ORIGINAL RESEARCH

Is long interval from neoadjuvant chemoradiotherapy to surgery optimal for rectal cancer in the era of intensity-modulated radiotherapy?: a prospective observational study

Hui Chang[1,2,*]
Wu Jiang[1,3,*]
Wei-Jun Ye[1,2]
Ya-Lan Tao[1,2]
Qiao-Xuan Wang[1,2]
Wei-Wei Xiao[1,2]
Yuan-Hong Gao[1,2]

[1]State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, People's Republic of China; [2]Department of Radiation Oncology, Sun Yat-sen University Cancer Center, Guangzhou, People's Republic of China; [3]Department of Colorectal Surgery, Sun Yat-sen University Cancer Center, Guangzhou, People's Republic of China

*These authors contributed equally to this work

Correspondence: Wei-Wei Xiao;
Yuan-Hong Gao
Department of Radiation Oncology,
Sun Yat-sen University Cancer Center,
651 Dongfeng Road East, Guangzhou,
Guangdong 510060, People's Republic
of China
Tel +86 137 1039 0520;
+86 135 6018 2168
Email xiaoww@sysucc.org.cn;
gaoyh@sysucc.org.cn

Objectives: To evaluate the impact of interval between neoadjuvant chemoradiotherapy (NACRT) and surgery on therapeutic and adverse effects of surgery, and long-term outcome of patients with locally advanced rectal cancer (RC), in the era of intensity-modulated radiotherapy (IMRT).

Patients and methods: Patients diagnosed with stage II–III RC and treated with IMRT-based NACRT followed by radical surgery were enrolled consecutively from April 2011 to March 2014. The data of all the patients were collected prospectively and grouped according to their NACRT-to-surgery interval. The therapeutic and adverse effects of surgery, and survivals were compared between the patients with interval ≤7 weeks and those with interval ≥8 weeks.

Results: A total of 231 patients were eligible for analysis, including 106 cases with interval ≤7 weeks and 125 cases with interval ≥8 weeks. The therapeutic and adverse effects of surgery were similar between these two groups of patients. However, interval ≥8 weeks appeared to lead to poorer overall, distant-metastasis-free and disease-free survivals, compared with interval ≤7 weeks. The HRs were 1.805, 1.714, and 1.796 (*P*-values were 0.045, 0.049, and 0.028), respectively.

Conclusion: For patients with locally advanced RC, a long NACRT-to-surgery interval might bring a potential risk of increased distant metastasis rather than a better tumor regression in the era of IMRT.

Keywords: rectal cancer, interval, neoadjuvant chemoradiotherapy, surgery, survival

Introduction

Colorectal cancer, particularly rectal cancer (RC), is the third most common malignancy in People's Republic of China.[1] At initial diagnosis, about 74.0% of RC patients are found to have a locally advanced (stage II–III) disease.[2] For these patients, neoadjuvant chemoradiotherapy (NACRT) before surgery is necessary to facilitate R0 resection, sphincter preservation, and improvement of long-term outcome.[3] However, there are still problems to be clarified, such as appropriate time interval between NACRT and surgery.

It has been proven that pathologic complete remission (pCR) of RC often takes months after NACRT.[4] Hence, a prolonged NACRT-to-surgery interval is supposed to improve the therapeutic effects of surgery. In fact, Garcia-Aguilar et al[5] have conducted a Phase II trial to show that an interval of 11 weeks brought a higher pCR rate with comparable postoperative complications, when compared with the classical

6-week interval. A similar correlation between the NACRT-to-surgery interval and the pCR rate was seen in the meta-analyses by Petrelli et al[6] and Du et al.[7]

On the other hand, long NACRT-to-surgery interval has the possibility to increase dissection difficulty and surgery-related complications due to pelvic fibrosis. In the recent Phase III GRECCAR-6 trial, the 11-week interval appeared to cause higher morbidity and more difficult resection, instead of higher pCR rate, than the 7-week interval.[8] Moreover, distant metastasis (DM) is now reported to happen in nearly 20.2% of RC patients and to be the major cause of treatment failure.[9] There is also a concern that long interval results in delay of postsurgical adjuvant chemotherapy (ACT) and might increase the risk of DM. Therefore, further studies are needed to eliminate the divergence on the length of the NACRT-to-surgery interval.

Additionally, most of the patients in the published studies focusing on the NACRT-to-surgery interval were not irradiated with intensity-modulated radiotherapy (IMRT), which has gradually become the mainstream irradiating technique for RC due to optimized dose delivery and reduced toxicities.[10] So, this prospective observational study aimed to explore the impact of NACRT-to-surgery interval on treatment effects of surgery and long-term outcome of RC patients in the era of IMRT.

Patients and methods
Patient selection
The patients who were diagnosed as RC pathologically in our hospital from April 1, 2011 to March 31, 2014 were initially considered. A patient would be consecutively enrolled into this study and prospectively observed if he or she met the following enrollment criteria: 1) previously untreated RC; 2) stage cII–III (cT3-4N0M0, cT1-4N1-2M0) disease; 3) age between 18 and 75 years old; 4) Karnofsky performance score >70; 5) complete records of IMRT-based NACRT and surgery; and 6) R0 resection.

The exclusion criteria included: 1) recurrent RC; 2) DMs before or during treatment; 3) prior chemotherapy or radiotherapy; 4) severe heart, lung, liver, or kidney dysfunctions unsuitable for NACRT; 5) prior history of other malignancies; and 6) application of monoclonal antibody.

This study was approved by the Institutional Review Board of the Sun Yat-sen University Cancer Center. Written informed consent was obtained from each patient before treatment.

Diagnosis and staging
The pathologic diagnosis of RC was made through biopsy under rectoscope. Then pretreatment clinical stage was determined through a computed tomography (CT) of chest and abdomen, a magnetic resonance imaging (MRI) of pelvis, an endoscopic ultrasonography, and a whole-body bone scan. Positron emission tomography was performed to confirm suspicious DM lesions. All the patients enrolled were staged according to the TNM staging standard (seventh edition) of the Union for International Cancer Control/American Joint Cancer Committee (UICC/AJCC).[11] The baseline carcino-embryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels were also tested before treatment.

Treatment strategies
The treatment was performed according to the practice guidelines of our hospital and the National Comprehensive Cancer Network (NCCN). The radiotherapy technique for all the patients in this study was IMRT. The patients were first immobilized by an AIO Bellyboard and Pelvic Solution system (AIO solution, Orfit Industries, Wijnegem, Belgium) and simulated with a moderately full bladder. After a CT simulation with 3-mm slice thickness, the target volumes were delineated and the dose prescription was made (more details can be found in our previous work).[12] Radiotherapy was done in a conventional fractionation (2 Gy per fraction, 1 fraction per day, 5 days per week), in which the total dose for the planning target volumes of gross tumor volume and clinical target volume were 50 and 46 Gy, respectively. A linear accelerator delivering an 8-MV photon beam was used to perform the IMRT.

The neoadjuvant chemotherapy was performed with a XELOX (capecitabine + oxaliplatin) regimen, 21 days per cycle, for a total of four cycles. Capecitabine was given 1,000 mg/m^2 twice daily on the 1st to the 14th day of a chemotherapy cycle. Oxaliplatin was given 130 mg/m^2 on the first day (100 mg/m^2 concurrently with radiotherapy). The regimen of the ACT after surgery was also XELOX. A total of four cycles were planned to be performed, if there was no contraindication.

The surgery after NACRT was done according to the total mesorectal excision standard. When tumor infiltrated or adhered to the adjacent organs, the surgeons would apply a multivisceral resection, in which partial or total of the attached organs was removed. The postsurgical pathology of each patient was assessed to decide the pathologic stage, also on basis of the seventh edition of the UICC/AJCC TNM staging classification.[11]

Follow-up
After treatment, the patients were planned to receive follow-up by outpatient interview every 3–6 months in the

first 3 years. The main tasks of the outpatient interview included complete physical examination, thoracoabdominal CT, pelvic MRI, serum CEA and CA19-9 assessment, and annual rectoscope and whole-body bone scan (or positron emission tomography). After the third year, the patients were followed up every 6–12 months by outpatient interview or telephone, until death from RC, or December 31, 2017, whichever came first. Causes of deaths were confirmed by death certificates.

Treatment effect evaluation

The treatment effects of surgery were evaluated through the down-T, the pCR, and the sphincter-preserving rates. Of those, pCR was defined as absence of microscopically viable tumor cells both in the primary site and the regional lymph nodes (stage ypT0N0), according to the Dworak standard.[13]

The long-term outcome of the patients was evaluated through the overall survival (OS), the local recurrence-free survival (RFS), the distant-metastasis-free survival (MFS), and the disease-free survival (DFS). The survivals were defined as the percentage of patients without corresponding events after a certain time period from diagnosis. The events for OS, RFS, and MFS were death, local recurrence (LR), and DM, respectively; the events for DFS included death, LR, and DM. The patients without the corresponding events or those lost to follow-up were regarded censored.

Adverse effect evaluation

Indexes of surgery-related adverse effects included the rate of grade 3 postsurgical complications and the intraoperative bleeding volume, the surgery time, and the days of hospitalization during which the surgery was performed. The medical or surgical complications within 90 days after surgery were defined as postsurgical complications and evaluated according to the Clavien–Dindo classification.

Definition and cutoff of variables

During analysis, the patients were grouped according to the NACRT-to-surgery interval, which was defined as the time period from the ending date of NACRT to the date of surgery. The cutoff value of the NACRT-to-surgery interval was 8 ($\leq$7 vs $\geq$8) weeks, according to the study by Du et al.[7]

Except the NACRT-to-surgery interval, the candidate prognostic factors in the survival analysis also included age, gender (male vs female), tumor differentiation (poorly differentiated vs moderately-well differentiated), perioperative chemotherapy cycle ($\leq$7 vs 8) and pretreatment anemia (yes vs no), clinical stage (cIII vs cII), CEA, CA19-9, surgery

technique (open vs laparoscopic), and pathologic N stage (pN+ vs pN–). The cutoff value of the age was the median age of the whole cohort. Anemia was defined as hemoglobin <130 g/L for males and <120 g/L for females, according to the standard of the WHO.[14] The threshold was modified to 110 g/L when a patient was aged $\geq$65 years old, according to the standard of elderly Chinese described by Peng and Zhang.[15] The upper normal limit of CEA and CA19-9 were determined as 5.00 ng/mL and 35.00 U/mL respectively, according to the standard of our hospital.[16]

Statistical analyses

Continuous data was presented as median with range and compared through a Mann–Whitney U-test. Categorical data were presented as number with proportion (%) and compared through a χ^2 test.

The survivals were first calculated by a Kaplan–Meier approach and compared using a log-rank test. The factors exhibiting statistical significance in the univariate analysis were then entered in the multivariate analysis as covariates. The independence of the prognostic factors on predicting survivals was tested through a Cox proportional hazards model. The hazard ratio (HR) and 95% confidence interval (CI) of each variable were calculated. The adjusted survival curves of patients with different NACRT-to-surgery intervals were also depicted.

A two-sided P-value of <0.05 was considered statistically significant. All statistical analyses were done using IBM SPSS Statistics 23.0 (IBM Corporation, Armonk, NY, USA). The procedure of this study is summarized in Figure 1.

Results
Patient enrollment

Between April 2011 and March 2014, a total of 247 patients diagnosed with untreated stage cII–III RC and treated with IMRT-based NACRT plus surgery were enrolled consecutively. After exclusion of the cases with DM during treatment (N=8) and non-R0 resection (N=8), there were finally 231 patients eligible for analysis. In these patients, 106 cases (45.9%) had an NACRT-to surgery interval $\leq$7 (range, 4–6) weeks, and 125 cases (54.1%) had an interval $\geq$8 (range, 8–12) weeks.

Clinicopathological profiles

The median age of the eligible patients was 54 (22–75) years old. So, the cutoff value of the age in survival analysis was also 54 ($\leq$54 vs $\geq$55) years old. There were 50 (21.6%) and 181 (78.4%) cases with stage cII and cIII disease, respectively. The distribution of the baseline clinicopathological profiles were balanced between the patients with
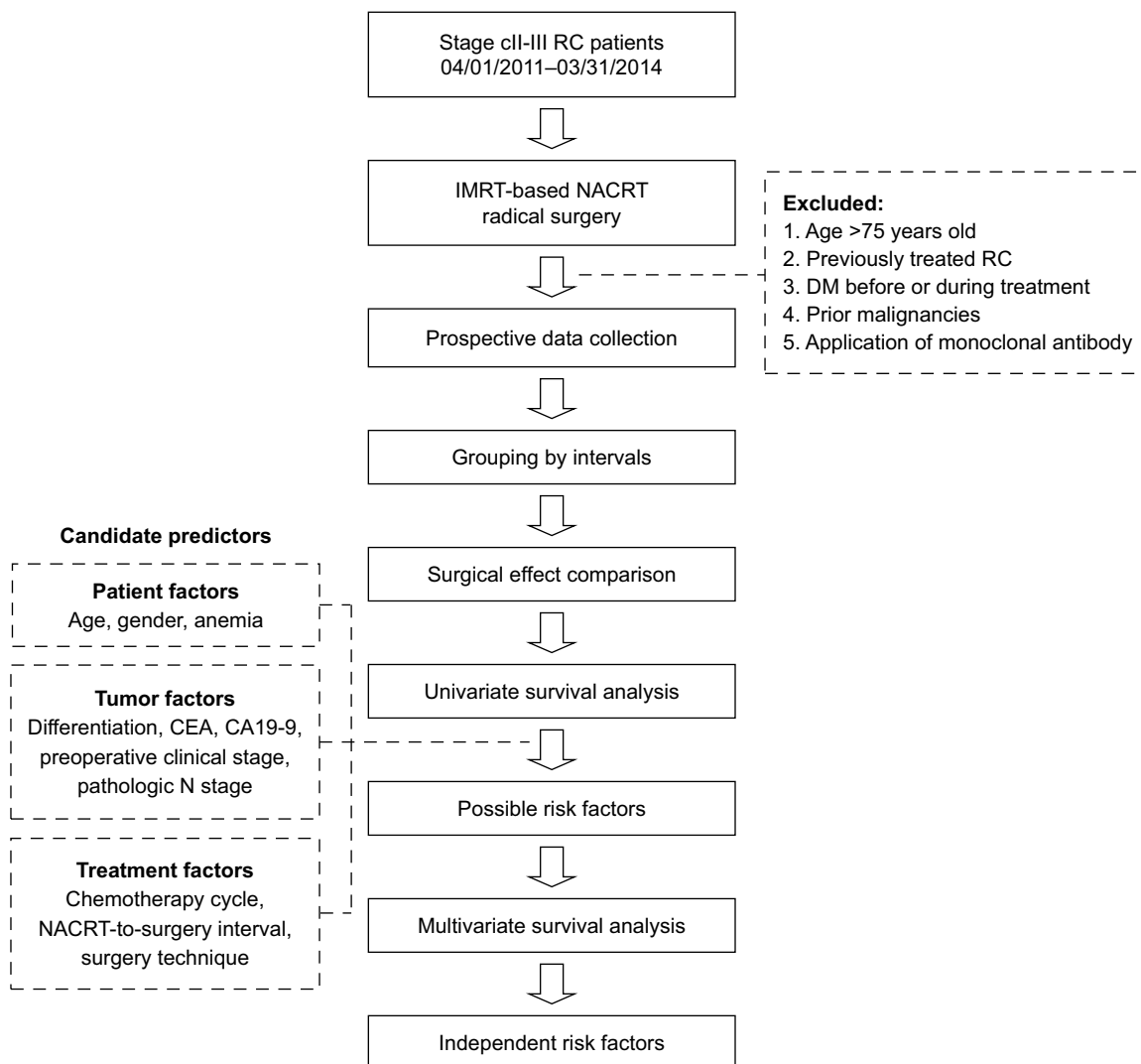
Figure 1 The procedure of this study.
Abbreviations: RC, rectal cancer; NACRT, neoadjuvant chemoradiotherapy; DM, distant metastasis; IMRT, intensity-modulated radiotherapy; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

NACRT-to-surgery interval ≤7 weeks and those with interval ≥8 weeks (Table 1).

Treatment effects of surgery

The down-T, the pCR, and the sphincter-preserving rates of the patients with NACRT-to-surgery interval ≤7 weeks were 75.5%, 30.2%, and 67.9%, respectively. The figures of the patients with interval ≥8 weeks were 78.4%, 34.4%, and 76.0%, respectively. There was no statistical difference between the two groups of patients in treatment effects of surgery (Figure 2).

Adverse effects of surgery

The patients with NACRT-to-surgery interval ≤7 weeks had a rate of grade 3 postsurgical complications similar to that of the patients with interval ≥8 weeks (4.7% vs 2.4%,

P=0.337). No grade 4 complication was seen. There was no difference in the intraoperative bleeding volume, the surgery time, and the hospitalization days between the two groups of patients (Figure 3).

Survival analysis

The median follow-up time of the patients was 47 (range, 10–73) months. A total of 31 cases (13.4%) were lost to follow-up. Until December 2017, there were totally 47 deaths (20.3%), 8 LRs (3.5%), and 63 DMs (27.3%).

In univariate analysis, CEA, CA19-9, NACRT-to-surgery interval, and pathologic N stage presented as possible predictors of the OS, the MFS, and the DFS (Table 2). The patients with NACRT-to-surgery interval ≥8 weeks had a poorer OS (76.0% vs 84.0%, P=0.037), MFS (69.6% vs 80.2%, P=0.036), and DFS (67.2% vs 79.2%, P=0.021) than those

Table 1 Clinicopathological characteristics of the patients

Characteristics	NACRT-to-surgery interval/weeks		P-value
	≥8 (N=125)	≤7 (N=106)	
Age/years old	54 (22–75)	54 (27–75)	0.650
Gender			0.171
Male	79 (63.2%)	76 (71.7%)	
Female	46 (36.8%)	30 (28.3%)	
Anemia			0.655
Yes	29 (23.2%)	22 (20.8%)	
No	96 (76.8%)	84 (79.2%)	
Differentiation			0.116
Poorly	8 (6.4%)	15 (14.2%)	
Moderately	99 (79.2%)	80 (75.5%)	
Well	18 (14.4%)	11 (10.3%)	
CEA/ng/mL	4.00 (0.00–392.00)	4.00 (0.99–123.00)	0.723
CA19-9/U/mL	14.79 (0.00–321.00)	13.04 (0.00–757.00)	0.659
Clinical stage			0.193
cII	23 (18.4%)	27 (25.5%)	
cIII	102 (81.6%)	79 (74.5%)	
Chemotherapy cycle			0.141
≤7	61 (48.8%)	62 (58.5%)	
8	64 (51.2%)	44 (41.5%)	
Surgery technique			0.084
Open	99 (79.2%)	93 (87.7%)	
Laparoscopic	26 (20.8%)	13 (12.3%)	
Pathologic N stage			0.557
pN+	25 (20.0%)	18 (17.0%)	
pN−	100 (80.0%)	88 (83.0%)	
Lost to follow-up			0.635
Yes	107 (85.6%)	93 (87.7%)	
No	18 (14.4%)	13 (12.3%)	

Abbreviations: NACRT, neoadjuvant chemoradiotherapy; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19–9.

with interval ≤7 weeks. Through multivariate analysis, CEA, CA19-9, NACRT-to-surgery, and pathologic N stage were still present to predict the OS, the MFS, and the DFS independently (Table 3). The HRs of NACRT-to-surgery interval on predicting the OS, the MFS, and the DFS were 1.805 (95% CI, 1.016–3.303), 1.714 (95% CI, 1.001–2.934), and 1.796 (95% CI, 1.066–3.025), respectively. The adjusted survival curves are shown in Figure 4.
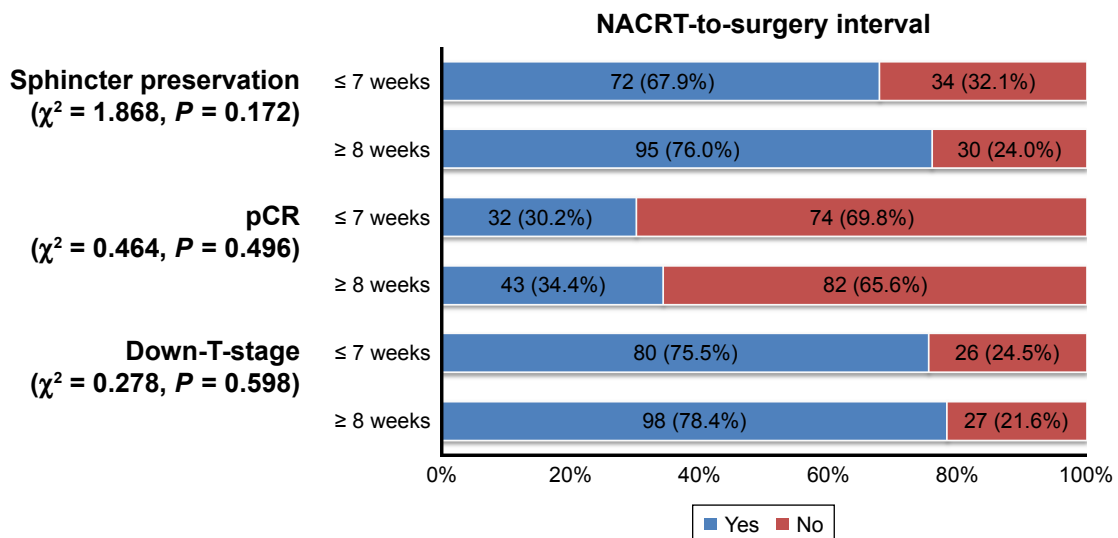

Figure 2 Down-T, pCR, and sphincter – preserving rates between patients with different intervals from NACRT to surgery.
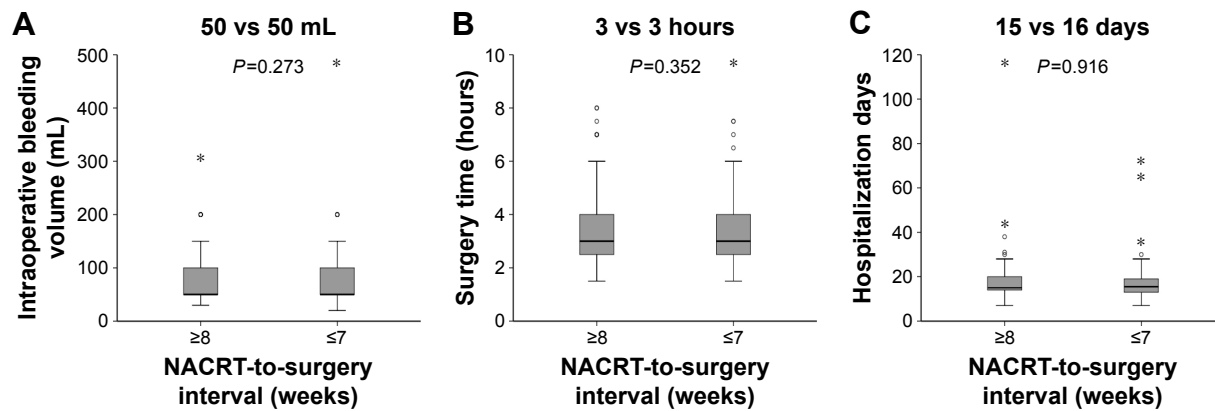**Abbreviations:** NACRT, neoadjuvant chemoradiotherapy; pCR, pathological complete remission.

Figure 3 No difference was seen in intraoperative bleeding volume (**A**), surgery time (**B**) and hospitalization days (**C**), between patients with different intervals from neoadjuvant chemoradiotherapy (NACRT) to surgery.
Notes: *extreme outliers (> upper quartile + 3 × interquartile range), °mild outliers (> upper quartile + 1.5 × interquartile range).
Abbreviation: NACRT, neoadjuvant chemoradiotherapy.

Table 2 Results of univariate survival analysis

Factors	OS	P-value	RFS	P-value	MFS	P-value	DFS	P-value
All	184/231 (79.7%)		223/231 (96.5%)		172/231 (74.5%)		168/231 (72.7%)	
Age/years old		0.523		0.185		0.258		0.292
≥55	89/109 (81.7%)		107/109 (98.2%)		85/109 (78.0%)		83/109 (76.1%)	
≤54	95/122 (77.9%)		116/122 (95.1%)		87/122 (71.3%)		85/122 (69.7%)	
Gender		0.760		0.171				0.971
Male	123/155 (79.4%)		148/155 (95.5%)		116/155 (73.7%)		113/155 (72.4%)	
Female	61/76 (80.3%)		75/76 (98.7%)		56/76 (74.8%)		55/76 (72.9%)	
Anemia		0.494		0.881		0.782		0.563
Yes	43/51 (84.3%)		49/51 (96.1%)		39/51 (76.5%)		39/51 (76.5%)	
No	141/180 (78.3%)		174/180 (96.7%)		133/180 (73.9%)		129/180 (71.7%)	
Differentiation		0.899		0.122		0.394		0.919
Poorly	18/23 (78.3%)		21/23 (91.3%)		19/23 (73.6%)		17/23 (72.6%)	
Moderately-well	166/208 (79.8%)		202/208 (97.1%)		153/208 (82.6%)		151/208 (73.9%)	
CEA/ng/mL		0.001[a]		0.060		0.001[a]		<0.001[a]
≥5.00	68/97 (70.1%)		90/97 (92.8%)		62/97 (63.9%)		59/97 (60.8%)	
<5.00	116/134 (86.6%)		133/134 (99.3%)		110/134 (82.1%)		109/134 (81.3%)	
CA19-9/U/mL		<0.001[a]		0.932		0.002[a]		0.007[a]
≥35.00	21/34 (61.8%)		33/34 (97.1%)		19/34 (55.9%)		19/34 (55.9%)	
<35.00	163/197 (82.7%)		190/197 (96.4%)		153/197 (77.7%)		149/197 (75.6%)	
Clinical stage		0.686		0.869		0.532		0.546
cII	38/50 (76.0%)		48/50 (96.0%)		35/50 (70.0%)		34/50 (68.0%)	
cIII	146/181 (80.7%)		175/181 (96.7%)		137/181 (75.7%)		134/181 (74.0%)	
Chemotherapy cycle		0.640		0.808		0.527		0.406
≤7	96/123 (78.0%)		119/123 (96.7%)		89/123 (72.4%)		86/123 (69.9%)	
8	88/108 (81.5%)		104/108 (96.3%)		83/108 (76.9%)		82/108 (75.9%)	
NACRT-to-surgery interval/weeks		0.037[a]		0.981		0.036[a]		0.021[a]
≥8	95/125 (76.0%)		121/125 (96.8%)		87/125 (69.6%)		84/125 (67.2%)	
≤7	89/106 (84.0%)		102/106 (96.2%)		85/106 (80.2%)		84/106 (79.2%)	
Surgery technique		0.054		0.872		0.109		0.151
Open	45/192 (76.6%)		7/192 (96.4%)		54/192 (71.9%)		57/192 (70.3%)	
Laparoscopic	2/39 (94.9%)		1/39 (97.4%)		5/39 (87.2%)		6/39 (84.6%)	
Pathologic N stage		0.013[a]		0.109		0.016[a]		0.014[a]
pN+	13/43 (69.8%)		3/43 (93.0%)		16/43 (62.8%)		17/43 (60.5%)	
pN−	34/188 (81.9%)		5/188 (97.3%)		43/188 (77.1%)		46/188 (75.5%)	

Note: [a]$P<0.05$.
Abbreviations: OS, overall survival; RFS, local recurrence-free survival; MFS, distant-metastasis-free survival; DFS, disease-free survival; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; NACRT, neoadjuvant chemoradiotherapy.

Table 3 Results of multivariate survival analysis

Survivals	Factors	Parameters	*P*-value	HR	95% CI
OS	CEA/ng/mL	≥5.00 vs <5.00	0.012[a]	2.146	1.181–3.906
	CA19-9/U/mL	≥35.00 vs <35.00	0.003[a]	2.717	1.406–5.236
	NACRT-to-surgery interval/weeks	≥8 vs ≤7	0.045[a]	1.805	1.016–3.303
	Pathologic N stage	pN+ vs pN−	0.040[a]	1.980	1.032–3.802
MFS	CEA/ng/mL	≥5.00 vs <5.00	0.007[a]	2.070	1.221–3.509
	CA19-9/U/mL	≥35.00 vs <35.00	0.015[a]	2.092	1.152–3.788
	NACRT-to-surgery interval/weeks	≥8 vs ≤7	0.049[a]	1.714	1.001–2.934
	Pathologic N stage	pN+ vs pN−	0.049[a]	1.786	1.002–3.185
DFS	CEA/ng/mL	≥5.00 vs <5.00	0.002[a]	2.242	1.344–3.745
	CA19-9/U/mL	≥35.00 vs <35.00	0.045[a]	1.825	1.013–3.289
	NACRT-to-surgery interval/weeks	≥8 vs ≤7	0.028[a]	1.796	1.066–3.025
	Pathologic N stage	pN+ vs pN−	0.046[a]	1.767	1.010–3.096

Note: [a]*P*<0.05.
Abbreviations: OS, overall survival; MFS, distant-metastasis-free survival; DFS, disease-free survival; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; NACRT, neoadjuvant chemoradiotherapy; HR, hazard ratio; CI, confidence interval.

Discussion

To date, there is no consensus on the best NACRT-to-surgery interval for patients with locally advanced RC. In the latest version of NCCN guidelines, the interval between NACRT and surgery is recommended to be 5–12 weeks,[17] which is not an exact value. Many recent studies supported a longer interval. Retrospective studies by Moore et al[18] and Tulchinsky et al[19] found that the pCR rate increased from 12%–17% to 19%–35% when the NACRT-to-surgery interval was prolonged to 7 weeks. Kalady et al[20] reported that an interval ≥8 weeks made the pCR rate increase to 30.8%, and the interval was the sole factor predicting the pCR rate.

Sloothaak et al[22] and Probst et al[21] further made analyses based on large-scale cohorts to confirm a positive correlation between the NACRT-to-surgery interval and the pCR rate. Since good tumor response after NACRT is convinced as a favorable prognosticator of locally advanced RC,[23] patients might achieve benefit of long-term outcome through prolonging the interval from NACRT to surgery. Nevertheless, studies by Habr-Gama et al[24] and de Campos-Lobato et al[25] showed that improved tumor regression from prolonged interval did not necessarily translate into survival benefit.

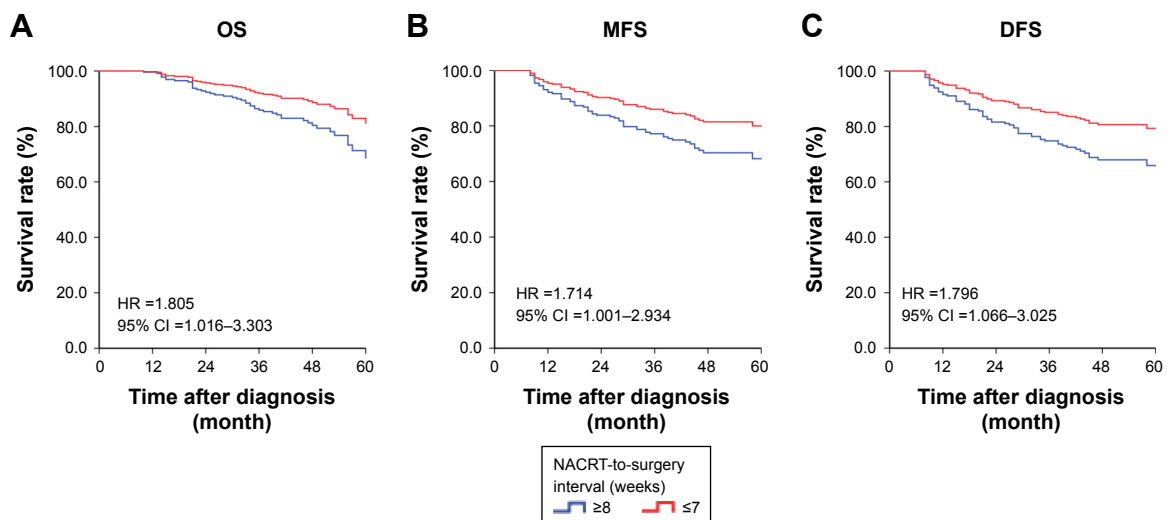There were also prospective studies conducted to figure out a proper NACRT-to-surgery interval. But the results

Figure 4 Adjusted survival curves of patients with different intervals from NACRT to surgery.
Notes: (**A**) OS; (**B**) MFS; (**C**) DFS. The covariates in the Cox model included CEA, CA19-9, NACRT-to-surgery interval, and pathologic N stage.
Abbreviations: OS, overall survival; MFS, distant-metastasis-free survival; DFS, disease-free survival; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; NACRT, neoadjuvant chemoradiotherapy.

were inconsistent. The first prospective study to support the favorable impact of a prolonged interval on the pCR rate was the Lyon R90-01 randomized trial.[26] A Phase II trial by Garrer et al[27] revealed that patients with NACRT-to-surgery interval of 9–14 weeks had a better 18-month RFS than those with interval of 6–8 weeks (73.8% vs 100.0%, P=0.031). A decreased 3-year LR rate was also seen in patients with interval ≥8 weeks through a study by Zeng et al.[28] Conversely, a study by Stein et al[29] showed that there was no favorable impact of prolonged interval on the pCR rate. The Istanbul R-01 randomized trial failed to show an improved pCR rate, 5-year LR rate, or OS in patients with 8-week interval, either.[30] In the latest Phase III GRECCAR-6 trial, the 11-week interval group exhibited a similar pCR rate (15.0% vs 17.4%, P=0.598) to that of the 7-week interval group. Instead, a higher morbidity was seen in the 11-week interval group (44.5% vs 32.0%, P=0.04) as well as a worse quality of mesorectal resection (78.7% vs 90.0%, P=0.015).[8]

IMRT has gradually become the primary technique of radiotherapy for locally advanced RC. Therefore, we assessed how NACRT-to-surgery interval affected surgical effects of locally advanced RC, through analyzing a relatively large cohort treated uniformly with IMRT. Our study indicated that short interval (≤7 weeks) was not inferior to long interval (≥8 weeks) in short-term therapeutic effects. The down-T rate (75.5% vs 78.4%, P=0.598), the pCR rate (30.2% vs 34.4%, P=0.496), and the sphincter-preserving rate (67.9% vs 76.0%, P=0.172) were similar between patients with different intervals. The adverse effects were also similar. No difference was seen in the rate of severe postsurgical complications, the intraoperative bleeding volume, the surgery time, or the hospitalization days, between the two groups of patients. Both the intervals were tolerable selections.

We also assessed the influence of NACRT-to-surgery interval on long-term outcome, and attained results which were a bit different from those of many previous studies. After a follow-up of nearly 4 years, we showed in this study that the patients with long interval appeared to have a worse OS (76.0% vs 84.0%, P=0.037), MFS (69.6% vs 80.2%, P=0.036), and DFS (67.2% vs 79.2%, P=0.021) than those with short interval. And through multivariate analysis, long interval maintained its independence on predicting a poorer OS (HR =1.805, P=0.045), MFS (HR =1.714, P=0.049), and DFS (HR =1.796, P=0.028). In other words, long NACRT-to-surgery interval resulted in an increased risk of DM and cancer death. The explanation might be that prolongation of NACRT-to-surgery interval inevitably prolonged the interval from NACRT to ACT as well. As we know, DM is now

the leading cause of RC-related death.[9] Although necessity of ACT remains controversial, it is believed that systemic chemotherapy of sufficient intensity is needed to eradicate DM effectively. A total of 6-month (8-cycle) XELOX chemotherapy is proposed by the NCCN guidelines to be performed periopratively.[17] Therefore, ACT of 4–6 cycles is often needed after surgery, especially in patients with a residual tumor after NACRT.[31] Delay of the ACT may provide sufficient time for subclinical DM lesions to grow to a size which can no longer be eradicated by the currently available cytotoxic agents. There have been studies revealing that a 2- or 3-month delay of ACT from surgery could negatively influence both the cancer-specific and the all-cause mortality of colorectal cancer,[32–34] though no study directly reported the impact of a delayed ACT from NACRT. Hence, a long NACRT-to-surgery interval could probably impair elimination of DM and survival of RC patients. Additionally, in the recent Stockholm III trial, 4–8 weeks emerged as a reasonable NACRT-to-surgery interval which brought an acceptable DM rate and OS.[35] It was in accordance with our results. However, a longer interval (8–12 weeks) was not assessed in that study.

Actually, it might be more appropriate to apply an individualized interval, which could be decided mainly by the possibility of pCR and the risk of DM. And since pathologic stage is the most important predictor of DM and can only be known after surgery,[36] it may be more practical to determine NACRT-to-surgery interval through prediction of pCR. There have been studies focusing on predicting pCR at initial diagnosis. The reported predictors included tumor size, clinical N stage, and some well-known biomarkers such as p53, p21, Ki67, and VEGF.[37,38] Further study is needed to build an accurate, practical predicting system to determine individualized interval for each locally advanced RC patient.

Indeed, there are still three main limitations in this study. First, it was not a controlled study with random allocation of the patients. Second, it was a single-institutional experience. Third, circumferential resection margin was not included in survival analysis of the study cohort because it was not routinely assessed in our hospital before 2017. Thus, a multi-center randomized controlled trial is needed to further validate the results of this study, before popularization to clinical use.

Conclusion

For patients with locally advanced RC, a long NACRT-to-surgery interval might bring a potential risk of increased DM instead of a better tumor regression, in the era of IMRT. Prolonged interval should be allowed in patients with caution before more evidence can be attained.

Disclosure

The authors report no conflicts of interest in this work.

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