Original Article

A Study and Clinical Observation on Patients with Stage III Colorectal Cancer and End-stage Renal Disease

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Key Words
Stage III colorectal cancer;
End stage renal disease

Introduction. Here we carried out a clinical observational study on patients with Stage III colorectal cancer concurrent with end-stage renal disease, aiming to identify factors that affect patient survival, and to observe if the prognostic benefit after postoperative adjuvant chemotherapy.
Method. This study is a retrospective cohort study. The inclusion criteria were patients newly diagnosed with Stage III colorectal cancer in a single medical center (Taichung Veterans General Hospital), and these patients concurrent with end-stage renal disease were receiving dialysis. The time of admission spanned from 2001 to 2019. The exclusion criteria were: if the colorectal cancer was in stage 1, 2, or 4, or the patient had other cancers, or the postoperative pathology report was neuroendocrine tumor (NET), or the dialysis method was peritoneal dialysis, or the patient had received a kidney transplant. Judging on survival, patients were divided into inter-group, a survival group and a non-survival group.
Results. For patients with Stage III colorectal cancer combined with end-stage renal disease, it appears that if the patients are at older age, right sided primary tumor, N2 stage, and positive tumor recurrence have a lower survival rate. Such differences were statistically significant. There are 18 patients died of other disease, complications such as aspiration pneumonia, espiratory failure such as ARDS, anastomotic leakage, etc. After adjuvant chemotherapy, there was no prognostic benefit between inter-group (survival versus non-survival), showed no significant difference.
Conclusion. For patients with Stage III colorectal cancer combined with end-stage renal disease, it appears that if the patients are at older age, the colorectal cancer is right sided primary tumor, N2 stage, and positive tumor recurrence, the survival is significantly poorer. There was no prognostic benefit after adjuvant chemotherapy. The risk of death from complications is relatively high due to multiple comorbidities.
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In Taiwan, about 90,000 patients with end-stage renal disease undergo routine dialysis, a percentage of the population being top of the world. At the same time, the incidence of colorectal cancer is about 70 cases per 100,000 people, according to the Taiwan Cancer Registry. This incidence rate has been the highest among all cancers for 14 consecutive years. Some studies have pointed out that end-stage renal

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disease likely increases the incidence of colorectal cancer,[1,2] but few studies have investigated the factors affecting survival in colorectal patients with end-stage renal disease. Among them, the stage III colorectal cancer patients account for about 25% of full-stage colorectal cancer cases. For Stage III colorectal cancer patients, chemotherapy is currently the standard treatment to improve survival after surgery. Chemicals used include the early fluorouracil (5-FU) in 1957, to later FOLFOX combined with 5-Fu + Oxaliplatin in 2003. However, for colorectal cancer patients suffering from end-stage renal disease, physician have to consider the absorption and response to the chemotherapy drugs or pharmacokinetic reactions.[3-5] It is also necessary to study whether chemotherapy produces adverse drug reactions[6] and increases the risk of death, leading to the clinical misunderstanding whether this special group of patients should receive adjuvant chemotherapy.

Our study objectives are as follows: (a) to carry out a clinical observational study of patients with Stage III colorectal cancer concurrent with end-stage renal disease, and (b) to identify factors affecting survival.

Methods

This study is a retrospective cohort study. The inclusion criteria were patients newly diagnosed of Stage III colorectal cancer at a single medical center (Taichung Veterans General Hospital), concurrent with end-stage renal disease receiving dialysis, collected by ICD 10 number of diagnosis from discharge note. Their time of admission spanned from 2001 to 2019. The exclusion criteria were: if the colorectal cancer was in stage 1, 2, or 4, or the patient had other cancers, or the postoperative pathology report was neuroendocrine tumor (NET), or the dialysis method was peritoneal dialysis, or the patient had received a kidney transplant. Judging on survival, patients were divided into inter-group, a survival group and a non-survival group. Postoperative adjuvant chemotherapy was defined as the treatment with oral or intravenous chemotherapy within 6 months after surgery for colorectal cancer. Recurrence was defined as post-operative imaging examinations, like computed tomography, that revealed distant metastases to liver, lung, peritoneum, or colonoscopy finding of local recurrence, or from tumor marker CEA, though high CEA alone did not mean recurrence. Overall survival (OS) was defined as the time from surgery to death. DOOD was defined as the cause of death was other diseases unrelated to colon cancer. The confirmation of survival condition are via discharge note, outpatient department note, phone confirmation and death certificate from government. The follow-up protocol is based on NCCN guideline.

Statistical analyses

All continuous variables were expressed as the mean ± SD and were compared with the Man-Whitney U test. Categorical variables, expressed as percentages, were analyzed with the Fisher's Exact Test. Variables tested in the three treatment groups were compared using the χ^2 test. A p-value of < 0.05 was considered statistically significant. A Cox Proportional Hazard Model was used for univariate and multivariate analyses of factors. The multivariate analysis was applied to factors shown to be significant in the univariate analysis. OS was estimated using the Kaplan-Meier Method and statistically evaluated by the Log-Rank Test. A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, Inc. Chicago, IL) for Windows, version 22.0.

Results

A total of 44 cases were analyzed in this study. Among these patients, their average age was 71.7 years; 25 were males and 19 were females; and their mean BMI was 24.57. The average tumor size was 45.43 mm, and the average number of positive lymph nodes was 15.82. Among these tumors, 5 cases were cut-end involved, 15 cases had emergency surgery, 9 cases were Stage 3A, 19 cases were Stage 3B, and 16 cases were Stage 3C. Pathology of tumors showed

poor differentiation in 8 cases, and moderate differentiation in 31 cases. There were 10 recurrences and 12 survived. The median follow up time was 29.5 months. The median disease free survival (DFS) was 2.17 years, and the median overall survival (OS) was 1.58 years (Table 1).

Up to now, the 3-year OS rate was 30.3%, and the median survival was 1.58 ± 0.42 years (Fig. 1). The 3-year OS excluding DOOD rate was 61.7%, and the median survival was 7.16 ± 1.86 years (Fig. 2).

Judging on survival, patients were divided into inter-group, a survival group and a non-survival group. A significant inter-group difference was found in mean age (p = 0.012) (survival group 66.83 years versus non-survival group 73.53 years). There was a significant difference in terms of tumor sidedness (p = 0.025), with the survival group involving more on the left side. A significant inter-group difference was found in pathological N stage (p = 0.034): survival group,

Table 1. Participants' characteristics

Total	44
Age	71.7 ± 10.52
Gender	
Male	25 (56.8%)
Female	19 (43.2%)
BMI	24.57 ± 4.73
Tumor size (mm)	45.43 ± 23.62
Harvest lymph nodes number (N)	28.66 ± 23.56
Positive lymph nodes number (N+)	15.82 ± 30.23
Cut end involved (Y/N)	
N	39 (88.6%)
Y	5 (11.4%)
Emergent operation (Y/N)	
N	29 (65.9%)
Y	15 (34.1%)
Regimen of adjuvant chemotherapy	
FOLFOX	8 (18.2%)
UFUR + XELODA	14 (31.8%)
Nil	22 (50%)
Stage	
3A	9 (20.4%)
3B	19 (43.2%)
3C	16 (36.4%)
Differentiation	
Moderate	31 (79.5%)
Poor	8 (20.5%)
Recurrence (Y/N)	
N	34 (77.3%)
Y	10 (22.7%)
Survival (Y/N)	
N	32 (72.7%)
Y	12 (27.3%)
DFS = date of 1st recurrence – date of OP	2.17 ± 2.69
OS = date of last contact – date of OP	2.45 ± 2.72

Mean ± standard deviation.

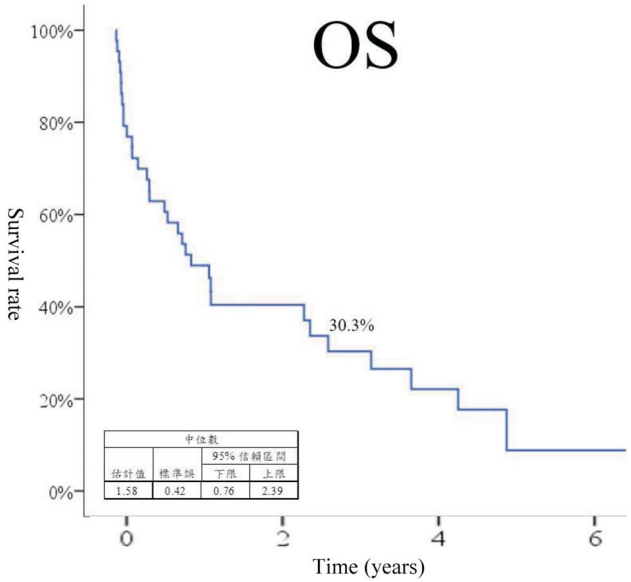

Fig. 1. 3-year OS rate was 30.3%, and the median survival was 1.58 ± 0.42 years.

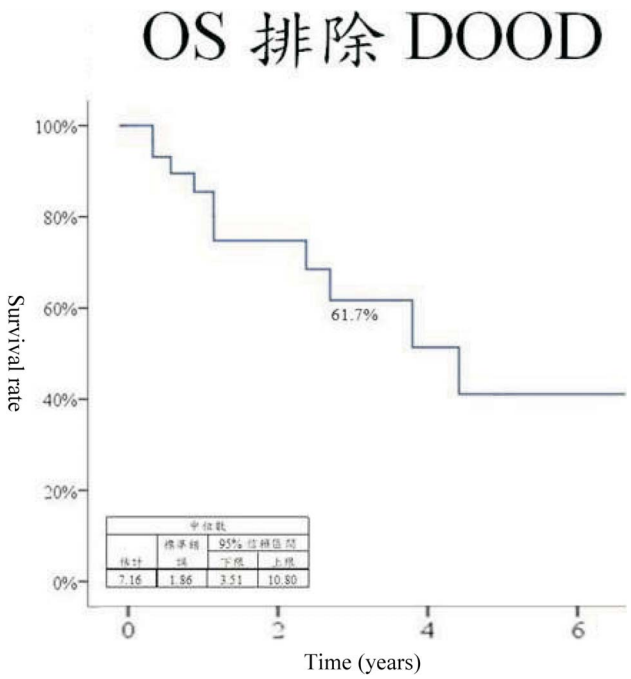

Fig. 2. The 3-year OS excluding DOOD rate was 61.7%, and the median survival was 7.16 ± 1.86 years.

N1 75%, N2 16.7%; non-survival group, N1 46.9%, N2 53.1%. There was also a significant difference (p = 0.041) in terms of recurrence (from post-surgery to the present). There was no case of recurrence in the survival group, in contrast with 10 cases of recurrence in the non-survival group (accounting for 31.3% of the non-survival group and 22.72% of all cases) (Table 2).

No significant inter-group difference was found in the analyses of other factors like BMI, gender, the location of the primary tumor in the large intestine or the rectum, pathological T stage, pathological stage, with or without cut-end involvement, emergency or non-emergency surgery, with or without radiation therapy, normality of CEA (3 patients in survival group weren't collected with serum CEA and respectively, 12 patients in non-survival group weren't collected with serum CEA). After adjuvant chemotherapy, there was no prognostic benefit between inter-group, also showed no significant difference (Table 2).

There were 14 patient died of tumor related factors, and 18 patients died of other disease (Table 2). Causes for the non-survival group in 18 cases (Table 3) included aspiration pneumonia, respiratory failure such as ARDS, anastomotic leakage, septic shock, liver failure, heart failure, ischemic stroke, and hemorrhage. Simultaneous respiratory failure, liver failure, and septic shock accounted for one case; aspiration pneumonia combined with septic shock (cholangitis) accounted for one case; aspiration pneumonia, liver failure, and bleeding (suspected UGI bleeding) accounted for one case.

Discussion

At present, studies across different countries have discussed the prognosis of colorectal cancer patients with end-stage renal disease dialysis. End-stage renal disease dialysis is associated with a worse overall prognosis, higher mortality and morbidity, and greater chances of reintubation and sepsis.[11,12] However, in patients with Stage III colorectal cancer and dialysis with end-stage renal disease, the factors that affect survival and related prognostic factors are rarely discussed.

In Taiwan, patients with ESRD who under peritoneal dialysis have relatively lower population when comparing to the population of hemodialysis. In this study we exclude the colorectal patient with peritoneal dialysis in our study. Few patients in Taiwan are able to receive kidney transplants, so we also exclude the colorectal patient with ESRD who are received kidney transplants. This study, therefore, aimed to explore the treatment of patients with Stage III colorectal cancer concurrent with end-stage renal disease.

It was found in the MOSAIC trial that if Stage III colorectal cancer patients with postoperative adjuvant chemotherapy with 5-Fu have a 4% higher recurrence risk compared with those who received adjuvant chemotherapy with FOLFOX.[7,8] Our study found there was no significant difference in prognosis with or without postoperative adjuvant chemotherapy. Colorectal cancer patients with end-stage renal disease have many comorbidities. In the event of postoperative complications, like aspiration pneumonia, or anastomotic leakage, chances of death are higher from non-cancer factors (DOOD). In fact, we found 18 out of 32 deaths of our patients were due to non-cancer causes. Therefore, when caring for patients in this group it is necessary to pay greater attention to comorbidity.

In terms of pharmacokinetics, the study of Danping Wang et al.[5] pointed out that the metabolism of 5-FU is mostly through hepatic circulation, only 10% is metabolized in the kidney. Platinum is metabolized almost entirely in the kidney. The concentration of injected platinum shows a bimodal curve. If dialysis is started ~2 hours after injection, platinum will reach its lowest level at the end of dialysis, and then be released from body tissues into the blood. The highest concentration of platinum reached is 85 mg/m^2, which does not require dose reduction and has no adverse reaction. However, the time before and after chemotherapy needs to be extended to 3 weeks. The findings of Yoshiaki Nagatani et al. and Takahiro Horimatsu et al. are consistent with those of Danping Wang et al. it is noteworthy that patients with MSI-H/dMMR (accounting for 10% of Stage III CRC) have worse prognosis when using fluorouracil only chemotherapy.[9,10]

The limitation of this study is that this is a retro-

Table 2. Results between survival group versus non-survival group

	Survival (Y/N)		*p* value
	Y	N	
Age	66.83 ± 6.87	73.53 ± 11.15	0.012
BMI	24.80 ± 4.77	24.47 ± 4.80	0.964
Gender (%)			0.507
Male	8 (66.7)	17 (53.1)	
Female	4 (33.3)	15 (46.9)	
Primary tumor (%)			0.183
Rectum	7 (58.3)	11 (34.4)	
Colon	5 (41.7)	21 (65.6)	
Primary tumor (%)			0.025
Appendix	0 (0)	1 (3.1)	
L't colon	12 (100)	20 (62.5)	
R't colon	0 (0)	11 (34.4)	
Pathological T stage (%)			0.687
1 + 2 + 3	9 (75)	26 (81.3)	
4	3 (25)	6 (18.8)	
Pathological N stage (%)			0.034
1	10 (83.3)	15 (46.9)	
2	2 (16.7)	17 (53.1)	
Stage (%)			0.344
3A	4 (33.3)	5 (45.6)	
3B	5 (41.7)	14 (43.8)	
3C	3 (25)	13 (40.6)	
Cut end involved (Y/N) (%)			1.000
N	11 (91.7)	28 (87.5)	
Y	1 (8.3)	4 (12.5)	
ER OP (Y/N) (%)			0.171
N	10 (83.3)	19 (59.4)	
Y	2 (16.7)	13 (40.6)	
Radiotherapy (%)			1.000
N	10 (83.3)	27 (84.4)	
Y	2 (16.7)	5 (15.6)	
CEA in normal range (%)			0.508
Not collected	3 (25)	12 (37.5)	
N	5 (41.7)	15 (46.9)	
Y	4 (33.3)	5 (15.6)	
Group (%)			0.231
FOLFOX	4 (33.3)	4 (12.5)	
UFUR + XELODA	4 (33.3)	10 (31.3)	
nil	4 (33.3)	18 (56.3)	
Adjuvant C/T (%)			0.487
N	3 (25)	13 (40.6)	
Y	9 (75)	19 (59.4)	
Recurrence (Y/N) (%)			0.041
N	12 (100)	22 (68.8)	
Y	0 (66.7)	10 (31.3)	
DOOD (Died of other disease) (%)			
N	12 (100)	14 (43.8)	
Y	0 (0)	18 (56.2)	
Differentiation (%)			0.653
Moderate	9 (90)	22 (75.9)	
Poor	1 (10)	7 (24.1)	

Mann-Whitney U test. Mean ± standard deviation. Fisher's exact test. Pearson's chi-square test.

Table 3. Non-cancer-related death causes

Other disease	N	Cause	N
Respiratory failure (%)	9/23 (39.1)	Aspiration pneumonia	6/23 (26.08)
		ARDS	1/23 (4.34)
		Other	2/23 (8.69)
Septic shock (%)	8/23 (34.78)	Anastomotic leakage	3/23 (13.04)
		Small bowel leakage	1/23 (4.34)
		Cholecystitis	2/23 (8.69)
		Cholangitis	1/23 (4.34)
		Other	1/23 (4.34)
Liver failure (%)	2/23 (8.69)		
Hypovolemic shock (%)	2/23 (8.69)	R't bronchus hemorrhage	1/23 (4.34)
		Suspected UGI bleeding	1/23 (4.34)
Ischemic stroke (%)	1/23 (4.34)		
Cardiogenic shock (%)	1/23 (4.34)		

spective study with a small number of cases. In addition, patients who completed adjuvant chemotherapy after surgery was small in number, making it difficult to determine with confidence benefits from postoperative adjuvant chemotherapy. This case study has been combined with other hospitals and medical centers in Taiwan to obtain a larger sample size, the clinical evidence will be much stronger.

Conclusion

From the clinical evidence of this study, for patients with Stage III colorectal cancer combined with end-stage renal disease, it appears that if the patients are at older age, the colorectal cancer is right sided primary tumor, N2 stage, and positive tumor recurrence, the survival is significantly poorer. But there was no prognostic benefit after adjuvant chemotherapy, due to patients who completed adjuvant chemotherapy after surgery was small in number, making it difficult to determine with confidence benefits from postoperative adjuvant chemotherapy. The risk of death from complications is relatively high due to multiple comorbidities. We recommend that patient care after surgery should be tailored and individualized to improve outcomes.

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原　著

大腸直腸癌第三期併末期腎臟病之臨床觀察性研究

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目的　本篇研究想探討大腸直腸癌第三期的患者，若同時併有末期腎臟病，嘗試找出影響存活的因子，並分析患者術後輔助化療是否影響預後的臨床觀察性研究。

方法　本篇研究是一篇 Retrospective，Cohort study。納入標準為單一醫學中心，收案時間從西元 2001 年至 2022 年，新診斷的第三期大腸直腸癌，且合併有末期腎臟病接受洗腎治療。

結果　顯著差異的項目為非癌症相關 (因其他因素) 導致病人死亡，$p < 0.0001$。

結論　患者屬於高齡，sidedness 位於 Left colon，pathological N2 stage 的占比較多，腫瘤有復發者或因其他因素死亡，存活率皆較低並有統計上顯著差異。

關鍵詞　第三期大腸直腸癌、末期腎臟病。