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Adjuvant chemotherapy for locally advanced rectal cancer in elderly patients after neoadjuvant chemoradiotherapy and surgery

Toxicity and survival outcomes

Quanquan Sun, MD[a,b], Tongxin Liu, MD[a,b], Peng Liu, MD[a,b], Ke Lu, MD[a,b], Na Zhang, MD[a,b], Luying Liu, MD[a,b], Yuan Zhu, MD[a,b,*]

Abstract

The treatment strategy for elderly patients with locally advanced rectal cancer (LARC) remains controversial. The aim of this study was to identify the significance of adjuvant chemotherapy (AC) for elderly patients with LARC after neoadjuvant chemoradiotherapy (nCRT) and surgical resection. Between February 2002 and December 2012, a total of 43 patients aged ≥70 years with LARC following nCRT and surgery were retrospectively reviewed. The median follow-up time was 51 months (range 15–161 months). All patients completed the programmed chemoradiotherapy, of which 20 patients (46.5%) received 5-fluorouracil-based AC, and other 23 patients (53.5%) received no adjuvant chemotherapy. The 5-year overall survival and disease-free survival rates for AC group and non-adjuvant chemotherapy (NAC) group were 74.7% vs 63.4% ($P = .562$) and 73.4% vs 66.3% ($P = .445$), respectively. More patients in AC group suffered from severe leucopenia than that in NAC group (60% vs 17.4%, $P = .004$). For elderly patients with LARC following nCRT and surgery, AC may not benefit for survival, but increase treatment related leucopenia.

Abbreviations: 3-DCRT = three-dimensional conformal radiation therapy, AC = adjuvant chemotherapy, AJCC = American Joint Committee on Cancer, CEA = carcino-embryonic antigen, CRC = colorectal cancer, CTCAE = Common Terminology Criteria for Adverse Events, DFS = disease-free survival, ECG = electrocardiogram, ESMO = European Society for Medical Oncology, IMRT = intensity-modulated radiation therapy, LARC = locally advanced rectal cancer, NAC = non-adjuvant chemotherapy, NCCN = National Comprehensive Cancer Network, nCRT = neoadjuvant chemoradiotherapy, OS = overall survival, SIOG = International Society of Geriatric Oncology, TME = total mesorectal excision.

Keywords: adjuvant, chemotherapy, colorectal neoplasms, geriatrics

1. Introduction

It is well demonstrated that elderly patients with cancer were estimated underrepresented in clinical trials, constituting less than 10% of patients enrolled.[1] Although the incidence of rectal cancer in patients over the age of 70 has declined in the past decade, there is little clinical data to guide treatment decisions for these patients.[2] For the last decade, neoadjuvant chemoradiotherapy (nCRT) followed by total mesorectal excision (TME) was the standard treatment for locally advanced rectal cancer (LARC, T3-4/N+).[3,4] According to the recommendation of NCCN guidelines,[5] all patients with LARC should receive fluorouracil-based adjuvant chemotherapy after surgery. While ESMO guidelines proposed that the decision on adjuvant chemotherapy should balance the risk of tumor recurrence and possible toxicity for a particular patient.[6] However, as most studies included in these guidelines were focused on patients under 70 years old,[7,8] there is scarcity of evidence to guide treatment decision for the elderly patients with LARC.

In the present study, we retrospectively evaluated the efficacy and toxicities of adjuvant chemotherapy for LARC patients over 70 years old after neoadjuvant chemoradiotherapy and surgical resection, thus help to provide evidence for the utility of adjuvant chemotherapy for these patients.

2. Patients and methods

2.1. Patient selection

The records of 43 patients aged ≥70 years with LARC (clinically T3-4 and/or node positive) who underwent nCRT followed by surgical resection at the Zhejiang Cancer Hospital between February 2002 and December 2012 were retrospectively

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[a] Department of Radiation Oncology, Cancer Hospital of University of Chinese Academy of Sciences, [b] Zhejiang Key Laboratory of Radiation Oncology, Zhejiang Cancer Hospital, Hangzhou, Zhejiang Province, People's Republic of China.

[*] Correspondence: Yuan Zhu, Department of Radiation Oncology, Cancer Hospital of University of Chinese Academy of Sciences, Zhejiang Cancer Hospital, Hangzhou, Zhejiang Province, People's Republic of China (e-mail: zhuyuan63@hotmail.com).

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reviewed. Data pertaining to demographics, staging, tumor markers, pathology, treatment, and outcomes were collected for each patient. Due to the retrospective nature of the study, written informed consent was waived. This study was approved by the Independent Ethics Committee of Zhejiang Cancer Hospital.

2.2. Staging and treatment

The routine staging before treatment included physical examination and complete history, complete blood cell count, chemistry profile, carcino-embryonic antigen (CEA), electrocardiogram (ECG), chest, abdominal and pelvic CT scan, pelvic MRI with contrast, or endorectal ultrasound. All patients were restaged according to the American Joint Committee on Cancer (AJCC) 2010 staging system.[9] The main neoadjuvant for chemotherapy was 5-Fu or capecitabine-based chemotherapeutic regimen. Radiotherapy was delivered with a three-dimensional conformal radiation therapy (3-DCRT) or intensity-modulated radiation therapy (IMRT) technique at a dose of 45 Gy (1.8 Gy/fraction) to the whole pelvis, followed by a 5.4 Gy boost to the primary tumor in 3 fractions. Radical proctectomy was performed 6 to 10 weeks after completion of nCRT, and the type of surgery was left to the surgeons discretion. XELOX or FOLFOX postoperative adjuvant chemotherapeutic regimen was recommended for all patients 4 weeks after surgery. However, only 20 patients (46.5%) received adjuvant chemotherapy. Due to postoperative complications, economic problems or other reasons, the other 23 patients (53.5%) did not receive adjuvant chemotherapy.

2.3. Patient evaluation and follow-up

Treatment-related toxicities were scored according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. All patients were monitored every week during treatment, and were regularly followed up after completion of the treatment once every 3 months during the first 2 years, and then every 6 months thereafter. The follow-up assessments consist of patient history, physical examination, MRI examination for pelvic, chest CT, and ultrasonography of the abdomen or CT. Additionally, whole-body bone scan was performed when patient complaint about pain in bone.

2.4. Statistical analysis

Characteristics of patients were compared using Chi-Squared test or Fisher exact test. Disease-free survival (DFS) and Overall survival (OS) were calculated in months from the start of treatment to the date of relapse (DFS) and death or the last follow-up (OS). DFS was censored at the time of the last follow-up for disease-free or non-cancer-related death patients. OS was censored at the time of the last follow-up for alive patients. DFS and OS were determined using the Kaplan–Meier method, and survival curves were compared via the log-rank test. Multivariate analysis was performed using the Cox proportional hazards model. A P value $< .05$ was considered statistically significant. All statistical analyses were performed using SPSS 22.0 software (SPSS, Chicago, IL).

3. Results

3.1. Patient characteristics

A total of 43 patients were included in this study. Patients characteristics are listed in Table 1. Median patient age at the time of diagnosis was 72-year-old (range, 70 to 76-year-old). In our cohort, 20 patients (46.5%) received 5-fluorouracil-based adjuvant chemotherapy, the other 23 patients (53.5%) did not receive adjuvant chemotherapy (Fig. 1). The distribution of age, gender, tumor location, CEA level at diagnosis, radiation dose, tumor stage, nodal status, and regimen of concurrent chemotherapy did not differ between the 2 groups.

3.2. Pathologic characteristics after neoadjuvant chemoradiotherapy

Pathologic features after neoadjuvant chemoradiation and surgery of our cohort are listed in Table 2. There were no statistically significant differences in ypT stage, ypN stage, AJCC stage, and tumor differentiation between adjuvant chemotherapy and no adjuvant chemotherapy groups (all $P > .05$).

3.3. Acute toxicity

Acute toxicities related to the 2 groups were listed in Table 3. There were 60% of patients in the AC group suffered from grade 3 to 4 leucopenia during the whole course of treatment, which was more than that in NAC group (60.0% vs 17.4%, $P = .004$). Except for leucopenia, there were no significantly differences between the 2 groups in other hematologic or non-hematologic toxicities, with all P value $> .05$.

Table 1

Patient characteristics.

Characteristic	NAC N = 23 (53.5%)	AC N = 20 (46.5%)	P
Age (median, 72)			.818
≤72	13 (56.5)	12 (60.0)	
>72	10 (43.5)	8 (40.0)	
Gender			.176
Female	6 (26.1)	2 (10.0)	
Male	17 (73.9)	18 (90.0)	
KPS			.756
≤80	3 (13.0)	2 (10.0)	
≥90	20 (87.0)	18 (90.0)	
Tumor location			.451
≤5cm	13 (56.5)	9 (45.0)	
>5cm	10 (43.5)	11 (55.0)	
CEA (ng/ml)			.474
≤5	9 (39.1)	10 (50.0)	
>5	14 (60.9)	10 (50.0)	
Radiation dose (Gy)			.362
≤48.0	10 (43.5)	6 (30.0)	
>48.0	13 (56.5)	14 (70.0)	
Tumor stage			.107
T3	13 (56.5)	5 (25.0)	
T4a	6 (26.1)	10 (50.0)	
T4b	4 (17.4)	5 (25.0)	
Nodal status			.425
N0	11 (47.8)	12 (60.0)	
N+	12 (52.2)	8 (40.0)	
Concurrent chemotherapy			.145
Non	2 (8.7)	0 (0.0)	
5-Fu	0 (0.0)	1 (5.0)	
OX+5-Fu	6 (26.1)	2 (10.0)	
Cape	7 (30.4)	12 (60.0)	
OX+Cape	8 (34.8)	5 (25.0)	

AC = Adjuvant chemotherapy, NAC = non-adjuvant chemotherapy.

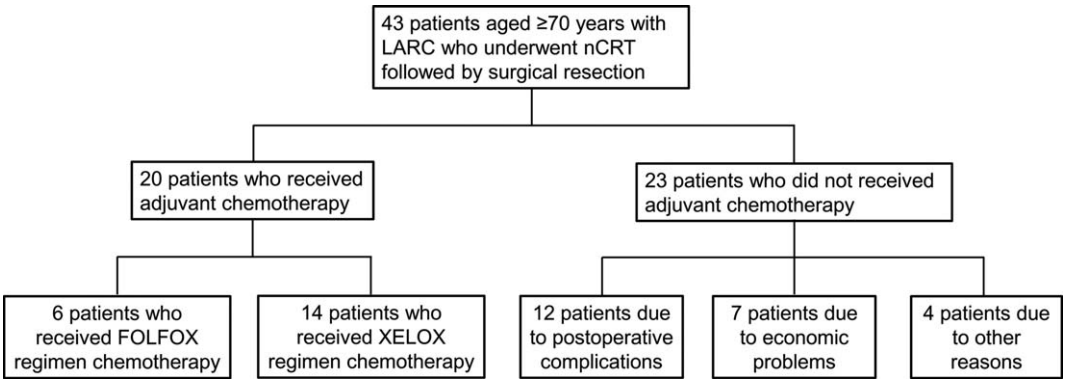

Figure 1. Flow chart showing selection of patients in this study.

3.4. Survival outcomes

The median follow-up was 51 months (range, 15–161 months). As shown in Figure 2 and Table 4, the 5-year overall survival and disease-free survival rates for AC and NAC group were 74.7% vs 63.4% ($P=.562$) and 73.4% vs 66.3% ($P=.445$), respectively. No statistically differences were found between the 2 groups. Multivariate analysis was performed to evaluate the influence of adjuvant chemotherapy and other relevant covariates on survival. After controlling for sex, age, ypT stage, ypN stage, and use of adjuvant chemotherapy, multivariate analysis indicated that ypN stage was an independent prognostic factor for DFS and OS (Table 5, all P value $<.05$).

4. Discussion

In the present study, we evaluated the efficacy and toxicities of adjuvant chemotherapy for LARC patients aged ≥70 years after nCRT and radical surgical resection. Our study has revealed that adjuvant chemotherapy may not benefit for survival, but increased treatment related leucopenia for elderly patients with LARC following nCRT and surgery.

Table 2

Pathologic features after neoadjuvant chemoradiation.

Characteristic	NAC N=23 (53.5%)	AC N=20 (46.5%)	P
ypT stage			.091
T0–2	9 (39.1)	13 (65.0)	
T3-4	14 (60.9)	7 (35.0)	
ypN stage			.930
N0	14 (60.9)	12 (60.0)	
N1	6 (26.1)	6 (30.0)	
N2	3 (13.0)	2 (10.0)	
AJCC stage			.149
0	4 (17.4)	7 (35.0)	
1	3 (13.0)	4 (20.0)	
2	7 (30.4)	1 (5.0)	
3	9 (39.1)	8 (40.0)	
Differentiation			.556
Well	1 (4.3)	0 (0.0)	
Moderately	11 (47.8)	13 (65.0)	
Poorly	6 (26.1)	3 (15.0)	
Other	5 (21.7)	4 (20.0)	

AC=Adjuvant chemotherapy, NAC=non-adjuvant chemotherapy.

In recent years, owing to the advances of early detection and treatment, the prognosis of colorectal cancer (CRC) has significantly improved.[10] However, for a variety of factors, such as diseases apart from cancer and complications of treatment, the survival time of elderly patients is still very low.[11,12] The role of adjuvant chemotherapy in elderly patients with CRC has been controversial for many years.[13,14] The effect of adjuvant chemotherapy in CRC mainly comes from the data of clinical trials. However, in most clinical trials, the proportion of elderly patients enrolled is small, and they were generally in better performance status. Therefore, it was not appropriate to generalize the conclusions of clinical studies directly to all elderly patients.[15]

Preoperative CRT is the standard components of the treatment of LARC before surgery, and may be followed by adjuvant chemotherapy in specific patients. According to the consensus recommendations of International Society of Geriatric Oncology (SIOG), 5-fluorouracil (5-Fu)-based adjuvant chemotherapy has survival benefits for elderly patients with locally advanced colorectal cancer.[16] However, due to an insufficient survival benefit,[17] elderly patients tend to less frequently receive adjuvant chemotherapy than younger or middle-age patients. In addition, patient preference,[18] frailty,[19] and quality of life[20] also influenced decision making in daily clinical practice for elderly patients. In our study, less than half of elderly patients received adjuvant chemotherapy. Elderly patients received adjuvant chemotherapy had no significant improvement in DFS or OS, but increased hematological toxicities, compared with those who did not receive adjuvant chemotherapy. Multivariate analysis indicated that ypN stage, rather than adjuvant chemotherapy or not, was an independent prognosticator for DFS and OS.

There were several potential limitations in the present study. As a retrospective analysis, the number of patients enrolled in the study was relatively small, which might reduce its statistical power. In addition, considering the needs of quality of life of patients after surgery, the course of adjuvant chemotherapy is inadequate to a certain extent. Although there was no statistical difference in the DFS or OS between the 2 groups, adjuvant chemotherapy seemed to have survival advantages to some extent. Except for leucopenia, adjuvant chemotherapy did not significantly increase the acute toxicities of elderly patients.

Table 3

Frequency of acute toxicities from the 2 groups by type and grade.

	NAC		AC			
Acute toxicities	**Grades0-2 n (%)**	**Grades 3–4 n (%)**	**Grades0–2 n (%)**	**Grades 3–4 n (%)**	**Z**	***P***
Hematologic						
Leucopenia	19 (82.6)	4 (17.4)	8 (40.0)	12 (60.0)	2.849	**.004**
Thrombocytopenia	18 (78.3)	5 (21.7)	15 (75.0)	5 (25.0)	0.250	.803
Anemia	22 (95.7)	1 (4.3)	18 (90.0)	2 (10.0)	0.717	.473
Non-Hematologic						
Nausea/vomiting	22 (95.7)	1 (4.3)	18 (90.0)	2 (10.0)	0.717	.473
Fatigue	23 (100.0)	0 (0.0)	20 (100.0)	0 (0.0)	0.0	1.0
Proctitis	23 (100.0)	0 (0.0)	20 (100.0)	0 (0.0)	0.0	1.0
Neurology	23 (100.0)	0 (0.0)	20 (100.0)	0 (0.0)	0.0	1.0
Liver dysfunction	23 (100.0)	0 (0.0)	20 (100.0)	0 (0.0)	0.0	1.0
Kidney dysfunction	23 (100.0)	0 (0.0)	20 (100.0)	0 (0.0)	0.0	1.0
Neurotoxicity	23 (100.0)	0 (0.0)	20 (100.0)	0 (0.0)	0.0	1.0

AC = Adjuvant chemotherapy, NAC = non-adjuvant chemotherapy.

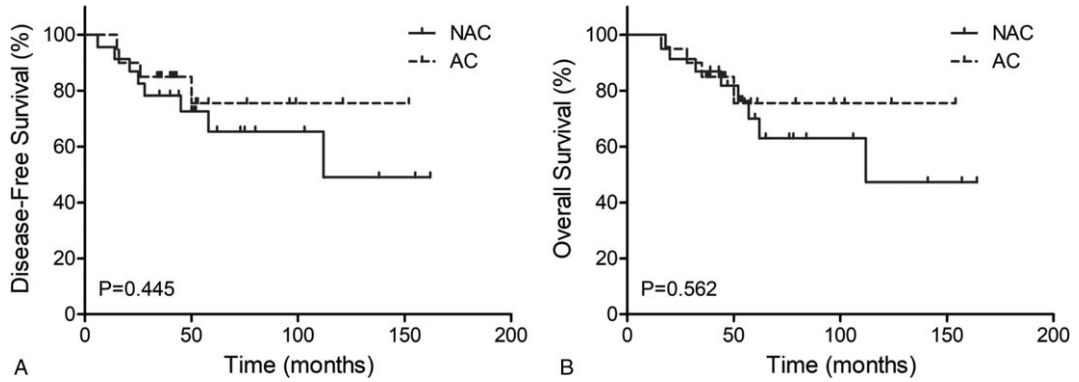

Figure 2. Comparison of survival between adjuvant chemotherapy and no adjuvant chemotherapy group in elderly patients. (A) DFS. (B) OS. AC = Adjuvant chemotherapy, NAC = non-adjuvant chemotherapy.

Table 4

Effect of prognostic factors on survival in univariate analyses.

	5y-DFS		5y-OS	
Factors	**%**	***P***	**%**	***P***
Gender		.847		.773
Male	69.0		66.3	
Female	71.6		70.0	
Age (years)		.459		.456
≤72	64.3		60.6	
>72	76.4		75.0	
Tumor location		.320		.307
≤5cm	73.7		73.1	
>5cm	65.5		61.2	
CEA (ng/ml)		.482		.496
≤5	73.0		67.7	
>5	70.0		67.5	
Radiation dose (Gy)		.774		.899
≤48.0	67.9		66.7	
>48.0	70.0		69.0	
ypT stage		.126		.126
T0-2	82.0		80.2	
T3-4	57.3		53.6	
ypN stage		**<.001**		**.001**
N0	86.7		86.3	
N+	43.4		38.6	
AC		.445		.562
No	66.3		63.4	
Yes	73.4		74.4	

The bold values are statistically significant.
AC = adjuvant chemotherapy.

5. Conclusions

Conclusively, our study showed that adjuvant chemotherapy may not benefit for survival in elderly patients with LARC following nCRT and surgery. However, except for leucopenia, the toxicities of adjuvant chemotherapy are tolerable. Large scale prospective studies are still needed to define the role of adjuvant chemotherapy in elderly patients with LARC following nCRT and surgery.

Table 5

Impact of prognostic factors on treatment results by multivariate analysis.

Endpoints	**Variables**	**HR (95% CI)**	***P***
DFS	Sex (Male vs Female)	0.656 (0.117–3.665)	.631
	Age (≤72 vs >72)	0.647 (0.177–2.363)	.510
	ypT stage (T0–2 vs T3–4)	0.892 (0.226–3.520)	.871
	ypN stage (N0 vs N+)	9.952 (2.054–48.209)	**.004**
	AC (No vs Yes)	0.478 (0.130–1.757)	.267
OS	Sex (Male vs Female)	0.848 (0.156–4.612)	.849
	Age (≤72 vs >72)	0.679 (0.184–2.509)	.562
	ypT stage (T0–2 vs T3-4)	1.086 (0.289–4.080)	.903
	ypN stage (N0 vs N+)	7s.927 (1.779–35.323)	**.007**
	AC (No vs Yes)	0.552 (0.151–2.021)	.369

The bold values are statistically significant.
AC = adjuvant chemotherapy.

Author contributions

Conceptualization: Yuan Zhu.
Formal analysis: Tongxin Liu.
Funding acquisition: Yuan Zhu.
Investigation: Peng Liu, Na Zhang.
Methodology: Ke Lu, Luying Liu.
Writing – original draft: Quanquan Sun.
Writing – review & editing: Yuan Zhu.
Quanquan Sun orcid: 0000-0002-6958-1523.

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