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TUMOUR-RELATED COMPLICATIONS IN PATIENTS WITH STAGE IV COLORECTAL CANCER TREATED WITH CHEMOTHERAPY WITHOUT PRIMARY TUMOR RESECTION

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ABSTRACT

Background: *Although the typical treatment of patients with stage IV colorectal cancer comprises removal of the primary tumor followed by chemotherapy, some studies suggest that in patients with limited symptoms, the first and only treatment should be chemotherapy.* ***Objectives:*** *To evaluate the complications related to the primary tumor in patients with stage IV colorectal cancer treated with chemotherapy without surgery.* ***Materials and methods:*** *This was a retrospective descriptive study, including 28 patients with stage IV colorectal cancer treated with chemotherapy without primary tumor resection.* ***Results:*** *The average age was 61.4 ± 10.7 years (range 30 - 83) and all of them had the performance status of 0-1. During follow-up, four (14.4%) patients experienced complications. Intestinal obstruction was the most common complication in 3 (10.7%) and there was one case of rectovaginal fistula. Emergency procedures were performed on these patients. The rate of complications was higher in patients with peritoneal metastases than in those without.* ***Conclusions:*** *The incidence of major intestinal complications in colorectal cancer patients with unresected metastases is low. Most patients with stage IV colorectal cancer benefit from chemotherapy rather than surgery.*

Keywords: *Colorectal cancer, chemotherapy, surgery, complications.*

I. INTRODUCTION

Colorectal cancer is one of the most common types of cancer in both sexes. About 20–25% of colorectal cancer patients have distant metastases at the time of diagnosis, and 80% of these patients have metastatic lesions that cannot be completely removed, limiting the possibility of surgery with curative intent [1-3]. The goal of treating stage IV colorectal cancer patients is to increase survival and alleviate symptoms, with chemotherapy as the main treatment. However, the benefits of surgical resection of the primary tumor in the setting of distant metastatic colorectal cancer are not well studied. Usually, the segment of the intestine containing the primary tumor can be removed before chemotherapy, regardless of the presence of tumor-related symptoms. The purpose of surgery in these cases is to relieve symptoms and prevent complications caused by the primary tumor that may occur in the future, such as intestinal perforation, intestinal obstruction, bleeding, and sometimes improved survival (although this benefit is not clear). However, patients may experience surgical complications, which can cause a delay in the use of systemic treatment, and in many cases, surgery is unnecessary because the tumor-related complications may not occur in the future. In recent years, the introduction of novel chemotherapy medications has raised the tumor response rate to chemotherapy by up to 50% and the mean survival time in these

patients by up to 20 months in prospective clinical studies [4, 5]. The increased effectiveness of chemotherapy has reduced the rate of primary tumor resection before chemotherapy in patients with distant metastatic colorectal cancer [6, 7]. The study was conducted with the purpose of surveying the rate and understanding some factors related to the occurrence of complications related to the primary tumor in patients with stage IV colorectal cancer receiving chemotherapy without surgical resection of the primary tumor, thereby identifying the group of patients who will benefit from prophylactic primary tumor resection.

II. MATERIALS AND METHODS

2.1. Materials

The study was conducted on patients with stage IV colorectal cancer treated with chemotherapy without primary tumor resection at Can Tho University of Medicine and Pharmacy Hospital.

- Inclusion criteria: The inclusion criteria were as follows: (1) Patients with stage IV colorectal cancer at the time of diagnosis. (2) Histopathology of the colorectal tumors were adenocarcinoma. (3) No evidence of bowel obstruction or perforation and no active bleeding requiring a transfusion

- Exclusion criteria: We excluded individuals in whom removal of the primary tumor was indicated for symptoms that could not be palliated with medication, as well as those patients who just needed palliative care. We also exclude patients with a history of primary tumor resection or bypass surgery.

2.2. Methods

- Study design: This was a retrospective descriptive study based on a prospectively maintained database, which includes all patients diagnosed and treated for colorectal cancer at the Oncology Department of Can Tho University of Medicine and Pharmacy Hospital.

- Study contents: General characteristics such as age, gender, symptoms for encounter, primary tumor location, tumor grade, number of metastatic sites, metastatic location, chemotherapy regimen, and tumor-related complications. We assessed the treatment response of our patients using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [8].

- Statistical analysis: Statistical analyses were performed using SPSS v 29.0. Category variables are expressed as frequencies and percentages and analyzed using the chi-square or Fisher exact tests. Continuous data are expressed as mean ± standard deviation. Statistical significance was defined as $P< 0.05$.

- Ethics approval: The study was conducted after approving the Ethics Committee of Biomedical Research of Can Tho University of Medicine and Pharmacy. Research subjects are informed, explained and agreed to voluntarily participate in the study. All personal information and illnesses are kept confidential through computerized encryption to ensure the privacy of study participants.

III. RESULTS

There were 28 patients with stage IV colorectal cancer treated with chemotherapy without primary tumor resection. The results were shown as follows.

Table 1. Baseline characteristics of patients

Characteristics		Number	Percentage (%)
Age (years)	< 50	4	14.3
	≥ 50	24	85.7
Sex	Male	15	53.6
	Female	13	46.4
PS	0	9	32.1
	1	19	67.9
Mean (± SD) age Age range (years)		61.4 ± 10.7 (30-83)	

In this study, the average age was 61.4 ± 10.7 years (range 30 - 83). The most common age group was ≥ 50 years (85.7%). All patients had the performance status of 0-1.

Table 2. Symptoms for hospitalization

Symptoms	Number	Percentage (%)
Abdominal pain	15	53.6
Rectal tenesmus	13	46.4
Bright red blood in stool	11	39.3
Weight loss	7	25.0
Screening colonoscopy	1	3.6

Abdominal pain was the most common symptom, with 53.6%. Followed by rectal tenesmus and bright red blood in stool (46.4% and 39.3%, respectively). Only one patient without any symptoms found a colorectal tumor accidentally during a screening colonoscopy.

Table 3. Tumor characteristics of patients

Characteristics		Number	Percentage (%)
Primary tumor location	Ascending colon	5	17.9
	Transverse colon	1	3.6
	Sigmoid	7	25.0
	Rectum	15	53.6
Tumor grade	Well differentiated	1	3.6
	Moderately differentiated	26	92.9
	Poorly differentiated	1	3.6
Number of metastatic site	One	16	59.1
	Two or more	12	42.9
Metastatic location	Liver	26	92.9
	Lung	11	39.3
	Supraclavicular lymph node	3	10.7
	Peritoneal	3	10.7
	Brain	1	3.6
	Adrenal gland	1	3.6

The most common tumor locations were the rectum and sigmoid colon in 15 (53.6%) and 7 (25%). Twenty-six (92.9%) patients had moderately differentiated tumors. Single-site distant spread occurred in 16 (59.1%) patients. The liver was the most common metastatic site, accounting for 92.9%, followed by the lung with 39.3%. The supraclavicular lymph node, peritoneal, brain, and adrenal gland were less common distant metastastic sites.

Table 4. Treatment and outcome characteristics of patients

Characteristics		Number	Percentage (%)
Chemotherapy regimen	CapeOx	11	39.3
	CapeOx plus Bevacizumab	17	60.7
Number of cycle	< 3	1	3.6
	≥ 3	27	96.4
RECIST 1.1	Partial Response	8	28.6
	Stable Disease	16	57.1
	Progressive Disease	2	7.1
	Not assessment	2	7.1
	Complete Response	0	0
Tumor-related complications	Intestinal obstruction	3	10.7
	Rectovaginal fistula	1	3.6

Bevacizumab, a monoclonal antibody medication, was combined with chemotherapy (CapeOx regimen: Oxaliplatin and Capecitabine) in 17 (60.7%) patients. Only one patient had less than three cycles of chemotherapy. The disease control rate was reported in 24 (85.7%) patients. Intestinal obstruction was the most common complication in 3 (10.7%) and there was one case of rectovaginal fistula. Surgery was performed in all cases with complications.

Table 5. Risk factors of tumor-related complications by univariate analysis

Category		Complication		*p*
		Yes	No	
Age (year)	< 50	1	3	0.5
	≥ 50	3	21	
Tumor location	Colon	1	10	0.9
	Rectum	3	14	
Multiple metastatic site	Yes	1	15	0.4
	No	3	9	
Peritoneal metastases	Yes	2	1	< 0.0001
	No	2	23	
Chemotherapy regimen	CapeOx	2	9	0.5
	CapeOx plus Bevacizumab	2	15	

Patients who had peritoneal metastases were more likely to have tumor-related complications compared with those without (66.7% vs 8%, p <0.0001).

IV. DISCUSSION

Colorectal cancer is the fifth most common cause of cancer death in Vietnam [9]. Maintaining quality of life is an important goal of therapy for people with stage IV colorectal cancer. The value of any treatment must be carefully assessed based on its effects on tumor-related symptoms and complications, as well as the potential negative effects of treatment on overall quality of life.

The standard treatment for colorectal cancer with unresectable metastases is to remove the primary tumor followed by chemotherapy. Although the procedure has no curative intent, it is nonetheless used in the vast majority of patients; its primary goal is to avoid complications associated with the primary tumor. Clancy *et al.* reported that 66.7% of patients underwent resection of the primary tumor [10]. In a recent review that analyzed

seventy-seven comparative studies with a total of more than 159,000 cases, 94,745 (59.2%) underwent primary tumor resection [11]. Currently, the NCCN guidelines also recommend surgery for stage IV colorectal cancer patients if they are at risk of tumor-related complications such as obstruction, bleeding, and perforation or if complete removal of all visible tumors is feasible [12]. However, some studies have reported an increasing trend toward nonoperative management, with up to 40% of patients undergoing upfront chemotherapy without surgery [13, 14]. The key advantage is the ability to start systemic treatment early and prevent delays caused by surgical intervention. Chemotherapy tends to be delayed by several weeks, particularly when postoperative complications occur. One potential disadvantage of this therapeutic strategy is the development of complications associated to the unresected primary tumor. In this regard, multiple studies have demonstrated that chemotherapy without surgery is associated with a low rate of major intestinal complications in patients with stage IV colorectal cancer. One study reported the incidence of peritonitis, fistula formation, and intestinal haemorrhage in the unresected group was 2.4%, 3.7%, and 3.7%, respectively. Intestinal obstruction affected only 13.4% of patients in the unresected group [15]. Cáceres *et al.* observed that the most serious complications, such as perforation or tumor necrosis with abcess formation, occurred in 4 (6.6%) cases, while intestinal obstruction affected 15 (24.6%) patients. The complications required surgical treatment in six cases [16]. In a case-matched study of 27 patients with asymptomatic colorectal cancer and irresectable synchronous liver metastases treated by chemotherapy without initial primary resection, Benoist *et al.* reported a tumor-related complications rate of 14.8% (4 patients experienced intestinal obstruction) [17]. One study using the new chemotherapy regimens showed that only 12 patients (14%) with major morbility related to intact primary tumor, and 10 of them required emergent surgery for primary tumor obstruction (8 cases), perforation (1 case), or abdominal pain (1 case) [18]. In our study, the rate of tumor-related complications among patients with stage IV colorectal cancer treated with chemotherapy without primary tumor resection was also low (14.4%). The most common complication was intestinal obstruction (10.7%), with one case of rectovaginal fistula. Surgery was required in all cases with complications. These results suggest that upfront chemotherapy without primary tumor resection may be a safe and effective option in appropriately selected patients. Surgery was undertaken in all cases with complications. The complications rate in our study is much lower than those in the literature because 27 (96.4%) patients get more than 3 cycles of chemotherapy (bevacizumab was combined in 17 cases), and this may result in better local tumor and distant metastasis control. This results suggest that upfront chemotherapy without primary tumor resection is a good option in patients with stage IV colorectal cancer.

Factors associated with tumor-related complications in patients with stage IV colorectal cancer have been extensively studied in the literature. However, the results are varied among studies. Tebbutt *et al.* showed that patients with younger age ($p = 0.002$) and peritoneal or omental disease ($p=0.007$) were more likely to experience intestinal obstruction. In this study, the author did not find a statistically significant association between the primary tumor location and the incidence of intestinal obstruction [15]. Cáceres *et al.* reported that there was no statistically significant difference in the rate of complications according to clinical characteristics, although this rate was twice as high in the group of patients who received an endoscopic stent compared to those who did not receive one initially [16]. The use of bevacizumab has been reported to be associated with

an increased risk of tumor perforation for patients with chemotherapy without surgery as the initial approach; the incidence was 1-2% in one prospective clinical trial [19]. In this study, we discovered that patients with peritoneal metastases had a higher risk of complications than those without ($p<0.0001$). However, we did not observe differences in the incidence of complications between patients who were administered bevacizumab and those without, while 24 (85.7%) patients had their disease well controlled. We believe our findings support systemic chemotherapy without surgery as the best treatment option for patients with stage IV colorectal cancer.

This study has several limitations. The sample size was small and we only analyzed the patients who received chemotherapy without surgery; we did not compare with patients with initial primary tumor resection.

V. CONCLUSION

Systemic therapy without colonic surgery had a low rate of tumor-related complications. Most patients with stage IV colorectal cancer benefit from chemotherapy rather than surgery.

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