Original Paper

High Serum CA19-9 Concentration Predicts Poor Prognosis in Elderly Patients with Stage IV Colorectal Cancer

Eiji Hidaka Chiyo Maeda Kenta Nakahara Kunihiro Wakamura
Yasuhiro Ishiyama Shoji Shimada Junichi Seki Yojiro Takano
Sonoko Oae Yuta Enami Naruhiko Sawada Fumio Ishida Shin-ei Kudo

Digestive Disease Center, Showa University Northern Yokohama Hospital, Yokohama, Japan

Keywords

Carbohydrate antigen 19-9 · Stage IV colorectal cancer · Elderly patient

Abstract

Background/Aim: The optimal treatment strategy for elderly patients with stage IV colorectal cancer (CRC) remains controversial due to limited research data. The purpose of this study was to evaluate treatment results and to clarify the prognostic factors, especially poor prognosis factors, in elderly patients with stage IV CRC. **Methods:** We retrospectively reviewed the data of 82 elderly patients (aged ≥ 75 years) with stage IV CRC who underwent surgical treatment at our hospital between April 2001 and March 2017. Factors that affected prognosis and the ability to undergo treatment were analyzed via multivariate analysis. **Results:** The median overall survival (OS) in the patients with high pretreatment serum carbohydrate antigen 19-9 (CA19-9) concentration (> 370 U/mL) was significantly worse than in those with lower serum CA19-9 concentration (0–370 U/mL) (8.5 vs. 19.2 months, $p = 0.0059$). In univariate analysis, age (≥ 80 years) ($p = 0.014$), performance status of 1–3 ($p = 0.028$), and high pretreatment serum CA19-9 concentration ($p = 0.014$) were significant prognostic factors for poor OS. By contrast, resection of the primary tumor ($p = 0.024$), chemotherapy ($p < 0.0001$), and resection of distant metastasis ($p = 0.0005$) were significant prognostic factors for favorable OS. Multivariate analysis showed that a high pretreatment serum CA19-9 concentration was an independent prognostic factor for poor OS ($p = 0.01$). Meanwhile, resection of the primary tumor ($p = 0.033$), chemotherapy ($p < 0.0001$), and resection of distant metastasis ($p = 0.0008$) were prognostic factors for favorable OS. **Conclusions:** A high pretreatment serum CA19-9 concentration (> 370 U/mL) was a reliable predictive factor for poor prognosis, and aggressive treatments should be performed carefully in these patients. Moreover, various treatments, including surgery and chemotherapy, might improve OS in elderly patients with stage IV CRC.

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Eiji Hidaka, MD, PhD
Digestive Disease Center, Showa University Northern Yokohama Hospital
35-1 Chigasaki-chuo, Tsuzuki-ku
Yokohama 224-8503 (Japan)
E-Mail eiji-h07@coda.ocn.ne.jp

Introduction

Colorectal cancer (CRC) is one of the most common cancers worldwide [1, 2]. Although the incidence of CRC tends to increase with age [3], most clinical trials have included patients aged <75 years, and only few randomized studies on elderly patients (i.e., individuals aged ≥75 years) with CRC have been conducted. Therefore, data on the optimal treatment for elderly patients with CRC have only been derived from retrospective studies [4–8]. As such, the optimal treatment strategy for elderly patients with stage IV CRC is controversial. Some guidelines recommend surgical resection for primary CRC and resectable distant metastatic lesions [9, 10]. Meanwhile, chemotherapy is recommended for unresectable lesions [9, 10]. However, these treatments may not yield similar clinical benefits in elderly patients with stage IV CRC because of age-related physiological changes. Considering the average life span of elderly people and the poor prognosis of stage IV CRC [4], especially in elderly patients, it may be necessary to find a balance between palliative care and aggressive treatments. Therefore, it is important to investigate poor prognosis factors to be able to avoid unnecessary aggressive treatments in elderly patients. As such, there is limited knowledge regarding the prognostic factors and optimal treatment strategies in these patients. The purpose of this study was to investigate treatment outcome and determine poor prognostic factors in elderly patients with stage IV CRC.

Patients and Methods

Patients

We retrospectively reviewed the data of 82 elderly patients (aged ≥75 years) with stage IV CRC who underwent surgical treatment at Showa University Northern Yokohama Hospital between April 2001 and March 2017. CRC was confirmed via colonoscopy and pathological examination. Distant metastasis was confirmed via computed tomography, magnetic resonance imaging, or positron emission tomography computed tomography, while peritoneal dissemination was diagnosed via intraoperative findings. The clinical and pathological characteristics of the patients, treatment methods, and the overall survival (OS) rate were analyzed retrospectively.

Study Parameters

The following patient data were collected: age, sex, primary tumor location, Eastern Cooperative Oncology Group performance status (PS), pretreatment concentrations of serum carcinoembryonic antigen (CEA) and serum carbohydrate antigen 19-9 (CA19-9), resection of the primary tumor, emergency operation, lymphatic metastasis, number of metastatic organs (M1a and M1b), severe metastatic status (P3, H3, or PUL2), chemotherapy, and OS. Transverse colon cancer was categorized into the right-sided cancer group. Pretreatment concentrations of serum CEA and serum CA19-9 were divided into three categories, i.e., normal, elevated, and high. The cutoffs for normal, elevated, and high CEA were <5 ng/mL, 5–50 ng/mL, and >50 ng/mL, respectively, while they were <37 U/mL, 37–370 U/mL, and >370 U/mL for CA19-9, respectively. Metastatic organ involvement and severe distant metastasis status were defined according to the 8th edition of the Japanese Classification of Colorectal Carcinoma by the Japanese Society for Cancer of the Colon and Rectum [11]. OS was defined as the interval from the time of primary surgery or primary chemotherapy to the date of death or last follow-up.

Statistical Analysis

All statistical analyses were performed using the JMP® 13 software (SAS Institute Inc., Cary, NC, USA). OS was calculated via the Kaplan-Meier method, and log-rank tests were used for comparison. The Cox regression model was used to determine the impact of selected factors on OS. A Cox proportional hazards model was used to calculate hazard ratios and 95% confidence intervals for both univariate and multivariate analyses. *p* values <0.05 were considered to indicate significance.

Table 1. Characteristics of the 82 patients with stage IV colorectal cancers

Characteristics	n	%
Age		
75–79 years	43	52.4
≥80 years	39	47.6
Sex		
Male/female	42/40	51.2/48.8
Primary tumor location		
Right/left	38/44	46.3/53.7
Performance status		
0/1–3	57/25	70.0/30.0
Pretreatment serum CEA concentration		
Normal (<5 ng/mL)	21	25.6
Elevated (5–50 ng/mL)	32	39.0
High (>50 ng/mL)	29	35.4
Pretreatment serum CA19-9 concentration		
Normal (<37 U/mL)	41	50.0
Elevated (37–370 U/mL)	27	32.9
High (>370 U/mL)	14	17.1
Resection of the primary tumor		
Yes/no	66/16	80.5/19.5
Emergency operation		
Yes/no	22/60	26.8/73.2
Lymphatic metastasis		
N0/N(+)	52/13	80.0/20.0
Number of metastatic organs		
M1a/M1b	64/18	78.0/22.0
P3, H3, or PUL2		
Present/absent	36/46	43.9/56.1
Chemotherapy		
Yes/no	38/44	46.3/53.7
Resection of metastatic tumor		
Yes/no	6/76	7.3/92.7

CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen.

Results

The clinical and pathological characteristics of the 82 patients are presented in Table 1. The primary tumor was located on the right and left side in 38 patients (46.3%) and 44 patients (53.7%), respectively. The median pretreatment concentration of serum CEA and serum CA19-9 were 25.1 ng/mL and 32.6 U/mL, respectively. The pretreatment serum CEA concentration was elevated in 61 patients (74.4%) and high in 29 patients (35.4%). Meanwhile, the serum CA19-9 concentration was elevated in 41 patients (50.0%) and high in 14 patients (17.1%). A total of 66 patients (80.5%) underwent resection of the primary tumor, and 38 patients (46.3%) received chemotherapy. Of them, 16 patients (42.1%) received oral 5-fluorouracil (5-FU) anticancer agents, 12 patients (31.6%) received oxaliplatin or irinotecan combined with the 5-FU regimen, and 10 patients (26.3%) received targeted chemotherapy agents combined with cytotoxic anticancer agents. Resection for distant metastasis was performed in only 6 patients (7.3%).

The median OS in the high serum CA19-9 concentration group (>370 U/mL) was significantly worse than that of those with normal to elevated serum CA19-9 concentrations (0–370 U/mL) (8.5 vs. 19.2 months, $p = 0.0059$) (Fig. 1). Meanwhile, the median OS for those who

Fig. 1. Kaplan-Meier curve of the impact of pretreatment serum CA19-9 concentration on overall survival ($p = 0.0059$; log-rank test). CA19-9, carbohydrate antigen 19-9.

underwent resection in the primary tumor group was significantly higher than those in the nonresection group (18.1 vs. 11 months, $p = 0.0122$). The median OS in the chemotherapy group was also significantly higher than that in the nonchemotherapy group (25.1 vs. 8.4 months, $p < 0.0001$). OS was also significantly improved in the group of patients who underwent resection of distant metastasis compared with the nonresection group (39.4 vs. 11 months, $p = 0.0022$). By contrast, no difference in OS was noted between the oral monotherapy group and the combination chemotherapy group ($p = 0.7976$).

In univariate analysis, age (≥ 80 years) ($p = 0.014$), PS of 1–3 ($p = 0.028$), and high pretreatment serum CA19-9 concentration ($p = 0.014$) were significant prognostic factors for poor OS (Table 2). By contrast, resection of the primary tumor ($p = 0.024$), chemotherapy ($p < 0.0001$), and resection of distant metastasis ($p = 0.0005$) were significant prognostic factors for favorable OS (Table 2).

Multivariate analysis also showed that high pretreatment serum CA19-9 concentration (>370 U/mL) was an independent prognostic factor for poor OS ($p = 0.01$) (Table 2). Meanwhile, resection of the primary tumor ($p = 0.033$), chemotherapy ($p < 0.0001$), and resection of distant metastasis ($p = 0.0008$) were independent prognostic factors for favorable OS (Table 2).

Discussion

To our knowledge, this is one of the few retrospective studies on the prognostic factors in elderly patients (≥ 75 years) with stage IV CRC. Our results showed that high pretreatment serum CA19-9 concentration was an independent prognostic factor for poor OS. By contrast, various treatments, including chemotherapy and resection of the primary and distant tumor, might improve the prognosis in elderly patients with stage IV CRC.

CA19-9 is an established tumor marker in CRC. Many studies have reported that CA19-9 is associated with distant metastasis and a prognostic factor in CRC [12–15]. Some researchers reported that preoperative serum CA19-9 concentration was a reliable predictive marker of tumor recurrence and prognosis in patients with stage IV CRC who had undergone curative resection [16, 17]. Another study reported that preoperative high CA19-9 concentration was a poor prognosis factor in stage IV CRC with noncurable resection [18]. Moreover, postoperative CA19-9 at 3 months after curative resection in patients with stage IV CRC was reported to be a strong prognostic indicator of recurrence [19]. Although

Table 2. Univariate and multivariate analysis for overall survival

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	<i>p</i> value	OR	95% CI	<i>p</i> value
Age						
≥80 vs. 75–79 years	1.933	1.145–3.313	0.014	1.079	0.572–2.037	0.814
Sex						
Male vs. female	0.723	0.435–1.200	0.209			
Primary tumor location						
Right vs. left	0.836	0.500–1.386	0.489			
Performance status						
1–3 vs. 0	1.931	1.076–3.367	0.028	1.615	0.809–3.189	0.172
Pretreatment serum CEA concentration						
>5 vs. 0–5 ng/mL	1.377	0.790–2.522	0.266			
>50 vs. 0–50 ng/mL	1.308	0.744–2.231	0.342			
Pretreatment serum CA19-9 concentration						
>37 vs. 0–37 U/mL	1.378	0.824–2.298	0.219			
>370 vs. 0–370 U/mL	2.452	1.214–4.617	0.014	2.828	1.304–5.820	0.010
Resection of the primary tumor						
Yes vs. no	0.423	0.218–0.887	0.024	0.378	0.160–0.924	0.033
Emergency operation						
Yes vs. no	0.881	0.477–1.546	0.668			
Lymphatic metastasis						
N0 vs. N(+)	1.460	0.726–2.728	0.274			
Number of metastatic organs						
M1b vs. M1a	1.679	0.899–2.966	0.100	1.187	0.538–2.583	0.667
P3, H3, or PUL2						
Present vs. absent	1.588	0.935–2.685	0.087	1.079	0.546–2.053	0.821
Chemotherapy						
Yes vs. no	0.331	0.192–0.568	<0.0001	0.209	0.105–0.402	<0.0001
Resection of metastatic tumor						
Yes vs. no	0.190	0.046–0.528	0.0005	0.156	0.035–0.497	0.0008

Bold indicates statistical significance. CEA, carcinoembryonic antigen; CI, confidence interval; OR, odds ratio; CA19-9, carbohydrate antigen 19-9.

serum CA19-9 concentration might be associated with prognosis in stage IV CRC according to many reports, there were no studies concerning the association between serum CA19-9 concentration and OS in elderly patients with stage IV CRC. In this study, a serum CA19-9 concentration of >37 U/mL was unrelated to OS; however, 1 out of 10 times the normal range at >370 U/mL was a significant independent prognostic factor for OS. The median OS of the patients with stage IV CRC who had a serum CA19-9 concentration of >370 U/mL was quite poor at 8.5 months. As such, these patients may no longer be eligible for aggressive treatments and be more suited to palliative care. Accordingly, serum CA19-9 concentration was an important biomarker for determining eligibility for aggressive treatment in elderly patients with stage IV CRC.

Many researchers have reported that curative resection might improve long-term survival in patients with stage IV CRC [20–22]. Recent retrospective studies on curatively resected stage IV CRC patients reported a 5-year OS rate of 52.2–57% [22, 23]. Moreover, aggressive curative resection with perioperative chemotherapy might improve survival [22]. In general, curative resection and chemotherapy might be the optimal treatment strategy for middle-aged patients with stage IV CRC [9]. Some studies reported that resection

of only the primary tumor improved OS or relapse-free survival in stage IV CRC [23–25]. In this study, the OS of the 66 patients (80.5%) who underwent resection of the primary tumor was significantly longer than that of the patients who did not undergo primary tumor resection. Old age (≥ 75 years) at the time of surgery for stage IV CRC was reported to be an independent risk factor for mortality during the first year after surgery [6]. Additionally, another study showed that a PS of 2–4 was an independent prognostic factor in patients with stage IV CRC aged >80 years [5]. In the current study, age and PS were poor prognostic factors in univariate analysis, but not in multivariate analysis. Considering the results of the current study and those of previous ones, resection of the primary tumor might be a beneficial treatment to improve OS in elderly patients with stage IV CRC. In addition, the patient's general characteristics, such as age and PS, should be considered when performing primary resection.

Despite the low rate of resection of distant metastasis in the current study at only 7.3%, it significantly improved OS ($p = 0.0022$). In elderly patients, aggressive curative resection might yield the benefit of improving OS similar to that of younger patients. However, some studies reported that hepatic or pulmonary resection yielded higher mortality and complication rates in elderly compared to younger patients [26, 27]. Therefore, the operative indications for distant metastasis must be carefully decided upon in elderly patients with stage IV CRC.

Similar to surgical resection, chemotherapy is also an important treatment in the management of patients with stage IV CRC [9]. It was reported that palliative chemotherapy in selected elderly patients (≥ 80 years) with distant metastasis was considerably associated with improved OS, and oral 5-FU monotherapy in the palliative setting could be a reasonable option for elderly patients [5]. Kim [28] reported that chemotherapy in elderly patients should be individualized based on the nature of the disease, physiological or functional status, and patient's preference. In our study, 38 patients (46.3%) received chemotherapy, and they had significantly longer survival than those who did not ($p < 0.0001$). This is similar to the result previously reported in another study [5]. Regarding the chemotherapy regimen, some studies reported that combination chemotherapy was not superior to monotherapy in terms of OS in elderly patients with metastatic CRC [5, 29]. In the present study, OS was not significantly different between the patients who received mono-chemotherapy ($n = 16$, 42.1%) and combination chemotherapy ($n = 22$, 57.9%). We report results consistent with those of previous studies [5, 29]; mono-chemotherapy might be acceptable for these patients. However, randomized prospective studies are still needed to further determine the optimal chemotherapy regimen for elderly patients with stage IV CRC.

This study had some limitations, including its retrospective and single-institution design as well as the relatively small number of patients analyzed. All patients who were analyzed underwent surgical treatments including palliative surgery. The patients who underwent primary resection or chemotherapy might have been in a relatively better condition compared to the patients who did not undergo treatment. A large-scale or randomized study is necessary to confirm our results.

Conclusions

Our study demonstrated that a high pretreatment serum CA19-9 concentration (>370 U/mL) was a reliable predictive factor for poor prognosis in elderly patients with stage IV CRC, and aggressive treatments should be performed carefully in these patients. Moreover, various treatments, including surgery and chemotherapy, might improve OS in elderly patients with stage IV CRC.

Statement of Ethics

This study was approved by our hospital's review committee (approval No. 17H100). Informed consent for the use of the clinical and pathological data of all patients was obtained via opt-out presented on our hospital's homepage.

Disclosure Statement

The authors declare that they have no competing interests. No financial support was received.

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