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Original Article

Radical Proctectomy Followed by Adjuvant Chemoradiation with Oral Tegafur is Well Tolerated by Elderly Patients with Rectal Cancer

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SUMMARY

Background: Pre-operative and post-operative chemoradiotherapy (CCRT) have been widely used to improve outcomes in patients with locally advanced rectal cancer. Nonetheless, pre-operative CCRT may not be tolerable in elderly patients. In contrast, post-operative CCRT with oral tegafur may have benefits including aiding in the precise selection of radiation therapy as well as being more tolerable. In the present study, we aimed to evaluate the clinical outcome of radical proctectomy followed by CCRT with oral tegafur, focusing on overall survival, progression-free survival, and toxicity among elderly patients with locally advanced rectal cancer.

Methods: From 2007 to 2018, thirty-two rectal adenocarcinoma patients aged ≥ 65 years with stage II–III who underwent radical proctectomy and had oral tegafur 300–350 mg/m^2/day throughout and after an RT course that lasted for at least 6 months were included.

Result: The mean age of the patients was 71.3 ± 5.1 years, and the median follow-up time was 22.8 (2.4–113.9) months. The 9.5-year progression-free survival rate was 55.0% with a significantly better median survival time for non-progression patients (p = 0.031). The 9.5-year overall survival rate was 52.3%. None of the patients experienced hematological or gastrointestinal toxicities of exceeding grade 2. Only one patient (3.1%) experienced grade 3 radiation dermatitis.

Conclusion: Radical surgery followed by adjuvant CCRT using oral tegafur was well tolerated and resulted in fair clinical outcomes.

1. Introduction

Rectal cancer is the third most common malignancy worldwide and occurs more commonly in the older population.[1,2] Pre- and post-operative chemoradiotherapy (CCRT) have been widely used to improve outcomes in patients with locally advanced rectal cancer.

Older patients with locally advanced rectal cancer are generally less aggressively treated because of a potentially higher risk of treatment complication. However, the basis of this approach is not well documented due to the fact that older patients are underrepresented in trials of rectal cancer treatments.[3,4] During the long-term follow-up of the German Rectal Cancer Study, the median age of the study participants was 61–62 years.[4] Moreover in the NSABP R03 trial, 55.9% of patients were older than 60 years.[3] Thus, no data for elderly patients aged 65 years and older is available for clinical reference. In the treatment of older adults with cancer, the risk and tolerance of toxicity is one of the major factors informing the selection of therapy modality.

For systemic chemotherapy, the oral tegafur (furanyl nucleoside analog of 5-fluorouracil [5-FU]) has been shown to have a comparative clinical efficacy to infusional 5-FU as adjuvant treatment of rectal cancer.[5] NSABPC-06 study also demonstrated oral tegafur can be an acceptable alternative to infusional 5-FU regimen in patients with stage II and III colon cancer.[6] Moreover, oral tegafur was associated with improved convenience of care compared with infusional 5-FU.[6] Tegafur may also provide more 5-FU selective radiosensitization and is likely to be widely incorporated into chemoradiotherapy regimens for patients with gastrointestinal malignancies.[7] In addition, oral anticancer drugs had advantages of continuous drug release and feasible patient tolerance and therefore can exert an efficient effect on cancer treatment.[8] For upfront surgery, clinical advantage relates to the ability to exclude clinically over-staged patients from receiving CCRT, whereas the disadvantage might include less complete resection which is dependent on the skill and experience of each surgeon. Radical proctectomy followed by CCRT with oral tegafur has been performed for 19 years.[9]

In this retrospective study, we aimed to evaluate the clinical outcomes of radical proctectomy followed by CCRT with oral tegafur, focusing on overall survival, disease free survival, and toxicity among elderly patients with locally advanced rectal cancer.

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2. Patients and methods

2.1. Patients

Patients with rectal adenocarcinoma receiving radical proctectomy between 2007 and 2018 were included in the present retrospective analysis. The inclusion criteria as follows: age ≥ 65 years old, TNM stage II–III, and oral tegafur (UFUR^{TM}, TTY Biopharm, Taiwan) administered during RT which lasted for at least 6 months. Patients were excluded if they had synchronous colon cancer or recurrent or metastatic diseases at diagnosis. A total of 32 patients were selected for further analysis (Table 1). Baseline characteristics of patient (sex, comorbidities, Eastern Cooperative Oncology Group performance status and tumor (pathology, extracapsular extension, lymphatic invasion, perineural invasion, vascular invasion, and tumor deposit) were also collected. The study was approved by the institutional review board of the Mackay Memorial Hospital, Taipei, Taiwan (IRB No. 20MMHIS005e).

2.2. Surgery

Radical proctectomy with lymph node dissection and anastomosis was performed.

2.3. Radiation therapy

While immobilized with an alpha cradle, a computed tomography (CT) based simulation was performed on the patients. The clinical target volume was contoured to include tumor bed, internal iliac lymph nodes, obturator lymph nodes and presacral lymphatic regions. Treatment planning was performed by using the technique of intensity modulated radiotherapy (IMRT). A radiation dose of 50–54 Gy in 25–27 fractions was delivered by a linear accelerator (29/32, 90.6%) or helical tomotherapy (3/32, 9.4%).

2.4. Chemotherapy

Chemotherapy throughout and after the IMRT course was continued for 6–12 months and was administered with 300–350 mg/m^2/day of oral tegafur.

2.5. Clinical data and follow-up

After surgery and CCRT, follow-ups including a test for tumor marker carcinoembryonic antigen (CEA), an abdominal CT scan, and a scope were arranged at 3–6 months intervals. Rate of progression-free survival and cumulative overall survival were determined.

2.6. Adverse events assessment

Treatment toxicity was graded according to version 4.03 of the Common Toxicity Criteria for Adverse Events (CTCAE) published by the National Cancer Institute in 2009.

2.7. Statistics analysis

All statistical analyses were performed using IBM SPSS Statistics 22 (IBM Co., Armonk, NY, USA). Continuous data are presented as mean ± standard deviation (SD) or medians, and categorical data are presented as frequencies and proportions. We conducted chi-square tests or Fisher exact tests for categorical variables. The Kaplan–Meier method was used to estimate progression-free survival and cumulative overall survival. A p-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Tumor control and survival

The mean age of patients enrolled in this retrospective analysis was 71.3 ± 5.1 (65–82) years. The median follow-up duration was 22.8 (2.4–113.9) months, one patient (3.1%) had loco-regional recurrence, whereas 9 patients (28.1%) had distant metastases. One patient (3.1%) developed both loco-regional recurrence and distant metastases at 16 months. In this elderly population, the 9.5-year progression-free survival rate was 55.0% (Figure 1) with a significantly better median survival time for non-progression patients (the median progression time and median non-progression time was 11.4 months and 25.9 months, respectively, $p = 0.031$). The 9.5-year overall survival rate was 52.3% (Figure 2).

3.2. Pathological features

Among these elderly patients with rectal cancer, the pathological features with distinct profiles were relatively high positive rates of lymphatic invasion (24/31, 77.4%), perineural invasion (14/31, 45.2%), and tumor deposit (3/17, 17.6%). Other features are shown in Table 1.

3.3. Treatment toxicity

None of the elderly patients experienced hematological (anemia, neutropenia and thrombocytopenia) or gastrointestinal (nausea, vomiting and diarrhea) toxicity greater than grade 2 (Table 2). However, one patient (3.1%) experienced grade 3 radiation dermatitis (Table 2). We also compared the grade of treatment toxicity in patients aged ≤ 70 years and those aged > 70 years and found no

Table 1
Characteristics and pathological features of 32 radical proctectomy followed by adjuvant chemoradiation with oral tegafur patients.

Characteristics	N = 32
Sex (male/female)	
Male	19 (59.4%)
Female	13 (40.6%)
Age of diagnosis (mean ± SD; min, max)	71.7 ± 5.2 (65, 82) years
Follow up period (median, min–max)	22.8, 2.4–113.9 months
ECOG performance status	
0	24 (75.0%)
1	8 (25.0%)
Tumor differentiation	
Well	2 (6.3%)
Moderately	26 (81.3%)
Poorly	4 (12.5%)
AJCC stage	
IIA	1 (3.1%)
IIIA	2 (6.3%)
IIIB	22 (68.8%)
IIIC	7 (21.9%)
Extracapsular extension	7/12 (58.3%)
Lymphatic invasion	24/31 (77.4%)
Perineural invasion	14/31 (45.2%)
Vascular invasion	10/31 (32.3%)
Tumor deposit	3/17 (17.6%)

ECOG: Eastern Cooperative Oncology Group; AJCC: American Joint Committee on Cancer.

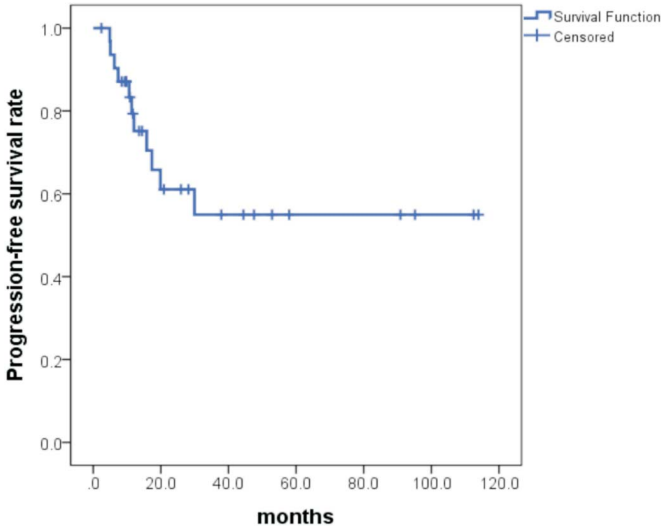

Figure 1. Progression-free survival curves for 32 proctectomy rectal cancer patients followed by adjuvant chemoradiation with oral tegafur.

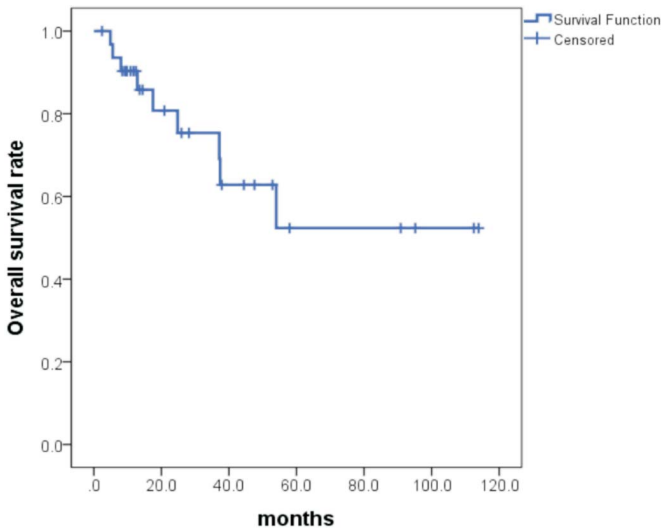

Figure 2. Cumulative overall survival curve for 32 proctectomy rectal cancer patients followed by adjuvant chemoradiation with oral tegafur.

significant difference (Table 2). In addition, nine of 32 patients (28.1%) in the study had more than one co-morbidity, and none of these elderly patients experienced treatment toxicity greater than grade 2.

4. Discussion

For older cancer patients, considerations for selection of treatment modalities include impaired physiological state, multiple co-morbidities, polypharmacy, presence of geriatric syndromes (such as sarcopenia), and risk of complications.[10–13] Among tri-modality treatments for rectal cancer, surgery remains the mainstay of therapy. Clinical evidence supports neoadjuvant RT and CCRT as the treatment of choice to down-stage tumors.[14] However, the risk of surgical complications after neoadjuvant RT/CCRT has been reported to be high.[15] In elderly cancer patients, concerns about intolerable complications are very important, suggesting the need for treatment modification to avoid intolerable toxicity.[10] This study shows that upfront major surgery without a pre-operative treatment-related modality to compromise surgical recovery is a rational strategy in the treatment of elderly patients.

Table 2
Treatment toxicity in 32 rectal patients followed with oral tegafur.

Treatment toxicity[1]	Age group			p-value[2]
	Overall N (%)	≤ 70 years N (%)	> 70 years N (%)	
Grade of anemia				0.117
0	11 (34.4)	8 (50.0)	3 (18.8)	
1	16 (50.0)	5 (31.3)	11 (68.8)	
2	5 (15.6)	3 (18.8)	2 (12.5)	
Grade of neutropenia				0.654
0	25 (78.1)	13 (81.3)	12 (75.0)	
1	6 (18.8)	2 (12.5)	4 (25.0)	
2	1 (3.1)	1 (6.3)	0 (0)	
Grade of thrombocytopenia				0.600
0	27 (84.4)	14 (87.5)	13 (81.3)	
1	4 (12.5)	1 (6.3)	3 (18.8)	
2	1 (3.1)	1 (6.3)	0 (0)	
Grade of diarrhea				0.776
0	4 (12.5)	3 (18.8)	1 (6.3)	
1	11 (34.3)	5 (31.3)	6 (37.5)	
2	17 (53.1)	8 (50.0)	9 (56.3)	
Grade of nausea				0.500
0	31 (96.9)	16 (100)	15 (93.8)	
1	1 (3.1)	0 (0)	1 (6.3)	
2	0 (0)	0 (0)	0 (0)	
Grade of vomiting				0.500
0	31 (96.9)	16 (100)	15 (93.8)	
1	1 (3.1)	0 (0)	1 (6.3)	
2	0 (0)	0 (0)	0 (0)	
Grade of acute kidney injury				1.000
0	31 (96.9)	15 (93.8)	16 (100)	
1	0 (0)	0 (0)	0 (0)	
2	1 (3.1)	1 (6.3)	0 (0)	
Grade of dermatitis radiation				0.159
0	18 (56.3)	7 (43.8)	11 (68.8)	
1	10 (31.3)	6 (37.5)	4 (25.0)	
2	3 (9.4)	3 (18.8)	0 (0)	
3	1 (3.1)	0 (0)	1 (6.3)	

[1] Treatment toxicity were graded according to version 4.03 of the Common Toxicity Criteria for Adverse Events (CTCAE), published by the National Cancer Institute in 2009.
[2] Fisher's exact test.

A major concern with systemic chemotherapy during and after RT is the distinct pharmacokinetics of the elderly patients compared to younger populations.[16] In general, impairment of drug metabolism enzyme activity may cause more severe adverse effects in the elderly. Thus, shifting from infusional 5-FU to oral tegafur to reduce toxicity has been adopted with evidence showing a comparative clinical effect.[5]

Upfront surgery with a pathology report before adjuvant CCRT may have the benefit of excluding patients for whom the treatment is not indicated and avoid unnecessary RT/CCRT due to imprecise clinical staging. A disadvantage is that the margin state may be more inadequate. In our results, the margin free rate was 87.5% (28/32) indicating no major disadvantage of upfront surgery in elderly rectal cancer patients.

A limitation of this study includes its retrospective design and as such susceptible to selection bias. Hence, further large studies are needed to confirm the finding in the present study.

In conclusion, radical proctectomy followed by adjuvant CCRT using oral tegafur was well tolerated and resulted in a fair clinical outcome among elderly rectal cancer patients.

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Conflict of interests

The authors declare that they have no conflict of interests.

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