Prognostic Implications of Primary Tumor Resection in Stage IVB Colorectal Cancer in Elderly Patients

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Purpose: The aim of this study was to identify prognostic factors in stage IVB colorectal cancer in elderly patients, focusing on the influence of treatment modalities, including palliative chemotherapy and primary tumor resection.
Methods: A cohort of 64 patients aged over 65 years who presented with stage IVB colorectal cancer at the Gangneung Asan Hospital between July 1, 2001, and December 31, 2009, was analyzed. Demographics, tumor location, tumor grade, performance status, levels of carcinoembryonic antigen (CEA), level of aspartate aminotransferase (AST), and distant metastatic site at diagnosis were analyzed. Using the treatment histories, we analyzed the prognostic implications of palliative chemotherapy and surgical resection of the primary tumor retrospectively.
Results: The cohort consisted of 30 male (46.9%) and 34 female patients (53.1%); the median age was 76.5 years. Primary tumor resection was done on 28 patients (43.8%); 36 patients (56.2%) were categorized in the nonresection group. The median survival times were 12.43 months in the resection group and 3.58 months in the nonresection group (P < 0.001). Gender, level of CEA, level of AST, Eastern Cooperative Oncology Group performance status, tumor location, and presence of liver metastasis also showed significant differences in overall survival. On multivariate analysis, male gender, higher level of CEA, higher AST level, and no primary tumor resection were independent poor prognostic factors. In particular, nonresection of the primary tumor was the most potent/poor prognostic factor in the elderly-patient study group (P = 0.001; 95% confidence interval, 2.33 to 21.99; hazard ratio, 7.16).
Conclusion: In stage IVB colorectal cancer in elderly patients, resection of the primary tumor may enhance survival.

Keywords: Colorectal neoplasms; Prognosis; Palliative surgery

INTRODUCTION

Almost 150,000 new cases of colorectal cancer are diagnosed every year, and it is the second leading cause of cancer death in the United States, being responsible for nearly 50,000 deaths per year

[1]. In Korea, colorectal cancer makes up 12.7% of all malignant diseases, and it is the fourth most common cause of cancer-related death [2]. Moreover, the incidence and the mortality of this disease have increased in recent years [3].

Recently, we have faced changes to the standards and classifications in the management of cancer patients. Since January 1, 2010, the seventh edition of the *American Joint Committee on Cancer (AJCC) Cancer Staging Manual* has been used as the standard for the staging of all new cancer cases. In this standard, stage IV colorectal cancer has been subdivided into stage IVA and IVB, as determined by the pattern of distant metastasis. Stage IVA (M1a) is defined as single metastatic site/organ, and IVB (M1b) is defined as more than one organ/site or seeding of the peritoneum.

Another change compared to past decades is the increasing proportion of elderly patients due to life extension. Deciding the

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treatment plan for elderly cancer patients is more difficult due to the higher levels of physical and psychological stress. In addition, because most elderly patients are excluded from clinical trials due to strict inclusion criteria and ethical problems, standard treatments are not necessarily suitable for uniform application. Hence, in the choice of treatment in these elderly stage IVB colorectal patients, whether surgical removal of the primary lesion will enhance the survival rate or not is still debatable [4-9]. Despite the increasing importance of this population, evaluation of the prognostic factors of stage IVB colorectal cancer in the elderly remains unreported. Therefore, the present study evaluated the prognostic factors for elderly stage IVB patients by performing a retrospective analysis. The analysis focused on the treatment modality, including palliative chemotherapy and primary tumor resection, used for elderly colorectal stage IVB patients. The main aim of this study is to help determine the optimal treatment modality by comparing survival rates attained by using various treatment modalities for elderly patients with stage IVB colorectal cancer.

METHODS

Participants and materials

The authors identified 226 patients over 65 years of age who were pathologically diagnosed with stage IV colorectal cancer, according to the *AJCC Cancer Staging Manual* (6th edition), at the Gangneung Asan Hospital from July 1, 2001, to December 31, 2009. Each tumor stage was recategorized as M1a (metastasis confined to one organ or site) or M1b (metastases in more than one organ/site or the peritoneum) according to the *AJCC Cancer Staging Manual* (7th edition). Sixty-four stage IVB patients were analyzed in this study. All the patients' pathologic findings indicated an adenocarcinoma. The median follow-up duration was 5.29 months (maximum duration, 36 months). The cancer-specific data for each patient contained the tumor location, tumor grade, performance status, level of carcinoembryonic antigen (CEA), level of aspartate aminotransferase (AST), metastatic sites, and treatment modalities. Tumor location was categorized as ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, left colon, sigmoid colon, and rectum, which were recategorized into three groups: right-side colon, left-side colon, and rectum. Tumors were categorized as low grade (well-to-moderately differentiated) or high grade (poorly differentiated). Performance status was defined according to the Eastern Cooperative Oncology Group (ECOG) guidelines. Levels of CEA and AST at diagnosis were analyzed. Distant metastatic sites were categorized in terms of the presence of liver, lung, peritoneum, and nonregional lymph nodes at diagnosis. From the treatment histories, palliative chemotherapy and surgical resection of the primary tumor or its absence were evaluated. This study was approved by the Institutional Review Board of Gangneung Asan Hospital of the University of Ulsan's College of Medicine (No. 2013-039).

Statistical analysis

The descriptive statistics were calculated, including the means and medians or the counts and percentages. Survival data based on the above-recorded variables were computed according to the Kaplan-Meir method, and the curves were compared using a log-rank test. Overall survival (OS) was measured from the date of the diagnosis to the last follow-up or death. Differences were considered statistically significant when the P-value was <0.05. Finally, a multivariate analysis was performed using the Cox proportions hazards model to assess the influence of the above prognostic factors on OS; again, statistical significance was set at P-value <0.05. All statistical analyses were performed using PASW Statistics ver. 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patients' characteristics

A total of 64 patients participated in this analysis, 30 male (46.9%) and 34 female patients (53.1%), with a median age of 76.5 years. We described the baseline characteristics of all the enrolled patients in Table 1. The anatomical location of the primary tumor was specified. Among all patients, 20 patients (31.3%) had tumors in the right colon (cecum, ascending colon, hepatic flexure, and transverse colon), 28 patients (43.7%) had tumors in the left colon (splenic flexure, descending, sigmoid colon), and 16 patients (25.0%) had tumors in the rectum. Liver metastasis was shown in 38 patients (59.4%), lung metastasis was shown in 20 patients (31.3%), seeding of the peritoneum was shown in 32 patients (50.0%), and nonregional lymph node metastasis was shown in eight patients (12.5%). Among all the patients in the cohort, 44 patients (68.7%) had low-grade tumors, and 20 patients (31.3%) had high-grade tumors.

Treatment modalities

Primary tumor resection was done in 28 patients (43.8%). Among them, 16 patients received an emergency surgical resection due to obstruction by the tumor, and two patients received the procedure due to perforation. Of the remaining ten patients, surgery was performed with an elective palliative aim due to an obstructive symptom. Of the 18 emergency resection patients, five Hartmann's operations, three right hemicolectomies, three abdominoperineal resections, three ileocecal resections, two left hemicolectomies, one total colectomy, and one anterior resection were conducted. Of the 10 elective resection patients, five right hemicolectomies, three low anterior resections, and two anterior resections were conducted. No patient underwent a metastasectomy in either group. In the nonresection group, two patients underwent an emergency colostomy, and four patients had stents inserted due to obstruction at diagnosis.

Other clinicopathological factors were not different between the nonresection and the resection groups (Table 2). Thirty patients (46.9%) received palliative chemotherapy. Of the 36 nonresection

Table 1. Baseline characteristics of the patients (n=64)

Characteristic	No. (%)
Gender	
Male	30 (46.9)
Female	34 (53.1)
Age (yr)	
≥65, <70	14 (21.9)
≤70, <75	16 (25.0)
≥75	34 (53.1)
Location	
Right side colon	20 (31.3)
Left side colon	28 (43.7)
Rectum	16 (25.0)
Histologic grade	
Low grade (well-to-moderately differentiated)	44 (68.7)
High grade (poorly differentiated)	20 (31.3)
CEA level[a]	
<25	22 (47.8)
≥25, <50	6 (13.0)
≥50	18 (39.2)
ECOG performance status	
1	12 (18.8)
2	36 (56.2)
3	16 (25.0)
AST level	
<40	46 (71.9)
≥40	18 (28.1)
Presence of liver metastasis	
No	26 (40.6)
Yes	38 (59.4)
Presence of lung metastasis	
No	44 (68.7)
Yes	20 (31.3)
Presence of peritoneal metastasis	
No	32 (50.0)
Yes	32 (50.0)
Presence of nonregional LNs metastasis	
No	56 (87.5)
Yes	8 (12.5)
Primary tumor resection	
No	36 (56.2)
Yes	28 (43.8)
Palliative chemotherapy	
Not done	34 (53.1)
Done	30 (46.9)

CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; AST, aspartate aminotransferase; LN, lymph node.

[a]CEA level data were available in 46 cases out of 64.

patients, 14 patients (38.9%) received chemotherapy; among the 28 resection patients, 16 patients (57.6%) received it. Thirty-four patients did not receive chemotherapy, the reasons for which were refusal of treatment, poor performance and general weakness, and family members' choice. Among the 30 patients treated with palliative chemotherapy, most underwent 5-fluorouracil (FU)-based combination chemotherapy with oxaliplatin or irinotecan; 17 patients (56.7%) were treated with fluorouracil combined with oxaliplatin (FOLFOX) as the first-line chemotherapy, six patients (20%) were treated with 5-fluorouracil plus leukovorin chemotherapy, three patients (10%) were treated with 5-FU-based combination chemotherapy with irinotecan (FOLFIRI), and four patients (13.3%) were treated with a capecitabine single regimen according to the clinician's decision. After first-line chemotherapy, eight patients underwent second-line chemotherapy, where four cases each were treated with FOLFOX and FOLFIRI regimens. The mean numbers of cycles of first-line and second-line chemotherapy were 3.92 cycles (2–8 cycles) and 1.5 cycles (1 or 2 cycles), respectively. There were no patients treated with third-line chemotherapy.

Analysis of the prognosis factors and the survival rate

The median survival time was 12.43 months in the resection group and 3.58 months in the nonresection group (P < 0.001) (Table 3, Fig. 1A). In addition, gender, level of CEA, level of AST, ECOG performance status, tumor location, and presence of liver metastasis showed significant differences in OS. The results of the univariate analysis of OS are shown in Table 2 and Fig. 1B-D.

In the multivariate analysis using the Cox proportional hazards model, male gender, higher level of CEA, higher AST level, and no primary tumor resection were independent poor prognostic factors. In particular, absence of primary tumor resection was the most potent risk factor in these elderly patients (P = 0.001; 95% confidence interval [CI], 2.33 to 21.99; hazard ratio: 7.16) (Table 3). However, histologic grade and presence of liver metastasis were not independent predictive factors of OS (Table 4). Primary tumor location and ECOG performance status influenced primary tumor resection; tumors with right-sided and rectal origins more frequently underwent a primary tumor resection, and patients with good performance status had a greater chance of undergoing primary tumor resection.

DISCUSSION

Prognostic implications of clinicopathologic features have been extensively studied in the earlier stages of colon cancer (I–III) that undergo resection. However, few studies have evaluated prognostic factors in patients with incurable metastatic colon cancer, especially the influence of primary tumor resection [4, 10]. In particular, elderly patients have a bad condition overall, with various underlying diseases, and whether surgical removal of the primary lesion will enhance the survival rate for these patients is still de-

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Table 2. Differences in clinical parameters according to primary tumor resection or not

Variable	Primary tumor resection		P-value[a]
	Not done	Done	
Gender			0.092
Male	20 (66.7)	10 (33.3)	
Female	16 (47.1)	18 (52.9)	
Age (yr)			0.839
≥65, <70	8 (57.1)	6 (42.9)	
≤70, <75	8 (50.0)	8 (50.0)	
≥75	20 (58.8)	14 (41.2)	
Location			0.006
Right side colon	8 (40.0)	12 (60.0)	
Left side colon	22 (78.6)	6 (21.4)	
Rectum	6 (37.5)	10 (62.5)	
Histologic grade			0.110
Low grade (well-to-moderately differentiated)	22 (50.0)	22 (50.0)	
High grade (poorly differentiated)	14 (70.0)	6 (30.0)	
CEA level[b]			0.061
<25	9 (40.9)	13 (59.1)	
≥25, <50	3 (50.0)	3 (50.0)	
≥50	14 (77.8)	4 (22.2)	
AST level			0.221
<40	24 (52.2)	22 (47.8)	
≥40	12 (66.7)	6 (33.3)	
Presence of liver metastasis			0.138
No	12 (46.2)	14 (53.8)	
Yes	24 (63.2)	14 (36.8)	
Presence of lung metastasis			0.110
No	22 (50.0)	22 (50.0)	
Yes	14 (70.0)	6 (30.0)	
Presence of peritoneal metastasis			0.599
No	18 (56.3)	14 (43.7)	
Yes	18 (56.3)	14 (43.7)	
Presence of nonregional LNs metastasis			0.495
No	32 (57.1)	24 (42.9)	
Yes	4 (50.0)	4 (50.0)	
ECOG performance status			0.001
1	2 (16.7)	10 (83.3)	
2	20 (55.6)	16 (44.4)	
3	14 (87.5)	2 (12.5)	
Palliative chemotherapy			0.115
Not done	22 (64.7)	12 (35.3)	
Done	14 (46.7)	16 (53.3)	

Values are presented as number (%).
CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; AST, aspartate aminotransferase.
[a]Chi-square. [b]CEA level data were available in 46 cases out of 64.

Table 3. Univariate analysis of overall survival (n=64)

Variable	No. (%)	Median survival (mo)	95% CI	P-value
Gender				0.041
Male	30 (46.9)	2.83	1.37–4.28	
Female	34 (53.1)	10.08	5.68–14.49	
Age (yr)				0.286
≥65, <70	14 (21.9)	5.25	2.33–8.17	
≤70, <75	16 (25.0)	11.09	7.42–14.76	
≥75	34 (53.1)	3.83	1.39–6.26	
Location				0.005
Right side colon	20 (31.3)	11.96	9.19–14.73	
Left side colon	28 (43.7)	3.48	2.41–4.55	
Rectum	16 (25.0)	7.85	6.97–8.73	
Histologic grade				0.124
Low grade (well-to-moderately differentiated)	44 (68.7)	5.49	1.27–2.99	
High grade (poorly differentiated)	20 (31.3)	3.82	0.05–3.72	
CEA level[a]				0.000
<25	22 (47.8)	13.60	8.53–18.67	
≥25, <50	6 (13.0)	6.16	0.00–13.89	
≥50	18 (39.2)	2.83	0.99–4.66	
ECOG performance status				0.004
1	12 (18.8)	11.96	8.56–15.35	
2	36 (56.2)	5.29	0.23–5.73	
3	16 (25.0)	1.96	0.15–3.76	
AST level				0.001
<40	46 (71.9)	7.55	3.55–11.56	
≥40	18 (28.1)	2.83	0.96–4.69	
Presence of liver metastasis				0.036
No	26 (40.6)	11.09	8.74–13.43	
Yes	38 (59.4)	5.19	2.63–7.69	
Presence of lung metastasis				0.087
No	44 (68.7)	5.49	0.18–10.79	
Yes	20 (31.3)	3.96	0.77–7.18	
Presence of peritoneal metastasis				0.601
No	32 (50.0)	5.39	4.04–6.73	
Yes	32 (50.0)	3.83	1.45–6.19	
Presence of nonregional LNs metastasis				0.228
No	56 (87.5)	5.29	4.69–5.89	
Yes	8 (12.5)	3.69	0.00–9.06	
Primary tumor resection				0.000
No	36 (56.3)	3.58	2.34–4.81	
Yes	28 (43.7)	12.43	9.38–15.49	
Palliative chemotherapy				0.158
Not done	34 (53.1)	3.48	2.06–4.91	
Done	30 (46.9)	10.09	5.34–14.83	

CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; AST, aspartate aminotransferase.
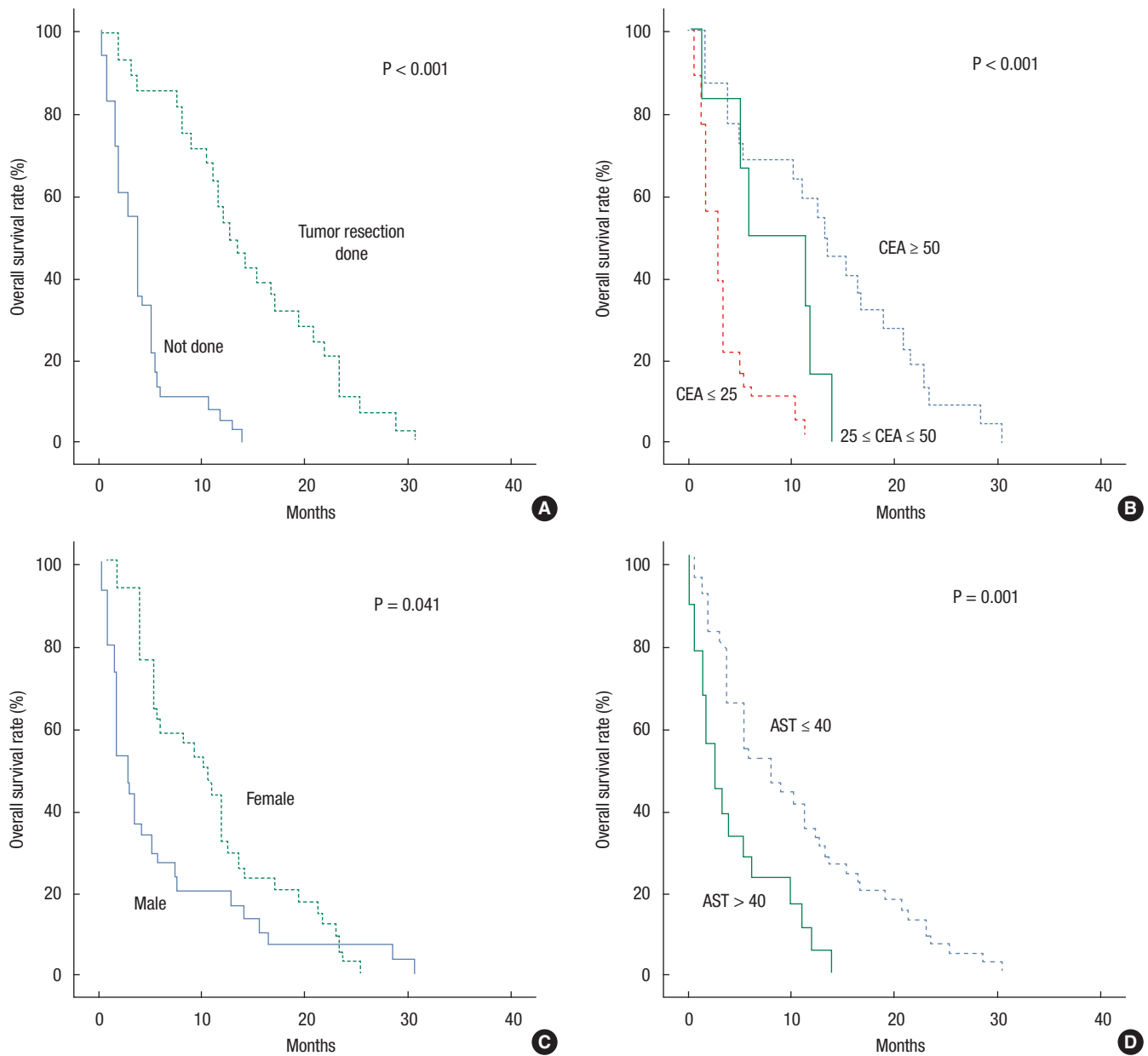[a]CEA level data were available in 46 cases out of 64.

Fig. 1. Kaplan-Meir estimates of overall survival according to primary tumor resection (A), carcinoembryonic antigen (CEA) level (B), gender (C), and level of aspartate aminotransferase (AST) (D) in elderly stage IVB colorectal cancer.

batable [4-9]. In general, nonoperative methods—chemotherapy, stent insertion, and bypass—are used in patients with incurable disease. A number of studies have reported that in the case of chemotherapy, the median survival period and the OS rate can be increased by using a single treatment modality without removing the primary lesion [11-13]. However, there is a lack of randomized controlled trials demonstrating the prognostic impact of resection of the primary colon tumor in the setting of metastatic disease. Generally, treatment decisions regarding the primary colon tumor in the metastatic setting are guided by the presence or

absence of symptoms and whether or not the metastases are resectable. If patients present with symptomatic primary tumors (bleeding, obstruction, or perforation), they are considered for either a palliative resection or for the placement of a colonic stent to help relieve an obstruction, followed by systemic chemotherapy if tolerable. However, elderly patients also have difficulties in being treated with palliative chemotherapy due to the comorbidities and poor performance status, considering the relatively long-term treatment periods involved in palliative chemotherapy. In practice, larger proportions of elderly patients give up on the treat-

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Table 4. Multivariate analysis of possible prognostic factors

Variable	Hazard ratio	95% CI	P-value
Male gender	3.92	1.55–9.92	0.004
High grade	2.03	0.86–4.79	0.104
High CEA level	2.48	1.45–4.23	0.001
High AST level	3.64	1.48–8.99	0.005
No primary tumor resection	7.16	2.33–21.99	0.001
Presence of liver metastasis	2.57	0.99–6.63	0.052

CI, confidence interval; CEA, carcinoembryonic antigen; AST, aspartate aminotransferase.

ment. Thus, palliative surgical treatment can be assumed to have a greater potential treatment role than palliative chemotherapy in elderly patients.

This analysis identified several clinicopathologic factors of significance in patients with metastatic colon cancer who underwent a surgical resection of their primary tumor. In the multivariate analysis, primary tumor resection, gender, level of CEA, and level of AST were all independent predictors of OS. In particular, absence of primary tumor resection was the most potent risk factor in the elderly-patient study group. However, palliative chemotherapy was not an independent prognostic factor. This finding supports the hypothesized importance of surgical treatment in the elderly group. The CEA level is a well-established prognostic factor in colorectal cancer; however, the prognostic implication of the AST level is a novel finding. This finding is not fully explainable, although it may be correlated with the tumor burden in the small bowel, peritoneum, and liver. Alanine aminotransferase levels were directly correlated with AST level, and there was no elevated bilirubin level.

Chemotherapy is a well-established palliative treatment strategy in stage IV metastatic colorectal cancer and has been shown to independently predict survival [10, 14, 15]. Even though chemotherapy is the standard therapy in the metastatic setting of colon cancer, only about half of the patients in the present study cohort received it. This could be due to the low contribution to the treatment outcome by palliative chemotherapy in this elderly population.

At the point of diagnosing advanced colorectal cancer, 10%–20% of the total cases are accompanied by partial obstruction and 8%–29% by complete obstruction [16]. In the present study, with the high incidence of obstruction and the high emergency surgical procedure rate compared to studies involving patients of all ages, the neglect of or indifference to the symptoms of the disease in the elderly patients groups could be considered a factor. This characteristic finding of frequent emergency settings at diagnosis can be explained as one of the reasons for the frequency of surgical treatments being higher than the frequency of administration of chemotherapies in these elderly patients (with metastases), even when they are unable to undergo surgical resection of the primary tumor site.

Previous studies reported an acceptable range of complications after surgical resection of the primary lesion, with 16.2% (17/105) as the postoperative major complication rate and 2.86% (3/105) as the postoperative death rate [9, 17]. In this study, no patient suffered postoperative death within one month, but two deaths occurred within two months. Even though the group was elderly and underwent frequent emergency operations, outcomes showed an acceptable postoperative mortality rate. This could be explained by the highly developed perioperative adjunctive care given to the patients and the highly selective indications used by the clinicians.

Tumor location may also influence the surgical outcome for elderly patients. The present study observed that patients with right colon cancer had significantly more advanced cancer stages than patients with left colon cancer, in accordance with a previous systematic literature review. In 1990, Bufill [18] was the first to propose that colon cancer located on either the right or the left side of the colon may arise from different biological pathways. Furthermore, right colon cancer and left colon cancer also differ in terms of patient characteristics, pathology, and prognosis [19]. A recent systematic review of the sparse literature on the topic supports the existence of such differences [20]. In a previous study, the present authors observed an almost linear relationship between tumor location and age; that is, the more proximally the tumor was located, the higher was the median age of the patients [21]. The present findings also showed a relatively higher incidence of right-sided colon cancer than in a general population. Eventually, right-sided colon cancer showed a higher rate of primary tumor resection than left-sided colon cancer. Even though right-sided colon cancer, with its poorer prognosis, showed longer median survival than left-sided colon cancer in the univariate analysis, this was not significant in the multivariate analysis in the present study of elderly patients.

The reason for the low rate of stent insertion, which is expected to develop fewer complications, may be that right-sided obstructive lesions have limited indications due to abdominal discomfort after stent insertion. In addition, the higher frequency of a right-sided obstruction in elderly patients influenced the poorer tolerability and compliance with the endoscopic procedure without general anesthesia. According to the findings of the current study, elderly stage IVB patients have different clinical disease situations compared to relatively younger patients; thus, special consideration is needed for the best treatment choice.

In conclusion, this study is too limited to be generalized to all elderly stage IVB colorectal cancer patients. Nevertheless, when patients are carefully selected, resection of the primary lesion may enhance the survival of patients.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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