Retrospective study of neoadjuvant therapy on tumor-downstaging, post-operative complications, and prognosis in locally advanced rectal cancer

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Supported by National Science Foundation of China, No. 81871933; and National Science Foundation of China for Youth, No. 81802326.

Institutional review board statement: The study was reviewed and approved by the

Abstract

BACKGROUND
Neoadjuvant therapy (NAT) is becoming increasingly important in locally advanced rectal cancer. Hence, such research has become a problem.

AIM
To evaluate the downstaging effect of NAT, its impact on postoperative complications and its prognosis with different medical regimens.

METHODS
Seventy-seven cases from Shanghai Ruijin Hospital affiliated with Shanghai Jiaotong University School of Medicine were retrospectively collected and divided into the neoadjuvant radiochemotherapy (NRCT) group and the neoadjuvant chemotherapy (NCT) group. The differences between the two groups in tumor regression, postoperative complications, rectal function, disease-free survival, and overall survival were compared using the χ² test and Kaplan-Meier analysis.

RESULTS
Baseline data showed no statistical differences between the two groups, whereas the NRCT group had a higher rate of T4 (30/55 vs 5/22, P < 0.05) than the NCT groups. Twelve cases were evaluated as complete responders, and 15 cases were evaluated as tumor regression grade 0. Except for the reduction rate of T stage (NRCT 37/55 vs NCT 9/22, P < 0.05), there was no difference in effectiveness between the two groups. Preoperative radiation was not a risk factor for poor reaction or anastomotic leakage. No significant difference in postoperative complications and disease-free survival between the two groups was observed,
Skin cancer can cause tumor downstaging preoperatively or even complete remission of the primary tumor. Radiochemotherapy could lead to better T downstaging and promising overall survival without more complications.

**CONCLUSION**

NAT can cause tumor downstaging preoperatively or even complete remission of the primary tumor. Radiochemotherapy could lead to better T downstaging and promising overall survival without more complications.

**Key Words:** Locally advanced rectal cancer; Neoadjuvant therapy; Tumor downstaging; Postoperative complications; Prognosis

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**Core Tip:** Neoadjuvant therapy can cause tumor downstaging preoperatively or even complete remission of the primary tumor. Radiochemotherapy had better T downstaging as well as promising overall survival without major complications. This may help clinicians realize the indispensability of preoperative radiation.

**INTRODUCTION**

After Macfarlane *et al.*[1] and Heald *et al.*[2] promoted the concept of total mesorectal excision (TME), the local recurrence rate of locally advanced rectal cancer (LARC) fell below 30%. The Stockholm I and Stockholm II trials[3-6] showed that preoperative radiation could reduce this rate to less than 15%. The side effects of neoadjuvant therapy (NAT) must not be neglected. Radiation can directly destroy normal rectal tissue[7-9], and chemotherapy always causes systematic side effects.

Therefore, this study assessed the efficacy of NAT in LARC and retrospectively explored its impact on postoperative complications and prognosis.

**MATERIALS AND METHODS**

**Patients and groups**

From January 1, 2016 to January 31, 2019, 1497 patients from Shanghai Ruijin Hospital affiliated with Shanghai Jiaotong University School of Medicine were diagnosed with rectal tumors. Seventy-seven patients met the inclusion criteria and were followed up for 2 years. Patient characteristics included the following: patient age between 18 to 75 years old, tumor location at the anal edge ≤15 cm according to endoscopy, histopathologically confirmed adenocarcinoma, tumor staging T3/T4 or N+ with magnetic resonance imaging (MRI), and willingly accepted and finished NAT. All patients were divided into the neoadjuvant chemotherapy (NCT) group and the neoadjuvant radiochemotherapy (NRCT) group according to the regimen they received.

**Regimen of NAT**

The NAT regimen was planned by our multiple discipline team and carried out with the full understanding of patients and their families. NRCT comprised radiation (50 Gy in 25 fractions) with simultaneous capecitabine (1000 mg/m²) plus chemotherapy (Capeox or mFolfox6 for 1-2 cycles). The NCT was Capeox or mFolfox6 for four cycles.

The interval time between surgery and NAT was at least 6 wk after NRCT or 2 wk

Although the NRCT group might have better long-term overall survival.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.

**Data sharing statement:** No additional data are available.

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**Manuscript source:** Unsolicited manuscript

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

| Grade | Description | Count |
|-------|-------------|-------|
| A     | Excellent   | 0     |
| B     | Very good   | 0     |
| C     | Good        | C     |
| D     | Fair        | 0     |
| E     | Poor        | 0     |

**Received:** October 9, 2020

**Peer-review started:** October 9, 2020

**First decision:** December 8, 2020

**Revised:** December 13, 2020

**Accepted:** January 15, 2021

**Article in press:** January 15, 2021

**Published online:** March 27, 2021

**P-Reviewer:** Kasztelan-Szczerbinska B

**S-Editor:** Gao CC
after NCT. Then radical TME of rectal cancer was carried out (Dixon, Miles, or Hartmann procedure).

Data comparison
Patients were divided into the NCT group and NRCT group to compare the baseline data, tumor-related data, operation-related data, and postoperative complication-related data. The tumor downstaging evaluation was based on the Response Evaluation Criteria in Solid Tumors (RECIST) standard\(^\text{[11]}\) according to MRI and tumor regression grade (TRG) from the American Joint Committee on Cancer, 7th edition according to pathology. Postoperative complications included anastomotic leakage (AL), incision complications, and stoma complications.

The Wexner Continence Grading Scale was used to evaluate postoperative rectal function. The time of distal or local recurrence was recorded to assess disease-free survival (DFS). Overall survival (OS) was also compared between groups.

Statistical analysis
All data were analyzed, described, and processed by SPSS 23. \(P < 0.05\) was considered statistically significant. The Mann-Whitney \(U\) or Wilcoxon test was used to compare the two groups, and the \(\chi^2\) test was used for comparison of categorical variables. Multivariable analysis was used to reveal the potentially influential factors of the NAT effect and postoperative complications. Kaplan-Meier analysis was used to describe and compare survival, and log-rank and Breslow tests were used to confirm the statistical significance.

RESULTS
General data
A total of 77 cases of LARC were included. General data are shown in Table 1. The average interval between radiotherapy and surgery was 61 ± 16 d (Table 1). The general data were analyzed and compared, as shown in Table 2. No significant difference in general data was found between the two groups.

Oncology data
There was only one significant difference in the preoperative characteristics (T stage) between the two groups before intervention (Table 3). A total of 43 cases showed retraction of the lower edge of the tumors by a median distance of 1.0 cm. Forty-one patients had T downstaging after treatment, and fifty-five patients had N downstaging. According to the RECIST standard, 12 cases were classified as complete response (CR). For TRG according to pathology, 15 cases were classified as TRG-0 (Table 4). Regarding the efficacy of NAT between the two groups (Table 5), there was only a significant difference in T downstaging, with no significant difference in the CR ratio or TRG-0 ratio.

Operation data
All 77 patients received surgical treatment, including Dixon \((n = 56)\), Hartmann \((n = 4)\), and Miles \((n = 17)\) procedures. The organ preservation rate was 77.9%. The median operation duration was 167 min, with a median blood loss of 60 mL. Reoperation was performed in four cases caused by stoma obstruction (1 case), stoma ischemia (2 cases), and stoma bleeding (1 case). Among the 56 patients who underwent Dixon surgery, 48 (85.7%) underwent ileostomy. The average distance of the anastomosis from the anal margin was 5.4 ± 1.6 cm. Comparing the operation-related data between the two groups (Table 6), there were no significant differences in organ-preserving rate, intraoperative bleeding volume, or operation time \((P > 0.05)\). In all cases receiving the Dixon operation, there was no difference in the ratio of ileostomy, but the distance from anastomosis to the anus in the NRCT group was lower than that in the NCT group.

Postoperative data
Among all of the cases included, the median postoperative hospital stay was 8 d, the median postoperative time of consuming a liquid diet was 3 d, and 16 cases had postoperative complications. Among the 56 Dixon cases, 6 (10.7%) had AL. No incision-related complications and two (2/48, 4.2%) stoma-related complications were observed. Among the four Hartmann cases, one had stoma ischemia, and one had
stoma obstruction. No incision complications were observed. Of the 17 Miles cases, 4 (23.5%) had incision-related complications, and no stoma-related complications occurred.

The data on perioperative management and complications were compared between the two groups (Table 7). There was no significant difference in the postoperative hospital stay, time of open fluid diet, reoperation rate, or occurrence of complications between the two groups ($P > 0.05$).

**Multivariate analysis of the effectiveness of NAT**

TRG-0 or 1 was used as the strain variable. Possibly related factors were selected as independent variables including sex, age, comorbidity, radiotherapy, pre-T stage, and tumor lower edge. The results of logistic regression analysis showed that radiation was not a risk factor, while male sex (odds ratio [OR] = 0.251, 95% confidence interval [CI]: 0.080-0.788; $P = 0.02$) and age $< 60$ years (OR = 0.306, 95% CI: 0.101-0.932; $P = 0.04$) were protective factors for TRG 0 or 1 (Tables 8 and 9).
Table 4 Effectiveness of neoadjuvant therapy

| Neoadjuvant therapy | n  |
|---------------------|----|
| RECIST, n           |    |
| CR                  | 12 |
| PR                  | 45 |
| SD                  | 20 |
| PD                  | 0  |
| TRG, n              |    |
| 0                   | 15 |
| 1                   | 12 |
| 2                   | 23 |
| 3                   | 27 |

CR: Complete response; PD: Progressive disease; PR: Partial response; RECIST: Response Evaluation Criteria in Solid Tumors; SD: Stable disease; TRG: Tumor regression grade.

Table 5 Effectiveness comparison between neoadjuvant radiochemotherapy and neoadjuvant chemotherapy

|                          | NRCT | NCT | P value |
|--------------------------|------|-----|---------|
| Retraction of lower edge, n |      |     | 0.72    |
| Yes                      | 30   | 9   |         |
| No                       | 25   | 13  |         |
| Median retraction distance of lower edge in cm | 1.0 | 1.0 | 0.97 |
| T-downstaging, n         |      |     | 0.03    |
| Yes                      | 37   | 9   |         |
| No                       | 18   | 13  |         |
| N-downstaging, n         |      |     | 0.50    |
| Yes                      | 37   | 13  |         |
| No                       | 18   | 9   |         |
| CR, n                    |      |     | 0.71    |
| Yes                      | 20   | 7   |         |
| No                       | 35   | 15  |         |
| TRG-0, n                 |      |     | 1.00    |
| Yes                      | 11   | 4   |         |
| No                       | 44   | 18  |         |

CR: Complete response; NCT: Neoadjuvant chemotherapy; NRCT: Neoadjuvant radiochemotherapy; TRG-0: Tumor regression grade 0.

**Multivariate analysis of AL occurrence after NAT**

AL occurrence was selected as the strain variable. Possible risk factors were selected as independent variables including age, sex, comorbidities, preoperative radiation administration, anastomotic site location, and TRG-0 or TRG-1 (Table 10). Preoperative radiation (OR = 0.177, 95%CI: 0.014-2.173; P = 0.18) was not a risk factor for AL (Table 11).

**NAT and prognosis**

The median follow-up time was 26 mo, with three cases that were lost to follow-up. Forty-one patients finished the Wexner scale, while thirty-six patients did not finish.
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Table 6 Comparison of operation data between neoadjuvant radiochemotherapy and neoadjuvant chemotherapy

|                          | NRCT | NCT | P value |
|--------------------------|------|-----|---------|
| Organ-preservation, n    |      |     | 0.15    |
| Yes                      | 40   | 20  |         |
| No                       | 15   | 2   |         |
| Defunctioning stoma, n   |      |     | 0.61    |
| Yes                      | 32   | 16  |         |
| No                       | 4    | 4   |         |
| Median operation duration in min | 168 | 142 | 0.23    |
| Intra-operation blood loss in mL | 70 | 50  | 0.59    |
| Anastomosis site in cm   | 5.0 ± 1.6 | 6.0 ± 1.4 | 0.03 |

1Including cases receiving Dixon or Hartmann.
2Including cases receiving Dixon only. NCT: Neoadjuvant chemotherapy; NRCT: Neoadjuvant radiochemotherapy.

Table 7 Comparison of post-operation data between neoadjuvant radiochemotherapy and neoadjuvant chemotherapy

|                                | NRCT | NCT | P value |
|--------------------------------|------|-----|---------|
| Median hospitalization time in d | 7    | 8   | 0.75    |
| Liquid diet time in d           | 3    | 2   | 0.96    |
| Re-operation, n                 |      |     | 0.47    |
| Yes                            | 4    | 0   |         |
| No                             | 51   | 22  |         |
| Complications, n               |      |     | 0.33    |
| Yes                            | 13   | 3   |         |
| No                             | 42   | 19  |         |
| Anastomotic leakage, n         |      |     | 0.56    |
| Yes                            | 5    | 1   |         |
| No                             | 31   | 19  |         |
| Incision complications, n      |      |     | 0.47    |
| Yes                            | 4    | 0   |         |
| No                             | 51   | 22  |         |

1Including cases receiving Dixon only. NCT: Neoadjuvant chemotherapy; NRCT: Neoadjuvant radiochemotherapy.

the Hartmann or Miles procedure (n = 22), died (n = 8), had a temporary to permanent stoma (n = 5), or were lost to follow-up (n = 1). The median score of the Wexner scale was 3 (0-14), with no significant difference between the NRCT group and NCT group (P = 0.26).

The 2-year DFS (91.7%) and OS (93.4%) are shown in Figure 1. The DFS between the NRCT group and NCT group showed no significant difference (83.1% vs 90.5%, P > 0.05), whereas the NRCT group had significantly better OS (98.2% vs 80.7%; Breslow test P = 0.046) (Figures 2 and 3).

**DISCUSSION**

NAT has a beneficial effect on tumor downstaging. In this study, preoperative radiation promised a better local tumor reduction rate and OS without increasing
Table 8 Influence factors and assignments for neoadjuvant therapy effectiveness

| Factor                | Variable | Assignment     |
|-----------------------|----------|----------------|
| Gender                | X1       | M = 1, F = 0   |
| Age                   | X2       | ≤ 60 yr = 1, > 60 yr = 0 |
| Hypertension          | X3       | N = 1, Y = 0   |
| Diabetes mellitus     | X4       | N = 1, Y = 0   |
| Pre-operative radiation| X5     | N = 1, Y = 0   |
| Pre-T stage           | X6       | T3 = 1, T4 = 0  |
| Tumor lower edge      | X7       | ≤ 5 cm = 1, > 5 cm = 0 |
| TRG-0 or 1            | Y        | Y = 1, N = 0   |

F: Female; TRG: Tumor regression grade; M: Meal; N: No; Y: Yes.

Table 9 Logistic regression analysis of predictors of neoadjuvant therapy effectiveness

| Variable            | β       | Wals value, $\chi^2$ | $P$ value | OR     | 95%CI Lower limit | 95%CI Upper limit |
|---------------------|---------|-----------------------|-----------|--------|-------------------|------------------|
| Gender              | -1.381  | 5.609                 | 0.02      | 0.251  | 0.08              | 0.788            |
| Age                 | -1.183  | 4.34                  | 0.04      | 0.306  | 0.101             | 0.932            |
| Hypertension        | 0.725   | 1.245                 | 0.26      | 2.065  | 0.578             | 7.385            |
| Diabetes mellitus   | 0.527   | 0.622                 | 0.43      | 1.694  | 0.457             | 6.273            |
| Pre-operative radiation| -0.601 | 1.012                 | 0.31      | 0.548  | 0.17              | 1.768            |
| Pre-T stage         | 0.526   | 0.967                 | 0.33      | 1.692  | 0.593             | 4.827            |
| Tumor lower edge    | 0.073   | 0.021                 | 0.89      | 1.075  | 0.401             | 2.884            |

CI: Confidence interval; OR: Odds ratio.

Table 10 Risk factors and assignments for anastomotic leakage

| Factor                | Variable | Assignment     |
|-----------------------|----------|----------------|
| Gender                | X1       | M = 1, F = 0   |
| Age                   | X2       | ≤ 60 yr = 1, > 60 yr = 0 |
| Comorbidities         | X3       | N = 1, Y = 0   |
| Radiation             | X4       | N = 1, Y = 0   |
| Stoma                 | X5       | N = 1, Y = 0   |
| TRG-0 or 1            | X6       | N = 1, Y = 0   |
| Anastomosis site location| X7     | ≤ 5.4 cm = 1, > 5.4 cm = 0 |
| Anastomotic leakage   | Y        | Y = 1, N = 0   |

F: Female; TRG: Tumor regression grade; M: Meal; N: No; Y: Yes.

operation difficulty and complications or causing worse rectal function.

Tumor downstaging after NAT of LARC
The EXPERT trial showed that chemoradiotherapy had a superior pathological complete remission (PCR) rate compared with chemotherapy alone. Additionally, the FORWARC trial showed the same results. In our study, the effect of NAT was not
Table 11 Logistic regression analysis of risk factors for anastomotic leakage after neoadjuvant therapy

| Variable         | β     | Wals value, χ² | P value | OR     | 95%CI Lower limit | 95%CI Upper limit |
|------------------|-------|----------------|---------|--------|-------------------|-------------------|
| Gender           | -0.777| 0.971          | 0.32    | 0.46   | 0.098             | 2.156             |
| Age              | -0.349| 0.136          | 0.71    | 0.706  | 0.11              | 4.514             |
| Comorbidity      | 0.146 | 0.024          | 0.88    | 1.157  | 0.185             | 7.239             |
| Radiation        | -1.732| 1.832          | 0.18    | 0.177  | 0.014             | 2.173             |
| Stoma            | 1.176 | 0.917          | 0.34    | 3.241  | 0.292             | 35.961            |
| TRG-0 or 1       | -1.198| 1.564          | 0.21    | 0.302  | 0.046             | 1.973             |
| Anastomosis site | -1.46 | 2.386          | 0.12    | 0.232  | 0.036             | 1.481             |

CI: Confidence interval; OR: Odds ratio; TRG-0: tumor regression grade 0.

Figure 1 Overall survival and disease-free survival in all cases. DFS: Disease-free survival; OS: Overall survival.

Impact of NAT on surgery and complications

Studies have previously shown the destruction of local rectal mucosa after radiation. Fibrosis is the unfortunate result of previous radiation, causing more difficulties during operation. However, operation duration or blood loss volume showed no difference between groups, in agreement with the results of many studies performed in China.

Overall, NAT means more dysfunctioning stoma. No significant difference was shown in this study between the groups. However, two patients had nonclosure stomas due to unfinished systemic therapy or other unclear personal reasons. Andrew revealed a nonclosure rate of 14.5% and was concerned about its physical and psychological impact.

Park et al. revealed that NAT increased the incidence of AL (hazard ratio [HR] = 6.284; 95%CI: 2.829-13.961; P < 0.001); another report showed the same findings (OR = 3.05, 95%CI: 1.26-7.37; P = 0.01). However, some studies have shown opposite results. Rahbari et al. conducted a meta-analysis and concluded that the incidence of...
AL did not increase (HR = 0.96; 95% CI: 0.58-1.60; \( P = 0.87 \)). Parc et al\textsuperscript{[22]} also found that there was no significant difference in the incidence of AL between groups (\( P = 0.25 \)). Although no difference in AL was observed in the study, a high proportion of dysfunctioning stoma could be overlooked, as it could conceal grade A AL from clinical observation. AL is also related to many other factors\textsuperscript{[23]-[25]}.

Incisional complications are mostly a concern for patients after the Miles procedure. El-Gazzaz et al\textsuperscript{[26]} carried out a multivariate analysis and found that preoperative radiation increased the risk of perineal incision infection (OR = 1.66, 95% CI: 1.10-2.48); Musters et al\textsuperscript{[27]} reached the same conclusion (OR = 1.74; 95% CI: 1.29-2.34).

Impact of NAT on prognosis
Rectal function did not show any difference in this study according to the Wexner scale. However, six patients suffered from temporary-to-permanent conversion of their stoma for different reasons. Rosa et al\textsuperscript{[28]} found that most patients could retain relatively good rectal function after NAT. Ghiselli et al\textsuperscript{[29]} observed that female and elderly patients might suffer from worse sphincter function after NAT.

NAT in LARC showed better DFS according to the EORTC 22921 study\textsuperscript{[30]}, while its superiority in OS failed to be observed even with a longer follow-up duration. The concept of total NAT has been raised in recent years. However, randomized clinical evidence for selective preoperative radiation is still lacking. This study did not find any difference in DFS between the groups. The Breslow test confirmed better OS in the
NRCT group, implying the advantage of NRCT.

**Limitations**

Despite its retrospective nature, one limitation of the study was the small sample size. Some of the differences in complications or survival data may not arise with such a small sample. The side effects of NAT were not taken into account in the research, which may have directly affected patient compliance and survival.

**CONCLUSION**

NAT can cause tumor downstaging preoperatively or even complete remission of the primary tumor. Radiochemotherapy had better T downstaging as well as promising OS without major complications. This may help clinicians realize the indispensability of preoperative radiation.

**ARTICLE HIGHLIGHTS**

**Research background**

Neoadjuvant therapy (NAT) is becoming the standard way to treat locally advanced rectal cancer (LARC). Radiation has been an important part of NAT. More research on preoperative radiation is warranted.

**Research motivation**

To explore what kind of impact preoperative radiation has on tumor downstaging, postoperative complications, and survival in LARC. To provide more evidence for choosing a NAT regimen.

**Research objectives**

To compare the downstaging effect, postoperative complications, and prognosis between two different NAT regimens: The combination of radiation and chemotherapy and chemotherapy alone.

**Research methods**

We retrospectively collected and analyzed the data of the two different regimens of NAT. The $\chi^2$ test was used to compare the downstaging effect, postoperative complications, etc. Kaplan-Meier analysis was used to describe and compare survival.

**Research results**

The study found that the primary tumor regression effect was better with the combination of radiation and chemotherapy than chemotherapy alone. This agrees with many previous articles. There were no significant differences in postoperative complications between the two groups, while overall survival was better in the radiochemotherapy group. However, no article comparing survival in LARC with or without radiation before surgery has been carried out. This waits to be confirmed by further studies.

**Research conclusions**

This study tried to compare two different NAT regimens in LARC. Preoperative radiation may contribute to radical surgery in LARC and improve the prognosis as well.

**Research perspectives**

A prospective study comparing postoperative complications and survival in NAT with or without preoperative radiation waits to be carried out.

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