abdominoperineal resection; LAR = Low anterior resection; ELAPE = extralevator abdominoperineal excision; DRM = Distal resection margin; CRM = circumferential resection margin; LNs = lymph nodes; CEA = Carcinoembryonic antigen; CRT = chemoradiotherapy.
| Variable                             | N | 5-year DFS (%) | P value | 5-year CSS (%) | P value |
|-------------------------------------|---|----------------|---------|----------------|---------|
| Yes                                 |   |                |         |                |         |
| No                                  |   |                |         |                |         |
| Adjuvant chemotherapy               |   |                |         |                |         |
| Yes                                 |   |                |         |                |         |
| No                                  |   |                |         |                |         |

ASA = American Society of Anesthesiologists; APR = Abdominoperineal resection; LAR = Low anterior resection; ELAPE = extralevator abdominoperineal excision; DRM = Distal resection margin; CRM = circumferential resection margin; LNs = lymph nodes; CEA = Carcinoembryonic antigen; CRT = chemoradiotherapy.

Table 5
Multivariate analysis of prognostic factors for disease-free survival (DFS)

| Variable                                           | Hazard ratio | 95% CI         | P value |
|----------------------------------------------------|--------------|----------------|---------|
| ASA (II-III vs. I)                                 | 4.216        | 1.383–12.850   | 0.011   |
| Operation (Non-restorative vs. Restorative)        | 2.920        | 1.080–7.898    | 0.035   |
| CRM (Positive vs. Negative)                        | 3.358        | 0.743–15.171   | 0.115   |
| Retrieved LNs (< 12 vs. ≥12)                       | 1.148        | 0.444–2.968    | 0.777   |
| Neoadjuvant CRT (Yes vs. No)                       | 1.654        | 0.576–4.748    | 0.349   |

ASA = American Society of Anesthesiologists; CRM = circumferential resection margin; LNs = lymph nodes; CRT = chemoradiotherapy; CI = confidence interval.

**Trg And Ac In The Crt Cohort**

The median time between surgery and the end of radiotherapy was 8 weeks (range, 6–10 weeks) for the CRT cohort. TRG 1, 2 and 3 after neoadjuvant CRT was found in 18 (28.6%), 39 (61.9%) and 6 (9.5%) patients, respectively. Subgroup analysis showed that patients with ypT1-2N0 disease had more cases of TRG 1 than patients with ypT3N0 disease (41.2% vs. 13.8%, P = 0.019). The 5-year DFS and CSS were 88.9% and 100% for patients with TRG 1, and 69.6% and 85.6% for TRG 2 and 3, respectively (P = 0.167 and P = 0.119, respectively). After radical proctectomy, 73.0% of patients who underwent neoadjuvant CRT received AC. This accounted for 64.7% and 82.8% in patients with ypT1-2N0 and ypT3N0 disease, respectively. There was no significant difference in the 5-year DFS and CSS between patients who received AC and those who did not (P = 0.289 and P = 0.221, respectively).

**Discussion**
Our study showed that the 5-year DFS was lower in patients with ypT1-3N0 disease who received neoadjuvant CRT than those who did not, the CSS presented a similar trend as well, though the difference was not statistically significant. However, the multivariate analysis revealed that neoadjuvant CRT was not an independent predictor of DFS. So far, few studies have compared the long-term survival of rectal cancer patients with ypN0 to those with pN0 disease [14, 17–19]. Erlenbach-Wünsch et al [17] retrospectively analyzed 132 patients with ypN0 rectal cancer who received TME after neoadjuvant CRT and compared their prognoses with those of 341 patients with pN0 without preoperative therapy. Their results presented a similar outcome between patients with ypN0 and pN0 in regard to local recurrence, distant metastases, DFS and CSS.

In subgroup analysis, we found that the 5-year DFS and CSS of patients with ypT1-2N0 disease were not significantly different from those with pT1-2N0 disease. This result means that patients with locally advanced rectal cancer who had good response after neoadjuvant CRT (ypT1-2N0) may have analogous long-term survival compared with those who initially had early rectal cancer (pT1-2N0), even though the former had more patients with low rectal cancer and presented more advanced clinical stage at initial diagnosis than the latter. These findings are consistent with the work done by Du et al [14] who evaluated the oncologic outcomes of ypT1-2N0 and pT1-2N0 patients and found no significant differences between them. On the contrary, other studies by Huh et al [18] and Yeop et al [19] have concluded that patients with ypT1-2N0 who underwent neoadjuvant CRT may have worse oncologic outcomes compared with those with pT1-2N0 disease. When we analyzed the data of patients with ypT3N0 disease, their DFS and CSS were inferior compared with those with pT3N0 disease. This may be explained by the fact that most ypT3N0 patients have more advanced tumor stage at the time of diagnosis, or present with worse tumor regression after CRT than ypT1-2N0 patients. Therefore, even with intensive perioperative therapy, these patients were more prone to local recurrence and distant metastasis, and could not achieve similar oncologic outcomes as those with initial pT3N0 disease.

The tumor response to neoadjuvant CRT is variable, there is no gold standard, and the reported grading systems vary from three to five tiers [6, 20, 21]. Several studies have evaluated tumor regression and its influence on survival in patients with rectal cancer treated with neoadjuvant CRT followed by curative resection [21–23]. Beddy et al [22] revealed that the 5-year DFS of patients with complete or near-complete response after neoadjuvant CRT and surgery was significantly better than that of partial or no response. Fokas et al [23] demonstrated that complete and intermediate tumor regressions were associated with improved long-term outcome in patients with rectal cancer after preoperative CRT compared with poor tumor regression. In the present study, TRG was evaluated by NCCN grading system. Although the 5-year DFS and CSS rates of patients with TRG 1 were better than that of TRG 2 and 3, the difference between them was not statistically significant, which may be related to the small sample size of this cohort.

The role of AC in patients who had a good response remains unclear because data supporting the benefits of AC are short. Two recent retrospective propensity score-matched cohort studies compared overall survival (OS) between AC and postoperative observation (OB) in rectal cancer patients with pCR
following preoperative CRT and resection [24, 25]. Both the results showed that the AC cohort had better OS compared with the OB cohort, especially in patients with pretreatment node-positive disease. Although these studies specifically focused on patients with pCR after CRT, they also provided evidence for AC in patients with an incomplete response following neoadjuvant CRT. In our study, the majority of patients with neoadjuvant CRT received AC postoperatively. Although there was no significant difference in the long-term outcomes between patients who received AC and those who did not, the result should be regarded with caution because the sample size was too small to draw a conclusion.

The present study has a few limitations. First, this is a single-institution retrospective analysis, which has an inherent selection bias. Second, the sample size is too small to provide enough strength for drawing any definitive conclusions about oncologic outcomes. Besides, due to the lack of accurate preoperative staging, as well as the limitations of patient compliance and economic conditions, the treatment options for the cases included in this study were not always reasonable. For example, some patients who underwent neoadjuvant CRT may be overtreated. On the contrary, other advanced patients who required neoadjuvant CRT accepted surgery directly. Finally, not all patients undergoing surgery after CRT received AC due to different physician decisions as well as differences in the patients' physical condition, financial ability and treatment compliance.

**Conclusion**

In conclusion, our study showed that patients with ypT1-2N0 rectal cancer who had good response to neoadjuvant CRT did not have an increased risk of adverse outcome compared with patients who initially had early rectal cancer (pT1-2N0). However, patients with ypT3N0 rectal cancer had inferior long-term survival compared with those with pT3N0 disease after surgery. This suggests that different treatment strategies are needed according to the pathological stage and tumor regression grade after neoadjuvant CRT. In the future, larger studies are warranted to validate these results and to further improve the treatment and outcomes of patients with ypT1-3N0 rectal cancer.

**Abbreviations**

| Abbreviation | Description |
|--------------|-------------|
| CRT          | chemoradiotherapy |
| TME          | total mesorectal excision |
| pCR          | pathologic complete response |
| DFS          | disease-free survival |
| CSS          | cancer-specific survival |
| CEA          |                         |
carcinoembryonic antigen
CT
computed tomography
MRI
magnetic resonance imaging
US
ultrasonography
LAR
low anterior resection
APR
abdominoperineal resection
ELAPE
extralevator abdominoperineal excision
CRM
circumferential resection margin
TRG
tumor regression grade
NCCN
National Comprehensive Cancer Network
AC
adjuvant chemotherapy
LNs
lymph nodes
DRM
distal resection margin
OS
overall survival
ASA
American Society of Anesthesiologists
BMI
body mass index

Declarations

Ethics approval and consent to participate

This is a retrospective study, and all the patients signed the consent for treating before the treatment. This study was approved by the Research Ethics Committee of Peking University Cancer Hospital & Institute, Beijing, China.

Consent for publication
Not applicable.

Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

Study conception and design: HY and XQS. Acquisition of data: HY, NZ, MXL, KX and FT. Analysis and interpretation of data: HY, JBD, MC, JDX, CHZ and ZDY. Writing manuscript: HY. All authors read and approved the final manuscript.

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