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The primary aim of *World Journal of Gastrointestinal Surgery* (WJGS, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, etc.

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Retrospective Study

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

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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 χ^2 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,

Shanghai Ruijin Hospital Ethics Committee (Approval No. 2016-072).

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

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.

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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^[7-10], 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 included patients underwent laparoscopic radical rectal cancer surgery. Patients unable to finish NAT, undergoing an emergency operation, with severe organic comorbidities, and with coexisting other malignant tumors were excluded. 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

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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^[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 χ^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

Table 1 General data

	Case counts	
Gender: Male/Female	62	15
Diabetes mellitus: Yes/No	11	66
Hypertension: Yes/No	19	58
Preoperative radiation: Yes/No	55	22

Table 2 General data comparison between neoadjuvant radiochemotherapy and neoadjuvant chemotherapy

	NRCT	NCT	P value
Median age in yr	60	62	0.64
Gender, <i>n</i>			1.00
Male	44	18	
Female	11	4	
Hypertension, <i>n</i>			0.80
Yes	14	5	
No	41	17	
Diabetes mellitus, <i>n</i>			0.80
Yes	7	4	
No	48	18	

NCT: Neoadjuvant chemotherapy; NRCT: Neoadjuvant radiochemotherapy.

Table 3 Baseline comparison of oncology data between neoadjuvant radiochemotherapy and neoadjuvant chemotherapy

	NRCT	NCT	P value
Pre-operative median distance of tumor lower edge in cm	5.0	6.0	0.37
T3	25	17	0.01
T4	30	5	
Pre-operative N stage, <i>n</i>			
N0	5	2	1.00
N+	50	20	

NCT: Neoadjuvant chemotherapy; NRCT: Neoadjuvant radiochemotherapy.

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	<i>n</i>
RECIST, <i>n</i>	
CR	12
PR	45
SD	20
PD	0
TRG, <i>n</i>	
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	<i>P</i> value
Retraction of lower edge, <i>n</i>			0.72
Yes	30	9	
No	25	13	
Median retraction distance of lower edge in cm	1.0	1.0	0.97
T-downstaging, <i>n</i>			0.03
Yes	37	9	
No	18	13	
N-downstaging, <i>n</i>			0.50
Yes	37	13	
No	18	9	
CR, <i>n</i>			0.71
Yes	20	7	
No	35	15	
TRG-0, <i>n</i>			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

Table 6 Comparison of operation data between neoadjuvant radiochemotherapy and neoadjuvant chemotherapy

	NRCT	NCT	P value
Organ-preservation, <i>n</i>			0.15
Yes	40	20	
No	15	2	
Defunctioning stoma ¹ , <i>n</i>			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 ² 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, <i>n</i>			0.47
Yes	4	0	
No	51	22	
Complications, <i>n</i>			0.33
Yes	13	3	
No	42	19	
Anastomotic leakage ¹ , <i>n</i>			0.56
Yes	5	1	
No	31	19	
Incision complications, <i>n</i>			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: Male; N: No; Y: Yes.

Table 9 Logistic regression analysis of predictors of neoadjuvant therapy effectiveness

Variable	β	Wals value, χ^2	P value	OR	95%CI	
					Lower limit	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: Male; N: No; Y: Yes.

operation difficulty and complications or causing worse rectal function.

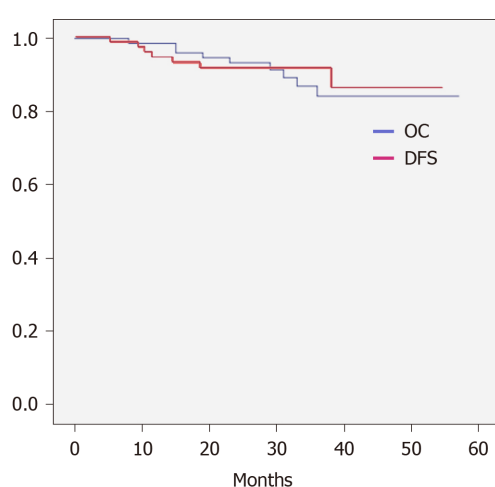
Tumor downstaging after NAT of LARC

The EXPERT^[12] trial showed that chemoradiotherapy had a superior pathological complete remission (PCR) rate compared with chemotherapy alone. Additionally, the FORWARC^[13] 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, χ^2	P value	OR	95%CI	
					Lower limit	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.

significantly different between the NCT and NRCT groups except for the T-downstaging rate. To some extent, it revealed the superior effect of the local tumor downstaging effect of preoperative radiation treatment.

Although female sex and age > 60 years were related to better tumor reaction, as shown in Tables 8 and 9, according to multivariate analysis, we failed to draw the same conclusion for preoperative radiation. Some experts have tried to find some clinical predictors of NAT response. Jung *et al*^[14] postulated that apparent diffusion coefficient parameters in MRI could somehow relate to tumor reduction volume. Qiu *et al*^[15] showed a poor response in patients with poor differentiation and T4 staging together.

Impact of NAT on surgery and complications

Studies have previously shown the destruction of local rectal mucosa after radiation^[7-10]. 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^[16,17].

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^[18].

Park *et al*^[19] 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; $P = 0.01$)^[20]. However, some studies have shown opposite results. Rahbari *et al*^[21] conducted a meta-analysis and concluded that the incidence of

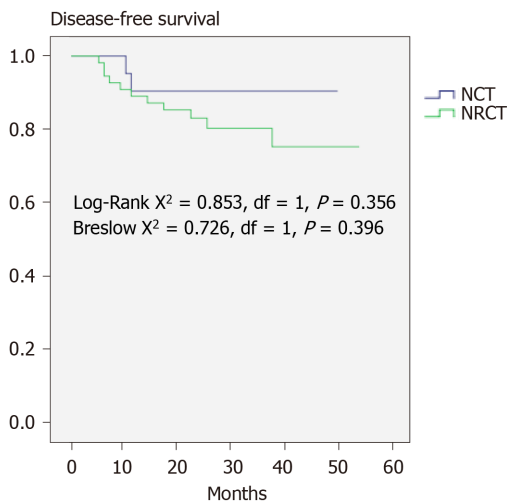


Figure 2 Disease-free survival between the neoadjuvant radiochemotherapy group and neoadjuvant chemotherapy group. NCT: Neoadjuvant chemotherapy; NRCT: Neoadjuvant radiochemotherapy.

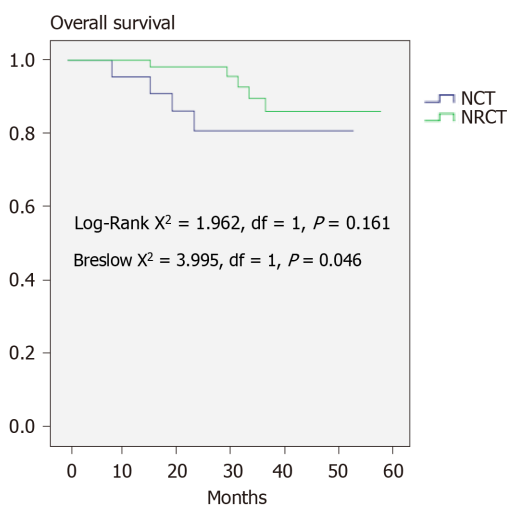


Figure 3 Overall survival between the neoadjuvant radiochemotherapy group and neoadjuvant chemotherapy group. NCT: Neoadjuvant chemotherapy; NRCT: Neoadjuvant radiochemotherapy.

AL did not increase (HR = 0.96; 95%CI: 0.58-1.60; $P = 0.87$). Parc *et al*^[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^[23-25].

Incisional complications are mostly a concern for patients after the Miles procedure. El-Gazzaz *et al*^[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*^[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*^[28] found that most patients could retain relatively good rectal function after NAT. Ghiselli *et al*^[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^[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 in to 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 χ^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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