

Treatment efficacy and prognosis analysis in locally advanced or metastatic colorectal cancer patients with hydronephrosis

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Abstract. The effect of hydronephrosis, a common complication of metastatic colorectal cancer (CRC), on the treatment outcome and prognosis of locally advanced or metastatic CRC remains to be elucidated. The present study investigated the clinical characteristics, outcomes, and prognoses of patients with locally advanced or metastatic colorectal cancer (CRC) with hydronephrosis. Clinical data of patients with locally advanced or metastatic CRC who were attending Peking University Shenzhen Hospital and Shenzhen Cancer Hospital between January 2016 and December 2020 were retrospectively collected. A total of 52 patients with hydronephrosis based on CT or MRI findings were selected, and their clinical characteristics, treatment outcomes, and survival times were analyzed. Of the 52 patients, 33 were male (63.5%), and the median age was 49 years (range, 31-76 years). A total of 15 (28.8%) patients with CRC had synchronous hydronephrosis and the remaining

37 patients had metachronous hydronephrosis. Ureters were either compressed by peritoneal or abdominal cavity metastatic lymph nodes in 34 cases (65.4%) or by direct tumor invasion in 18 cases (34.6%). However, objective response rate (ORR) was higher in the group in which ureters were compressed by peritoneal or abdominal cavity metastatic lymph nodes; ORR, disease control rate and median progression-free survival (PFS) between the two groups were not statistically different. ($P>0.05$). The median survival period was only 27.0 months (95% CI, 20.549-33.451) in patients complicated with malignant hydronephrosis. Univariate and multivariate analyses showed that CA19-9 might be a prognostic factor for locally advanced and metastatic CRC patients with hydronephrosis. Metachronous metastatic CRC has a high incidence rate of complicated hydronephrosis. Targeted drugs in combination with chemotherapy improve the treatment efficacy and prognosis of patients. Notably, the present study found that CA19-9 level might be a prognostic factor in CRC patients with hydronephrosis.

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Introduction

According to the global cancer incidence and mortality statistics from the International Agency for Research on Cancer, 19.3 million new cases of cancer were estimated worldwide in 2020, among which colorectal cancer (CRC) is the third most common cancer and the second leading cause of mortality (1). In China, the incidence of CRC is increasing annually, causing 560,000 new cases and 290,000 succumbed in 2020. China is now the country with the highest morbidity worldwide (1). In recent years, the prognosis of CRC has improved significantly due to the progress in treatment strategies. In a study, it was found that the 5-year survival rate of patients with early CRC was ~90%, while it was only 14% in metastatic CRC patients (2). The majority of CRC patients are diagnosed with locally advanced or distant metastasis. A previous study has shown that postoperative recurrence during the 5-year follow-up was detected in ~50% of stage III CRC patients, while the 5-year postoperative

recurrence rate was only ~12-38% in stage II CRC patients. With the advancement of precision medicine, the mortality rate of CRC has decreased over the past few years. However, some patients, when first diagnosed, are already at stage T4 or have peritoneal metastasis, whose prognosis is poor. Even after neoadjuvant radiotherapy and total mesorectal excision surgery, there is still a 4-10% local recurrence rate for rectal cancer, and the prognosis for these patients is poor (3). Zhang *et al* (4) showed that among 148 patients who received adjuvant chemotherapy or radiotherapy postoperatively, 13 patients developed hydronephrosis, of which five were considered to be caused by benign factors (e.g., surgical or radiotherapy factors), and eight patients were diagnosed with recurrent metastasis. The pelvic cavity is the most common site of recurrence of peritoneal or abdominal lymph node metastasis (5). The tumor mass can obstruct the upper urinary tract via compression or direct invasion of the ureters, causing hydronephrosis without any symptoms or manifesting as low back pain, renal failure, or urinary tract infection, which can be diagnosed based on computed tomography (CT), magnetic resonance imaging (MRI) or ultrasound (5). Using CT scans, Brown *et al* (6) found that a peritoneal centred focal tumor mass was the most common cause of postoperative hydronephrosis, especially in patients with R1 or R2 resection, or in those at stage pT4 with peritoneal or adjacent organ invasion. The median survival period and 1-year mortality rate in CRC patients with hydronephrosis were only 6 months and 62%, respectively. Larsen *et al* (7) reported that surgical resection in hydronephrotic CRC patients reduces the risk of recurrence, which is a prognostic factor for CRC recurrence. Malignant obstruction and concomitant hydronephrosis are common complications of metastatic CRC. Percutaneous nephrostomy (PCN) and antegrade stent implantation are commonly used to relieve obstruction, improve the patients' quality of life, and simultaneously create opportunities for active anti-cancer treatment. Sugimoto *et al* (8) reported that PCN or stent implantation relieves obstruction in metastatic breast cancer patients with hydronephrosis, delays renal failure progression, reduces the risk of infection, eases cancer pain and improves the patients' prognosis and quality of life. Similarly, Duan *et al* (9) found that PCN combined with stent implantation is effective in cervical cancer patients with hydronephrosis, urinary tract infection and renal insufficiency, which alleviates patient discomfort and creates an opportunity for anti-tumor therapy. Despite the widespread clinical application of targeted drugs in metastatic CRC and the development of techniques for obstruction relief, the effect of hydronephrosis on the outcome and prognosis of locally advanced or metastatic CRC remains unclear. The present study discussed the impact of hydronephrosis on the treatment outcome and prognosis of locally advanced or metastatic CRC. It retrospectively analyzed the clinical data of patients with ureterectasia and hydronephrosis, summarized their clinical characteristics and investigated the therapeutic effect and prognosis to provide a reference for better understanding of locally advanced or metastatic CRC patients with complicated malignant hydronephrosis.

Materials and methods

Patients and clinical data. The present study retrospectively analyzed the clinical data of patients with hydronephrosis at

Peking University Shenzhen Hospital and Shenzhen Cancer Hospital between January 2016 and December 2020. Written informed consent for use of their data for research purposes was signed by the patients or their legal guardians prior to treatment. The treatment and its outcome were assessed according to the institutional guidelines. Patient information and clinicopathological features were collected from the electronic medical records of the clinicians. The inclusion criteria were: i) Pathologically confirmed colorectal adenoma; ii) newly diagnosed locally advanced or metastatic CRC patients; iii) CT or MRI confirming CRC patients complicated by hydronephrosis; iv) Eastern Cooperative Oncology Group (ECOG) Performance Status 0-2; and v) expected survival period >3 months. The exclusion criteria were: i) Ureterectasia or hydronephrosis caused by benign factors such as urinary tract stones, trauma, surgery, or radiotherapy-induced injury; and ii) ureterectasia or hydronephrosis caused by primary urinary tract disease. These patients were observed until the time of mortality or the end of follow-up (August 1st, 2021), whichever came first. The dates of mortality were obtained via telephone from the hospital's follow-up centre. The research program and the study protocol were approved by the ethics committee of Peking University Shenzhen Hospital and Shenzhen Cancer Hospital.

Treatment. PCN or ureteral stent implantation was performed in patients with dysuria and/or renal dysfunction, which were palliative or radical. Treatment options were made according to rat sarcoma viral oncogene homolog (RAS) and B-Raf murine sarcoma viral oncogene homolog B1 (BRAF) mutational status, primary anatomic site of CRC, and ECOG score. Regimens included mFOLFOX6 [oxaliplatin 85 mg/m², IVGTT 2 h, d1; calcium folinate 400 mg/m², IVGTT 2 h, d1; fluorouracil, 400 mg/m², iv, d1, 1,200 mg/m², d1, 2, IVGTT (total 2,400 mg/m², 48 h), q2w], FOLFIRI [irinotecan 180 mg/m², IVGTT 90 min, d1; calcium folinate 400 mg/m², IVGTT 2 h, d1; fluorouracil, 400 mg/m², iv, d1, 1,200 mg/m², d1, 2, IVGTT (total 2,400 mg/m², 48 h), q2w], Bevacizumab 5 mg/kg, IVGTT 30-60 min (first administration time >90 min), d1, q2w, and Cetuximab 500 mg/m², IVGTT >60 min (first administration time >120 min), d1, q2w]. Radiation dose: Planning target volume, 40 Gy. CT or MRI was performed every two cycles.

Evaluation methods. The tumor response throughout the whole cycle was categorized into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The response was evaluated according to the Response Evaluation Criteria in Solid Tumors 1.1 (10). The objective response rate (ORR) was defined as the percentage of patients who achieved a CR or PR, and the disease control rate (DCR) was defined as the percentage of patients with CR, PR, or SD. Overall survival (OS) was defined as the duration from the time of treatment to the time of death. Progression-free survival (PFS) was defined as the time from treatment to the first occurrence of PD or death. Normal range for CA19-9 is 0-43 U/ml, CA19-9 >43 U/ml was defined as CA19-9 elevation.

Statistical analysis. Statistical analysis was performed using SPSS version 20.0 (IBM Corp.). The χ^2 test was used to compare categorical data. Kaplan-Meier test and Cox proportional

hazards regression model were used for survival analysis and univariable and multivariable analyses. Differences between the groups were compared using the log-rank test. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Clinical features of patients. A total of 52 patients, including 33 males (63.5%) with locally advanced or metastatic CRC with hydronephrosis, were selected. The median age was 49 years (range, 31-76 years). Tumors originating from the rectum were more commonly (36.5%) complicated with hydronephrosis. A total of 15 patients (28.8%) had synchronous hydronephrosis when diagnosed with CRC. In contrast, metachronous hydronephrosis at post-radical surgery recurrence was more common, accounting for 37 cases (71.2%). Regarding the causes of hydronephrosis, 34 cases were due to ureteral compression by peritoneal or lymph node metastasis, and 18 cases (34.6%) were caused by direct tumor invasion. A total of 36 cases (69.2%) with hydronephrosis were unilateral, and 16 (30.8%) were bilateral. A total of 46 stage IV CRC patients (88.5%) had a higher risk of hydronephrosis. Among the 52 patients, 18 had renal dysfunction and eleven patients had a urinary tract infection (Table I).

Treatment efficacy. Of the 52 patients, 22 had accompanying hydronephrosis with preserved renal function, and 30 developed dysuria and/or renal function impairment, in which 28 patients underwent ureteral stent implantation and two underwent PCN. After the intervention, the renal injury or dysuria was relieved. A total of four patients with stage III concurrent hydronephrosis were treated surgically (one R0 resection, three R1 resections). A total of two postoperative rectal cancer patients received palliative radiotherapy for relapse lesions due to cancer pain, which was relieved after the treatment. All patients received chemotherapy in combination with targeted therapy as first-line treatment.

In 34 patients, the ureters were compressed by peritoneal or lymph node metastasis. A total of nine had PR, 16 had SD and the ORR and DCR were 26.5 and 73.5%, respectively. There were 18 cases with direct tumor invasion of the ureters, where two had PR and 10 had SD. The ORR and DCR were 11.1 and 66.7%, respectively. ORR was higher in the group in which ureters were compressed by peritoneal or lymph node metastasis, but there was no statistically significant difference in the DCR between the two groups. ($P > 0.05$; Table II). The median PFS was eight months (95% CI, 4.654-11.346) and nine months (95% CI, 7.898-10.102), respectively, in the two groups receiving first-line treatment and there was no significant difference ($P > 0.05$; Table II).

Of the 15 patients complicated with synchronous hydronephrosis at the first diagnosis, two had PR and eight had SD and the ORR and DCR were 13.3 and 66.7%, respectively. Of the total 37 patients with metachronous hydronephrosis, nine had PR and 18 had SD. The ORR and DCR were 24.3 and 72.9%, respectively. There was no statistically significant difference in ORR between these two groups, although the ORR was higher in the metachronous hydronephrosis group ($P > 0.05$; Table II). The median PFS was six months (95% CI, 5.241-6.759) and nine months (95% CI, 8.187-9.813), respectively, in the two

Table I. Clinical features of 52 colorectal cancer patients with hydronephrosis.

Clinicopathological feature	Cases (n)	Percentages (%)
Median age (years)	49 (31-76)	
Sex		
Male	33	63.5
Female	19	36.5
Primary tumour site		
Left colon	15	28.9
Right colon	18	34.6
Rectum	19	36.5
Time of complicated hydronephrosis		
Synchronous	15	28.8
Metachronous	37	71.2
Pathological differentiation		
Poorly differentiated	8	15.4
Moderately differentiated	31	59.6
Well differentiated	13	25.0
CEA level		
Normal	26	50.0
Elevated	24	46.2
Unclear	2	3.8
CA19-9 level		
Normal	23	44.2
Elevated	27	51.9
Unclear	2	3.8
Causes of hydronephrosis		
Peritoneal or abdominal cavity		
Lymph node compression	34	65.4
Direct tumour invasion	18	34.6
Involved ureters		
Left side	22	42.3
Right side	14	26.9
Both sides	16	30.8
Stages		
III	6	11.5
IV	46	88.5
RAS status		
Wild-type	22	42.3
Mutated	30	57.7
BRAF status		
Wild-type	47	90.4
Mutated	5	9.60
Regimen		
Bevacizumab + mFOLFOX6/ FOLFIRI	27	51.9
Cetuximab + mFOLFOX6/ FOLFIRI	25	48.1

CEA, carcinoembryonic antigen.

Table II. Treatment outcome of patients receiving first-line chemotherapy.

Characteristics of Patients	Cases (n)	PR (n)	SD (n)	DCR (%)	χ^2	P-value	Median PFS (months)	95% CI	χ^2	P-value
Ureters compressed by peritoneal or metastatic lymph nodes	34	9	16	73.5	0.270	0.749	8	4.654-11.346	0.107	0.743
Ureters compressed by direct tumor invasion	18	2	10	66.7			9	7.898-10.102		
Complicated hydronephrosis at first diagnosis	15	2	8	66.7	2.294	0.149	6	5.241-6.759	0.315	0.575
Hydronephrosis at postoperative recurrence	37	9		72.9			9	8.187-9.813		

DCR, disease control rate; PFS, progression-free survival; PR, partial response; SD, stable disease.

groups after first-line treatment and there was no significant difference ($P>0.05$; Table II).

Survival time and influencing factor analysis. A total of three out of 52 patients were lost to follow-up and the mean follow-up period of the remaining 49 patients was 36 months (range, 5-59 months). Only 15 patients survived, while the rest succumbed. The median survival time of patients with concurrent hydronephrosis was 27.0 months (95% CI, 20.549-33.451). Univariate analysis showed that CA19-9 elevation affected the OS of patients. ($P<0.05$; Table III). In Cox proportional hazards regression model analysis, CA19-9 elevation affected the survival time of patients with hydronephrosis ($P<0.05$; Table III).

Discussion

Hydronephrosis is one of the commonest complications of locally advanced or recurrent CRC. In the present study, excluding pelvic effusion due to benign factors, the incidence of CRC with primary concurrent and metachronous hydronephrosis in patients with locally advanced or metastatic CRC was 28.8 and 71.2%, respectively. Rectal cancer with hydronephrosis usually has a higher risk of combined hydronephrosis, which may be related to the anatomical site of the rectum. Pelvic recurrence was more likely to lead to ureteral obstruction and hydronephrosis. CRC patients with hydronephrosis may present with no obvious systemic signs or symptoms, but some may experience low back pain or symptoms of urinary tract infection, and renal function impairment may be indicated by blood tests. Hydronephrosis can occur bilaterally or unilaterally, which is mostly seen in young patients with late tumor stage and large recurrent lesions (11). Clinical diagnosis of CRC with hydronephrosis is mainly based on CT or MRI. Local soft tissue masses in the abdominal cavity, local lymph node metastasis, large omental thickening, or nodules, and periureteral soft tissue thickening are usually seen on CT (12).

In the present study, 52 CRC patients with hydronephrosis with a median age of 49 years were screened by CT or MR. Of these, 65.4% of patients had ureteral compression due to

peritoneal or lymph node metastasis, while 34.6% were due to direct tumor invasion. A previous report has shown that hydronephrosis was more likely to occur in patients with recurrent CRC (6). After active treatment, the patients' obstructive symptoms were relieved and they all received first-line palliative therapy, which improved their prognosis and quality of life, creating suitable conditions for antineoplastic therapy.

There is limited evidence or data on locally advanced or metastatic CRC patients with hydronephrosis receiving palliative care. Aghalarov *et al* (13) reported a case of postoperative recurrence of rectal cancer with urinary tract infection and right-sided hydronephrosis caused by a ureteral mass, who underwent laparoscopic right nephroureterectomy. The resected mass was pathologically confirmed to originate from rectal cancer. No tumor recurrence was detected on postoperative follow-up after 6 months and the patient was doing well. Sato *et al* (14) reported a CRC patient who developed metachronous metastasis of the liver and lymph nodes at the root of the inferior mesenteric artery, which resulted from the invasion by lymph node metastasis at the root of the inferior mesenteric artery. The patient underwent laparoscopic partial resection of segment 5 of the liver, excision of the lymph nodes at the root of the inferior mesenteric artery (combined resection of the left ureter), bilateral ureteral stent placement and left ureteral reconstruction. In the present study, four patients underwent surgical treatment; one underwent R0 resection, and no recurrence was detected at 2 years postoperative follow-up, while the other three patients who underwent R1 resection had a recurrence. Larsen *et al* (7) reported that 22% of CRC patients with local recurrence and hydronephrosis could undergo R0 resection, and the prognosis of these patients improved accordingly. However, an R0 resection rate of only 10% was reported by Lev-Chelouche *et al* (15) in such patients, and the prognosis of patients who underwent R0 resection was similar to that of patients without surgical resection or those who received palliative surgery. Cheng *et al* (16) concluded that radical surgery did not improve the prognosis of patients with locally recurrent rectal cancer with hydronephrosis. Therefore, the benefit of surgery in patients with locally advanced or metastatic CRC with hydronephrosis is

Table III. Influencing factors on survival time of patients.

Clinicopathological features	Log Rank univariable analysis		COX multivariable regression analysis		
	χ^2	P-value	HR	95% CI	P-value
Vascular tumor thrombus	3.414	0.065	0.407	0.018-0.912	0.029
CA19-9 elevation	5.783	0.016	0.396	0.186-0.841	0.016
Involved ureteral sites	5.542	0.063			0.05

controversial. Hamanaka *et al* (17) reported a recurrent rectal cancer patient with concurrent hydronephrosis who underwent radiofrequency ablation for recurrent pelvic lesions, which relieved pain. Yoshitomi *et al* (18) reported that for patients with locally advanced colon cancer who were resistant to conventional preoperative chemotherapy, preoperative chemotherapy and radiotherapy might be effective. In the present study, two patients with recurrent rectal cancer received palliative radiotherapy for cancer pain, which was relieved after treatment, indicating that palliative radiotherapy could be considered for patients with concomitant cancer pain. Studies on the application of chemotherapy combined with targeted therapy in locally advanced or metastatic CRC with hydronephrosis are limited. Kagawa *et al* (19) reported an improvement in the prognosis of a metastatic cecum cancer patient with hydronephrosis who underwent resection surgery for the primary lesion and underwent treatment with systemic chemotherapy, bevacizumab, and cetuximab. Sakisaka *et al* (20) reported a patient with metastatic colon cancer with a PS score of 4, which was complicated with hydronephrosis, acute cholecystitis, and obstructive jaundice before chemotherapy. The patient's condition improved after cetuximab monotherapy. He received mFOLFOX7 for 6 months and was evaluated for PR according to the CT scan. Kuwabara *et al* (21) reported a case of bilateral upper urinary tract obstruction who received a modified chemotherapy regimen of oxaliplatin and fluorouracil in combination with bevacizumab following percutaneous nephrostomy, with improved renal function and a chance of long-term survival. It can be seen from these studies that locally advanced or metastatic CRC patients with hydronephrosis can benefit from conventional therapeutic agents such as chemotherapeutic agents and targeted agents, which are safe. All patients in the present study received first-line mFOLFOX6 or FOLFIRI regimen combined with bevacizumab or cetuximab according to the patients' primary tumor site, RAS/BRAF status, and ECOG score. The disease control rates in both groups were 66.7 and 72.9%, respectively.

Although the ORR was higher in the group with ureters compressed by peritoneal or abdominal cavity metastatic lymph nodes and the group with metachronous hydronephrosis, which were 26.5 and 24.3%, respectively, there were no statistically significant differences between the groups. In FIRE-3 and CALGB/SWOG 80405 clinical studies, bevacizumab or cetuximab in combination with mFOLFOX6 or FOLFIRI regimens for patients with RAS wild-type metastatic CRC had an ORR of ~55.6-72.1% (22), which was significantly better than the results of the present study. It is possible that this treatment modality has limited efficacy in locally advanced

patients or metastatic CRC patients with hydronephrosis, or it might also be related to the difficulty of imaging to accurately assess the efficacy of peritoneal metastases. Xiong *et al* (23) reported that the ORR and DCR of bevacizumab in combination with chemotherapy for metastatic CRC were 48.89 and 86.67%, respectively, which were also higher than the results of the present study. Thus, surgery or radiotherapy could improve the quality of life and prognosis of a subset of highly selected metastatic CRC patients with hydronephrosis. Conventional targeted therapy combined with chemotherapeutic agents could increase the treatment effectiveness and improve the prognosis of patients, but differences remain when compared with patients with metastatic CRC without hydronephrosis. Therefore, more evidence-based data are needed.

CRC with hydronephrosis has its own biological behavior. Westberg *et al* (24) found that locally recurrent rectal cancer patients with hydronephrosis had a worse prognosis than those without hydronephrosis. Additionally, Henry *et al* (25) found that pelvic recurrent CRC patients with hydronephrosis had poorer OS, PFS and DCR. The median survival period of patients in this study was 27 months, which was an improvement on our results because both recurrent and locally advanced patients were included in this study. Tanaka *et al* (26) reported that in gastrointestinal malignancies with hydronephrosis, the median survival period was only nine months, which was significantly different from the results of the present study, which might be related to patient selection and treatment difference. However, the OS of metastatic CRC patients in the CALGB/SWOG 80405 study was ≤ 35 months (22), which exceeded the results of the present study. Similarly, some studies have shown that carcinoembryonic antigen (CEA) level, unilateral or bilateral ureteral involvement, ureteral stenting, or PCN had no effect on survival (15,27), and the same result was obtained in the present study. The present study showed that CA19-9 level might be a prognostic factor in patients with locally advanced or metastatic CRC with hydronephrosis. However, the number of cases enrolled in the present study was relatively small, which limits the ability to fully explain the research results. A previous study indicated that urological disorders such as obstruction of the ureteropelvic junction or ureteral stones were significantly linked to elevated serum and urinary CA19-9 levels, and CA19-9 expression in renal tubular epithelial cells increased as obstructive uropathy developed (28). In contrast, the elevation of CA19-9 levels might affect patient survival. However, it might be related to urinary tract infection or renal tubular epithelial damage after urinary tract obstruction, and it deserves further study.

In conclusion, the incidence of metachronous metastatic CRC with hydronephrosis was high, especially in patients with rectal cancer. PCN or ureteral stenting not only improved the quality of life of patients but also provided more treatment opportunities for patients. Surgery and radiotherapy improve patient prognosis and quality of life. The use of targeted drugs in combination with chemotherapeutic agents is safe, which increases the efficiency of treatment and improves patient survival. CA19-9 might serve as a prognostic factor in CRC patients with hydronephrosis, and it might also be a predictor of urinary tract obstruction in CRC. Therefore, early detection and intervention of hydronephrosis is crucial in metastatic CRC patients. However, this study was retrospective and was limited due to the relatively small population size, which was insufficient to fully explore the results and more studies are needed to enrich the evidence.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

GT, BC and MZ were responsible for conception and design of the present study. SL and SW provided administrative support, study materials or patients. BC, MZ, TW, XW and YY collected and assembled data. GT, BC and MZ were responsible for data analysis and interpretation. All authors wrote the manuscript. GT and BC confirm the authenticity of all the raw data. All authors reviewed and approved the final manuscript.

Ethics approval and consent to participate

The research program and the study protocol were approved by the ethics committee of Peking University Shenzhen Hospital and Shenzhen Cancer Hospital. Written informed consent for use of their data for research purposes was signed by the patients or their legal guardians prior to treatment.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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