Am J Cancer Res 2025;15(7):3093-3105
www.ajcr.us /ISSN:2156-6976/ajcr0166578

Original Article

Efficacy and safety of first-line cetuximab therapy for older patients (aged ≥ 70 years) with *RAS* wild-type metastatic colorectal cancer: a nationwide real-world study

Ching-Wen Huang[1,2], Chou-Chen Chen[3], Shih-Ching Chang[4], Yu-Yao Chang[5,6], Bo-Wen Lin[7], Hong-Hwa Chen[8], Yao-Yu Hsieh[9,10], Hung-Chih Hsu[11,12], Meng-Che Hsieh[13], Tao-Wei Ke[14], Feng-Che Kuan[15], Chih-Chien Wu[16,17], Wei-Chen Lu[18], Yu-Li Su[19], Yi-Hsin Liang[20], Joe-Bin Chen[21], Shuan-Yuan Huang[5], Po-Jung Chen[2,22], Jaw-Yuan Wang[1,2,22,23,24]

[1]Division of Colorectal Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung 80708, Taiwan; [2]Department of Surgery, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung 80708, Taiwan; [3]Department of Surgery, Taichung Veterans General Hospital, Taichung 40705, Taiwan; [4]Division of Colon and Rectal Surgery, Department of Surgery, Taipei Veterans General Hospital 11217, Taipei, Taiwan; [5]Department of Colorectal Surgery, Changhua Christian Hospital, Changhua 50006, Taiwan; [6]Department of Post-Baccalaureate Medicine, College of Medicine, National Chung Hsing University, Taichung 402202, Taiwan; [7]Department of Surgery, National Cheng Kung University Hospital, Tainan 70101, Taiwan; [8]Division of Colon and Rectal Surgery, Department of Surgery, Chang Gung Memorial Hospital, Kaohsiung 83301, Taiwan; [9]Division of Hematology and Oncology, Shuang-Ho Hospital, Taipei Medical University, New Taipei 23561, Taiwan; [10]Division of Hematology and Oncology, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei 11031, Taiwan; [11]Division of Hematology Oncology, Chang Gung Memorial Hospital at Linkou, Taoyuan 333, Taiwan; [12]College of Medicine, Chang Gung University, Taoyuan 333, Taiwan; [13]Division of Hematology Oncology, Department of Internal Medicine, E-Da Hospital, I-Shou University, Kaohsiung 82445, Taiwan; [14]Division of Colorectal Surgery, Department of Surgery, China Medical University Hospital, Taichung 40402, Taiwan; [15]Department of Hematology and Oncology, Chang Gung Memorial Hospital, Chiayi 61363, Taiwan; [16]Division of Colorectal Surgery, Department of Surgery, Kaohsiung Veterans General Hospital, Kaohsiung 81362, Taiwan; [17]School of Medicine, National Yang Ming Chiao Tung University, Taipei 11221, Taiwan; [18]Department of Oncology, National Taiwan University Hospital Yunlin Branch, Yunlin 640, Taiwan; [19]Division of Hematology Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital, Kaohsiung 83301, Taiwan; [20]Department of Oncology, National Taiwan University Hospital, Taipei 10002, Taiwan; [21]Department of Surgery, Chung Shan Medical University Hospital, Taichung 402306, Taiwan; [22]Graduate Institute of Clinical Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung 80708, Taiwan; [23]Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung 80708, Taiwan; [24]Center for Cancer Research, Kaohsiung Medical University, Kaohsiung 80708, Taiwan

Received June 4, 2025; Accepted June 29, 2025; Epub July 15, 2025; Published July 30, 2025

Abstract: This study investigated the efficacy and safety of first-line cetuximab-based chemotherapy for patients aged 70 years and older with *RAS* wild-type metastatic colorectal cancer (mCRC) from nationwide registry data in Taiwan. The study included 756 patients with *RAS* wild-type mCRC who received cetuximab and chemotherapy as first-line therapy at multiple institutions in Taiwan from November 2016 to January 2021. After the prognoses of two age groups (≥ 70 and < 70 years) were determined, progression-free survival (PFS) and cancer-specific survival (CSS) were regarded as the primary endpoints and severe adverse events (SAEs) were also compared. The median PFS and CSS were similar in the two age groups (14.0 vs. 14.0 months, $P = 0.098$; 32.0 vs. 35.0 months, $P = 0.226$, respectively). Subgroup analysis revealed similar PFS and CSS in the two age groups for patients with synchronous versus metachronous mCRC and left-sided versus right-sided tumors (all $P > 0.05$). In terms of hematologic SAEs, the incidence of grade 3 or more severe anemia was significantly higher in the older group (13.3% vs. 5.0%, $P = 0.003$). No significant between-group difference was found in the incidence of nonhematologic SAEs (all $P > 0.05$). According to our nationwide real-world registry data, older patients with *RAS* wild-type mCRC who are treated with first-line cetuximab-based chemotherapy may experience similar benefits to those experienced by younger patients. Significant differences between patients aged ≥ 70 and < 70 years were found for no hematologic and nonhema-

https://doi.org/10.62347/QZFD8646

tologic SAEs except grade 3 or more severe anemia. In summary, cetuximab is an effective therapeutic agent as first-line therapy for older patients with *RAS* wild-type mCRC.

Keywords: Older patients, metastatic colorectal cancer, *RAS* wild-type, cetuximab

Introduction

Colorectal cancer (CRC) is the third most prevalent cancer and the second leading cause of cancer-related death worldwide [1]. In 2022, approximately 1.92 million new cases of CRC and approximately 903,000 CRC-related deaths were reported worldwide [1]. CRC is the second most common cancer in Taiwan, with rapidly increasing prevalence since 2006. The incidence of CRC increased from 45.5 per 100,000 individuals in 2006 (with 10,398 new cases) to 75.8 per 100,000 individuals in 2022 (with 17,643 new cases) [2]. Additionally, CRC is the third leading cause of cancer-related death in Taiwan, with 6,791 deaths reported in 2023. Its mortality rate increased from 21.2 per 100,000 individuals in 2010 to 29.1 per 100,000 individuals in 2023 [2]. Approximately 20% to 25% of patients with CRC present with metastatic disease at the time of the CRC diagnosis. Additionally, approximately 40% of patients with initially localized CRC experience relapse or metastasis during treatment. Consequently, nearly 50% to 60% of cases of CRC eventually progress to metastatic CRC (mCRC) [3, 4].

Given that the incidence of CRC increases with age [5], older adults are typically at an increased risk of CRC. In Taiwan, CRC primarily affects older individuals, with the median age at diagnosis being 66 years for men and 68 years for women [2]. In 2022, the median age at cancer-related death was reported to be 73 years for all patients with CRC (71 years for men and 76 years for women) [2]. Therefore, health-care providers offering treatment for patients with CRC must be aware that most of their patients are older than 70 years [6]. Despite these findings, oncological outcomes and survival do not depend on patient age, suggesting age-independent postoperative outcomes in older patients [7].

Over the past two decades, several clinical trials have explored the efficacy of integrating anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibodies into doublet regimens of FOLFOX (5-fluorouracil, oxaliplatin, and folinic acid) or FOLFIRI (5-fluorouracil, irinotecan, and folinic acid) and revealed the higher efficacy of these combinations compared with chemotherapy alone in patients with *RAS* wild-type mCRC [8-10]. Currently, combination of anti-EGFR monoclonal antibodies and doublet or triplet chemotherapy is recommended as first-line therapy for patients with *RAS* wild-type mCRC [11-15]. Older patients are often excluded from clinical trials because of selection bias and concerns regarding potential toxicity. Therefore, these patients are often underrepresented in clinical trials [16, 17]. A recent systematic review recommended adjuvant chemotherapy for older patients with localized CRC, suggesting that the efficacy of this treatment is similar to that in younger patients [18]. Notably, older patients undergoing targeted therapies tend to have similar survival outcomes to younger patients, without major safety concerns [19-27]. Multiple observational studies have indicated that targeted therapies are often prescribed to older patients in clinical settings. However, old age remains a barrier to accessing anticancer treatment, particularly targeted therapies, in clinical practice [19, 28].

Most of the conducted studies have been limited by small sample sizes and have not focused on a specific patient population. Our 2022 study evaluated UGT1A1 polymorphism-guided irinotecan escalation in combination with targeted therapy [29]. This study included 48.0% of patients aged 65 years or older who received first-line cetuximab therapy. Moreover, our 2023 work focused on the number of neoadjuvant cycles in patients undergoing metastasectomy [30]. This study included 43.8% of patients aged 65 years or older who received first-line cetuximab therapy. These two articles did not compare the efficacy and safety of chemotherapy between elderly and younger patients, but both articles indicated that the overall treatments were effective and safe. Therefore, we conducted this multicenter registry study to examine the efficacy and safety of first-line cetuximab-based chemotherapy for survival patients aged 70 years and older with *RAS* wild-type mCRC in real-world setting. The

present study extends our efforts by concentrating on real-world data in elderly patients receiving cetuximab-based regimens.

Materials and methods

Study design

This retrospective, multicenter observational study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The study protocol and all of its amendments were approved by the institutional review boards of all 14 participating institutions. The following is a list of their approval numbers:

1. Taipei Veterans General Hospital (approval number: 2017-12-003A). 2. National Taiwan University Hospital (approval no. 202108081-RINA). 3. Shuang Ho Hospital (approval no. N202110007). 4. Linkou Chang Gung Memorial Hospital (approval no. 202101933B0). 5. China Medical University Hospital (approval no. CMU-H111-REC3-054). 6. Taichung Veterans General Hospital (approval no. CE21536B). 7. Changhua Christian Hospital (approval no. 211001). 8. National Taiwan University Hospital Yunlin Branch (approval no. 202107123RIPB). 9. Chiayi Chang Gung Memorial Hospital (approval no. 2021019-33B0). 10. National Cheng Kung University Hospital (approval no. A-ER-110-471). 11. Kaohsiung Medical University Hospital (approval no. KMUHIRB-E(I)-20210246). 12. Kaohsiung Chang Gung Memorial Hospital (approval no. 202101933B0). 13. Kaohsiung Veterans General Hospital (approval no. KSVGH21-CT14-06). 14. E-DA Hospital (approval no. EMRP-110-167).

Given the retrospective nature of this study and the fact that we used anonymized clinical data, the requirement for written informed consent was waived by the institutional review boards of all participating hospitals and medical centers.

Patients

This study enrolled patients with mCRC who underwent cetuximab-based chemotherapy as first-line treatment between November 2016 and December 2020. Patients meeting the following criteria were included: 1) being 18 years of age or older at the time of mCRC diagnosis, 2) having histologically confirmed *RAS* wild-type mCRC (including exons 2, 3, and 4 of both *KRAS* and *NRAS*), and 3) having undergone more than three cycles of first-line cetuximab-based chemotherapy. Patients who did not meet these criteria or were unwilling to participate were excluded [25].

Evaluation of treatment response and adverse effects

Treatment response was evaluated in accordance with the routine clinical practice of each institution. Responses were categorized by radiologists on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) [31]. Each response was categorized from treatment initiation to disease progression as complete response (CR), partial response (PR), stable disease (SD), or disease progression (PD). Adverse effects (AEs) were graded in accordance with the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCT-CTCAE, version 5, http://https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf).

Statistical analysis

All statistical analyses were conducted using IBM SPSS statistics version 22.0 (IBM, Armonk, NY, USA). Clinicopathological characteristics and oncological outcomes were analyzed in two age groups (≥ 70 vs. < 70 years). Between-group comparisons of these characteristics and outcomes were conducted using a chi-square test for categorical variables and Student's *t* test for continuous variables. Categorical variables are presented as a frequency and percentage, continuous variables are presented as the mean ± standard deviation or median with the interquartile range. Progression-free survival (PFS) was defined as the interval between the first round of cetuximab-based chemotherapy and the first documentation of radiological progression or death, whichever occurred first. Cancer-specific survival (CSS) was defined as the interval between the first round of cetuximab-based chemotherapy and CRC-related death. Overall survival (OS) was defined as the interval from the date of mCRC diagnosis to the date of death from any cause, the date of the final follow-up, or the end of the study. The disease control rate (DCR) was defined as the proportion of patients

Table 1. Baseline characteristics according to age groups

Baseline Characteristics	Age < 70 (N = 560)	Age ≥ 70 (N = 196)	*P*
Gender			0.374
Male	375 (67%)	138 (70.4%)	
Female	185 (33%)	58 (29.6%)	
ECOG performance score			< 0.001*
0+1	546 (97.5%)	176 (89.8%)	
2	5 (0.9%)	15 (7.7%)	
Unknown	9 (1.6%)	5 (2.5%)	
Primary lesion site			0.552
Left-sided	508 (90.7%)	171 (87.2%)	
Right-sided	48 (8.6%)	24 (12.2%)	
Unknown/Both	4 (0.7%)	1 (0.5%)	
Synchronous/Metachronous mCRC			0.031*
Synchronous	359 (64.1%)	108 (55.1%)	
Metachronous	197 (35.2%)	88 (44.9%)	
Unknown	7 (0.7%)	0 (0.0%)	
BRAF genotyping			0.461
Wild type	411 (73.4%)	134 (68.4%)	
Mutant type	17 (3.0%)	4 (2.0%)	
Unknown	132 (23.6%)	58 (29.6%)	
Metastatic sites			0.016*
Liver	278 (49.6%)	91 (46.4%)	
Lung	71 (12.7%)	33 (16.8%)	
Liver + lung	58 (10.4%)	33 (16.8%)	
Others	153 (27.3%)	39 (19.9%)	
No. of metastatic sites			0.322
1	366 (65.4%)	124 (63.3%)	
≥ 2	188 (33.6%)	70 (35.7%)	
Unknown	6 (1.1%)	2 (1.0%)	
Serum CEA level before treatment			0.561
< 5 ng/ml	152 (27.1%)	49 (25.0%)	
≥ 5 ng/ml	335 (63.3%)	121 (61.7%)	
Unknown	73 (9.6%)	26 (13.3%)	
Cycles of first-line of cetuximab			0.100
< 14	237 (43.2%)	97 (50.0%)	
≥ 14	312 (56.8%)	97 (50.0%)	

ECOG: Eastern Cooperative Oncology Group; CEA: carcinoembryonic antigen; *$P < 0.05$.

whose best response indicated no disease progression (CR, PR, or SD). The objective response rate (ORR) was defined as the proportion of patients who achieved either CR or PR. The duration of treatment (DoT) was defined as the period from the initiation of first-line cetuximab-based chemotherapy to the date of the final treatment round. The duration of response (DoR) was defined as the period from the onset of response to disease progression or death for any reason, whichever occurred first. PFS, CSS, and OS were evaluated using the Kaplan-Meier survival method. Between-group comparisons of time-to-event distributions were conducted using a log-rank test. A *p* value of less than 0.05 was considered statistically significant.

Results

Clinical and pathological characteristics of patients

Table 1 presents a summary of the patients' demographic and clinicopathological characteristics. This study included 756 patients who underwent first-line cetuximab-based chemotherapy. These patients were divided into 560 patients aged under 70 years and 196 patients aged 70 years and order. Compared with those in the younger age group, those in the older age group were significantly more likely to have an Eastern Cooperative Oncology Group performance score of 2 (7.7% vs. 0.9%, P < 0.001), synchronous metastasis (44.9% vs. 35.2%, P = 0.031), and lung metastasis (16.8% vs. 12.7%, P = 0.016). However, no significant intergroup differences in terms of sex, primary lesion site, metastatic site count, serum carcinoembryonic antigen level before treatment, or first-line cetuximab cycles count were discovered.

Efficacy analyses and survival outcomes

Table 2 presents a summary of our efficacy analysis. No significant differences were found in any of the treatment responses CR, PR,

Table 2. The comparison of efficacy between age groups

	Overall		*P*
	Age < 70 (N = 560)	Age ≥ 70 (N = 196)	
Response to cetuximab in first-line treatment			0.054
CR	48 (8.6%)	23 (11.7%)	
PR	274 (48.9%)	93 (47.4%)	
SD	148 (26.4%)	45 (23.0%)	
PD	69 (12.3%)	20 (10.2%)	
Not evaluable/Unknown	21 (3.8%)	15 (7.6%)	
Metastectomy rate	72 (30.7%)	44 (22.4%)	0.058
Metastatic site resection			
No resection	386 (68.9%)	152 (77.6%)	
Resection	172 (38.7%)	44 (22.4%)	
R0 resection	119 (21.4%)	28 (14.3%)	
R1 resection	27 (4.8%)	7 (3.6%)	
R2 resection	4 (0.7%)	0 (0.0%)	
Unknown	22 (3.9%)	9 (4.6%)	
ORR			0.197
CR + PR	330 (60.8%)	121 (66.1%)	
SD + PD	213 (39.2%)	62 (33.9%)	
DCR			0.354
CR + PR + SD	479 (88.2%)	166 (90.7%)	
PD	64 (11.8%)	17 (9.3%)	
Survival			0.046*
Yes	222 (39.6%)	62 (31.6%)	
No	254 (45.4%)	92 (46.9%)	
Unknow	84 (15%)	42 (21.4%)	
DoT (median, month)	12.3±8.9 (2,59)	11.0±6.7 (2,31)	0.038*
DoR (median, month)	17.7±13.3 (2,65)	15.1±10.5 (2,53)	0.007*

ORR, objective response rate; DCR, disease control rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; DOT, duration of treatment; DOR, duration of response. *$P < 0.05$.

SD, and PD between the two age groups. Specifically, no significant between-group differences were discovered in the ORR (66.1% vs. 60.8%, P = 0.197) or DCR (90.7% vs. 88.2%, P = 0.354). In addition, no significant intergroup difference was found in the overall rate of metastasectomy (22.4% vs. 30.7%, P = 0.058). However, compared with the younger patients, the older patients had a significantly shorter median DoT (11.0 vs. 12.3 months, P = 0.038) and median DoR (15.1 vs. 17.7 months, P = 0.007) and were more likely to die during the study period (46.9% vs. 45.4%, P = 0.046). The median PFS was similar in the two age groups (14.0 vs. 14.0 months, P = 0.098, **Figure 1A**). In addition, no significant difference was found in median CSS between the two age groups. (32.0 vs. 35.0 months, P = 0.226, **Figure 1B**).

Subgroup analyses based on metastatic status, either synchronous or metachronous, were conducted. In the patients with synchronous mCRC, no significant between-group differences were discovered in PFS (14.0 vs. 14.0 months, P = 0.362, **Figure 2A**) or CSS (29.0 vs. 34.0 months, P = 0.708, **Figure 2B**). Similarly, in patients with metachronous mCRC, no significant between-group differences were found in PFS (14.0 vs. 13.0 months, P = 0.362, **Figure 2C**) or CSS (33.0 vs. 49.0 months, P = 0.128, **Figure 2D**).

Subgroup analyses based on primary tumor location were also conducted. In patients with right-sided colon tumors, no significant between-group differences were determined in PFS (13.0 vs. 11.0 months, P = 0.483, **Figure 3A**) or CSS (14.0 vs. 29.0 months, P = 0.087,

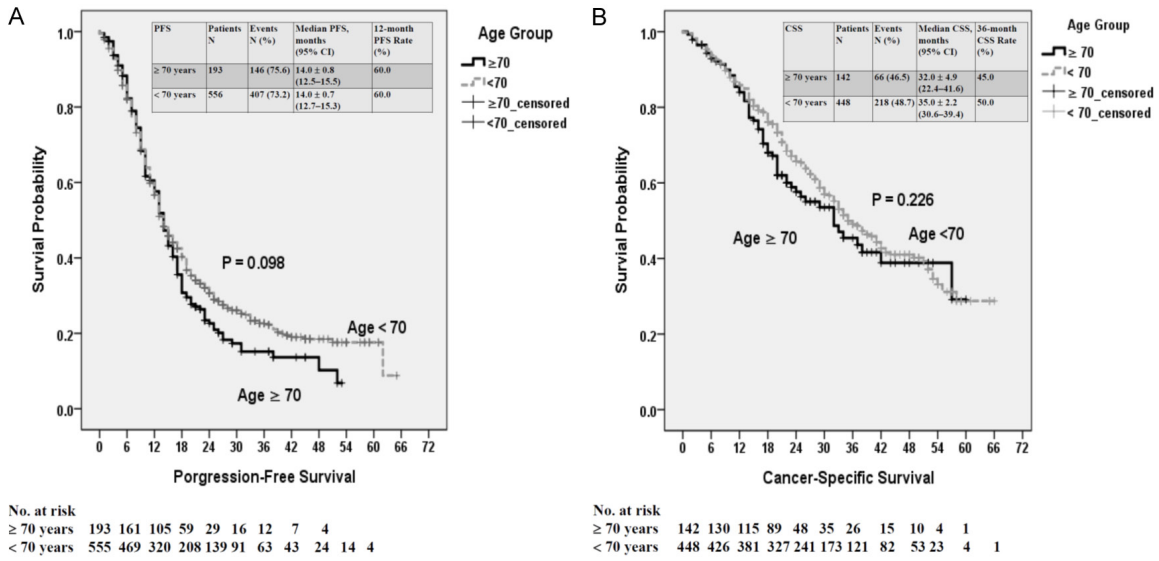

Figure 1. Kaplan-Meier survival curve for patients with mCRC stratified by age group. A. Progression-free survival. B. Cancer specific survival.

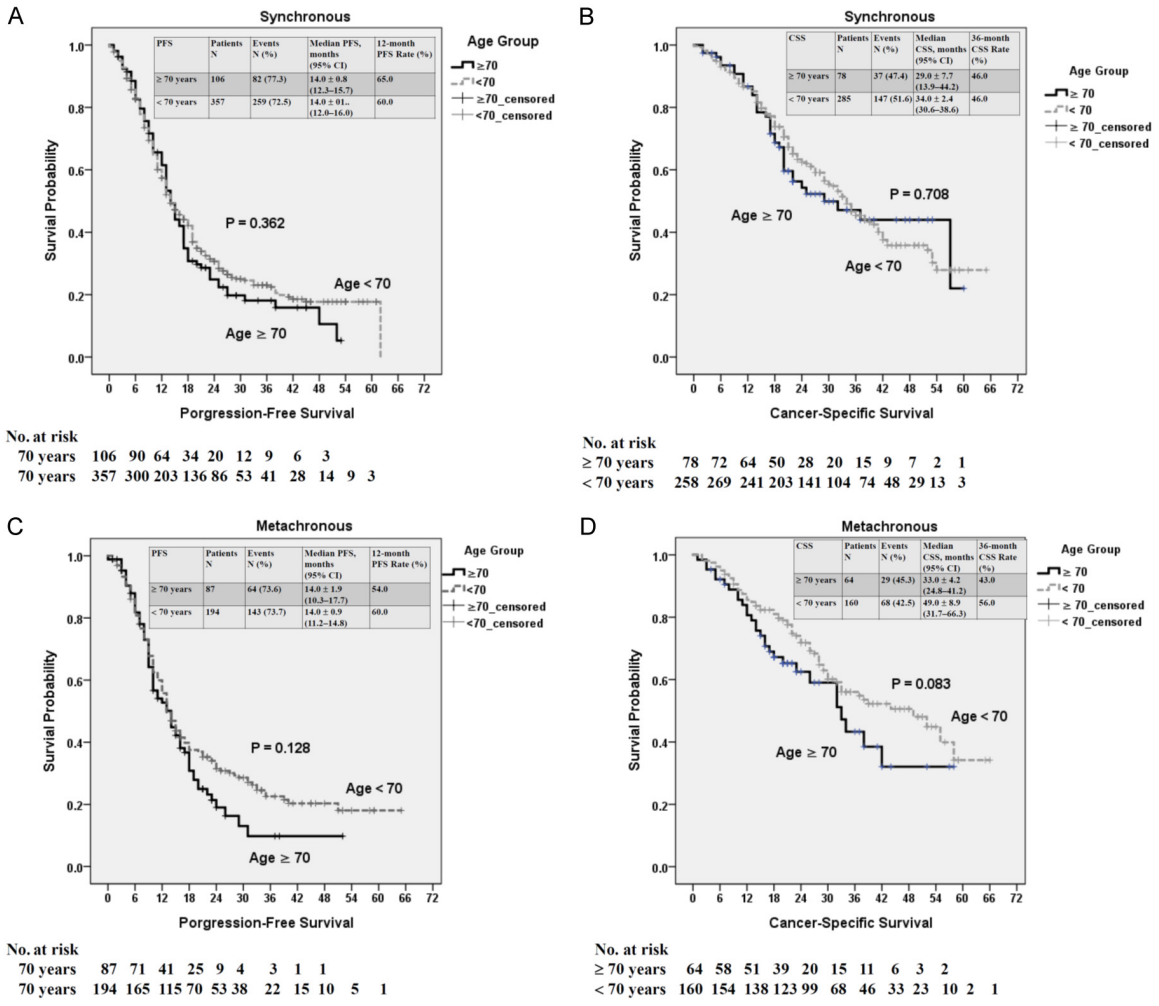

Figure 2. Kaplan-Meier survival curve for patients with mCRC stratified by age group and metastatic status. A. Progression-free survival of patients with synchronous mCRC stratified by age group. B. Cancer specific survival of patients with synchronous mCRC stratified by age group. C. Progression-free survival of patients with metachronous mCRC stratified by age group. D. Cancer specific survival of patients with metachronous mCRC stratified by age group.

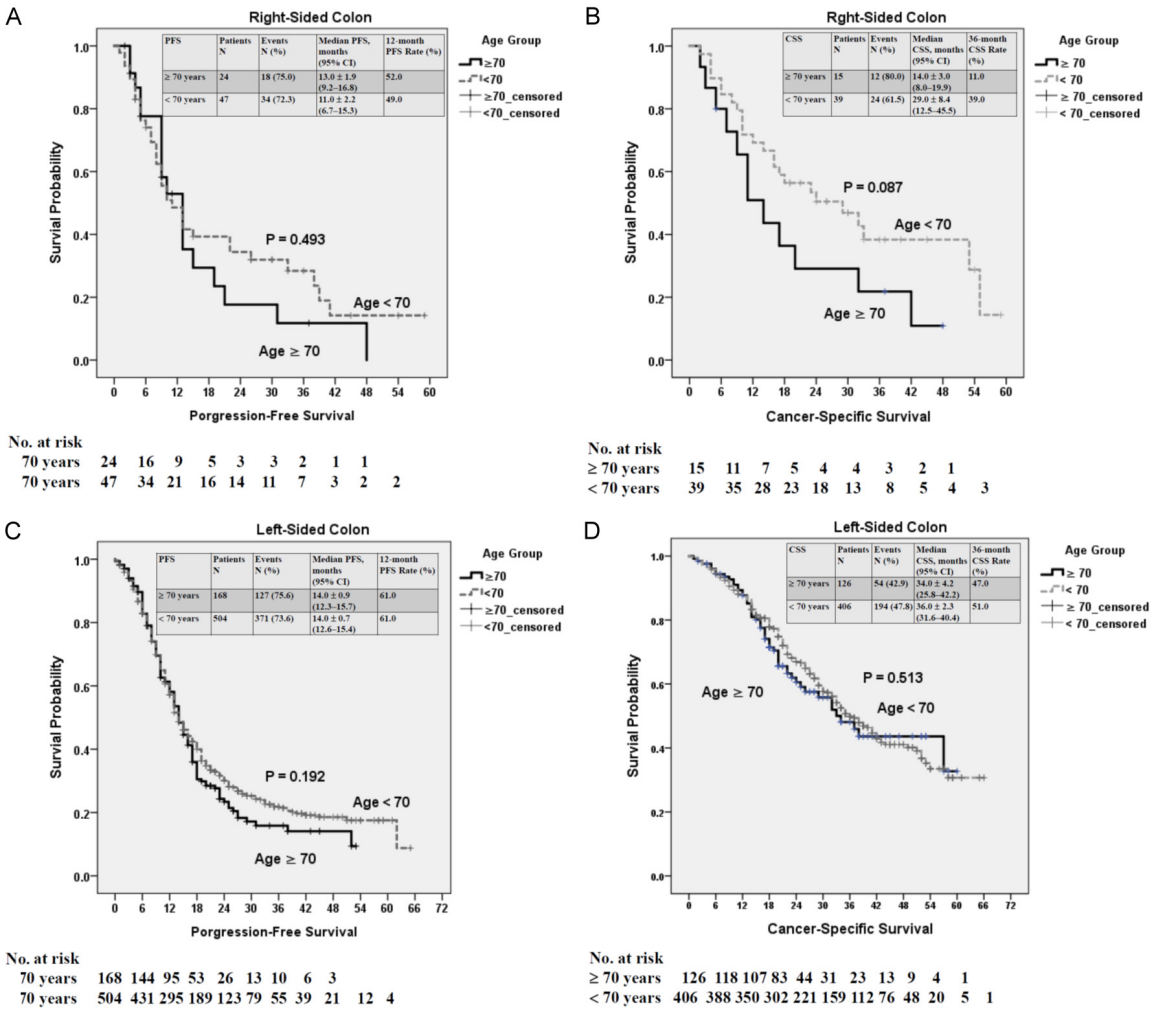

Figure 3. Kaplan-Meier survival curve for patients with mCRC stratified by age group and primary tumor location. A. Progression-free survival of patients with right-sided mCRC stratified by age group. B. Cancer specific survival of patients with right-sided mCRC stratified by age group. C. Progression-free survival of patients with left-sided mCRC stratified by age group. D. Cancer specific survival of patients with left-sided mCRC stratified by age group.

Figure 3B). Similarly, in patients with left-sided colon tumors, the intergroup differences in PFS (14.0 vs. 14.0 months, P = 0.192, **Figure 3C**) and CSS (34.0 vs. 36.0 months, P = 0.087, **Figure 3D**) were nonsignificant.

Subgroup analyses based on first-line cetuximab cycle count were counted. In patients with fewer than 14 cycles of first-line cetuximab, no significant between-group difference was determined in PFS (8.0 vs. 9.0 months, P = 0.209, **Figure 4A**) or CSS (19.0 vs. 27.0 months, P = 0.173, **Figure 4B**). Similarly, in patients with 14 cycles or more of first-line cetuximab, the between-group differences in PFS (17.0 vs. 18.0 months, P = 0.549, **Figure 4C**) and CSS (42.0 vs. 42.0 months, P = 0.828, **Figure 4D**) were nonsignificant. The median duration of PFS was significantly longer in older patients with 14 cycles or more of first-line cetuximab than in those with fewer than 14 cycles of first-line cetuximab (17.0 vs. 8.0

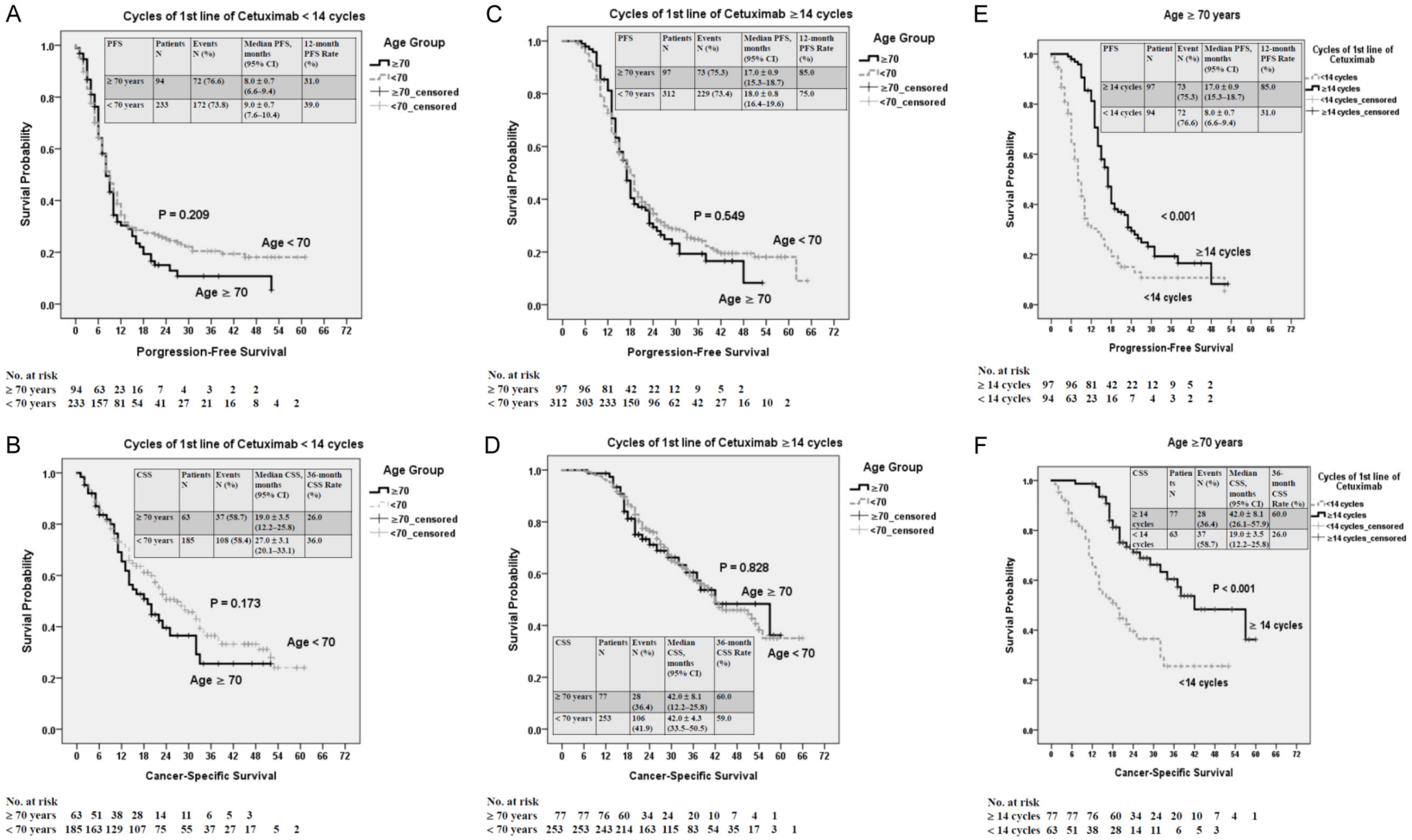

Figure 4. Kaplan-Meier survival curve for patients with mCRC stratified by age group and cycles of 1st line of cetuximab. A. Progression-free survival of patients with < 14 cycles of 1st line of cetuximab stratified by age group. B. Cancer specific survival of patients with < 14 cycles of 1st line of cetuximab stratified by age group. C. Progression-free survival of patients with ≥ 14 cycles of 1st line of cetuximab stratified by age group. D. Cancer specific survival of patients with ≥ 14 cycles of 1st line of cetuximab stratified by age group. E. Progression-free survival in patients ≥ 70 years stratified by treatment cycles (< 14 vs. ≥ 14) of 1st line of cetuximab. F. Cancer specific survival in patients ≥ 70 years stratified by treatment cycles (< 14 vs. ≥ 14) of 1st line of cetuximab.

Table 3. Adverse effects of patients according to age groups

	All grade			Grade 1-2			Grade ≥ 3		
	Age < 70 (N = 560)	Age ≥ 70 (N = 196)	*P*	Age < 70 (N = 560)	Age ≥ 70 (N = 196)	*P*	Age < 70 (N = 560)	Age ≥ 70 (N = 196)	*P*
Hematologic (overall)	287 (51.3%)	127 (64.8%)	0.001*	245 (43.8%)	99 (50.5%)	0.001*	41 (7.3%)	28 (14.3%)	0.113
Anemia	200 (35.7%)	100 (51.0%)	0.001*	171 (33.7%)	74 (37.8%)	0.012*	28 (5.0%)	26 (13.3%)	0.003*
Neutropenia	167 (29.8%)	77 (39.3%)	0.015*	133 (23.8%)	53 (27.0%)	0.154	33 (5.9%)	24 (12.2%)	0.145
Febrile neutropenia	6 (1.1%)	6 (3.1%)	0.056	3 (0.5%)	1 (0.5%)	0.989	3 (0.5%)	5 (2.6%)	0.116
Thrombocytopenia	26 (4.6%)	22 (11.2%)	0.001*	18 (3.2%)	18 (9.2%)	0.001*	8 (1.4%)	4 (2.0%)	0.773
Non-Hematologic (overall)	455 (79.5%)	160 (81.6%)	0.541	395 (70.5%)	131 (66.8%)	0.785	49 (8.8%)	29 (14.8%)	0.892
Skin reaction	355 (63.4%)	122 (62.2%)	0.753	315 (56.3%)	96 (49.0%)	0.324	39 (7.0%)	26 (13.3%)	0.266
Paronychia	129 (23.0%)	34 (17.3%)	0.093	117 (20.9%)	30 (15.3%)	0.176	12 (2.1%)	4 (2.0%)	0.266
Abdominal pain	47 (8.4%)	12 (6.1%)	0.302	43 (7.7%)	11 (5.6%)	0.441	4 (0.7%)	1 (0.5%)	0.415
Diarrhea	133 (23.8%)	57 (29.1%)	0.142	110 (19.6%)	44 (22.4%)	0.200	23 (4.1%)	13 (6.6%)	0.877
Nausea	214 (38.2%)	72 (36.7%)	0.701	193 (34.5%)	55 (28.1%)	0.253	21 (3.8%)	17 (8.7%)	0.177
Vomiting	165 (29.5%)	50 (25.5%)	0.302	143 (25.5%)	35 (17.9%)	0.077	22 (3.9%)	15 (7.7%)	0.549
Fatigue	241 (43.0%)	96 (49.0%)	0.155	210 (37.5%)	75 (38.3%)	0.395	31 (5.5%)	21 (10.7%)	0.403
Infusion reaction	8 (1.4%)	5 (2.6%)	0.303	6 (1.1%)	4 (2.0%)	0.258	2 (0.4%)	1 (0.5%)	0.879
Infection	15 (2.7%)	7 (3.6%)	0.527	8 (1.4%)	4 (2.0%)	0.484	7 (1.3%)	3 (1.5%)	0.623
ALT increased	58 (10.4%)	20 (10.2%)	0.946	46 (8.2%)	16 (8.2%)	0.827	12 (2.1%)	4 (2.0%)	0.266
AST increased	61 (10.9%)	21 (10.7%)	0.939	48 (8.6%)	18 (9.2%)	0.605	13 (2.3%)	3 (1.5%)	0.091
Bilirubin increased	17 (3.0%)	9 (4.6%)	0.384	14 (2.5%)	6 (3.1%)	0.577	3 (0.5%)	3 (1.5%)	0.494
Creatinine Increased	23 (4.1%)	21 (10.7%)	0.001*	15 (2.7%)	12 (6.1%)	0.015*	8 (1.47%)	9 (4.6%)	0.127
Hypomagnesemia	12 (2.1%)	5 (2.6%)	0.684	9 (1.6%)	3 (1.5%)	0.925	3 (0.5%)	2 (1.0%)	0.857

ALT: Alanine aminotransferase; AST: Aspartate Transaminase. *$P < 0.05$.

months, P < 0.001, **Figure 4E**). Similarly, the median duration of CSS was significantly longer in older patients with 14 cycles or more of first-line cetuximab than in those with fewer than 14 cycles of first-line cetuximab (47.0 vs. 19.0 months, P < 0.001, **Figure 4F**).

Safety analyses

Table 3 presents a summary of the safety profiles of the two age groups. The incidence of any-grade hematological AEs was significantly higher in the older age group than in the younger age group (64.8% vs. 51.3%, P = 0.001). In terms of hematologic severe adverse effects (SAEs), the older age group exhibited a significantly higher incidence of grade 3 or more severe anemia compared with the younger age group (13.3% vs. 5.0%, P = 0.003). However, no significant between-group differences were discovered in nonhematological any-grade AEs (81.6% vs. 79.5%; P = 0.541) or SAEs (14.8% vs. 8.8%, P = 0.892).

Discussion

In this study, we examined the efficacy and safety of first-line cetuximab and chemotherapy for patients aged 70 years and above with *RAS* wild-type mCRC. Our results indicated that the two investigated age groups (≥ 70 and < 70 years) had statistically similar PFS and CSS. No significant between-group difference was found in PFS or CSS, even if the results were stratified by synchronous versus metachronous mCRC and left-sided versus right-sided tumors. With the exception of grade 3 anemia or above, no significant between-group differences were discovered in other hematologic or nonhematologic SAEs.

In terms of demographic and clinicopathological characteristics, older patients were more likely to have a lower Eastern Cooperative Oncology Group performance score than younger patients. This finding is consistent with that of a previous study [22] but not with those of other studies [23, 24]. In the present study, we discovered no significant between-group differences in primary lesion site, which is consistent with the finding of a previous study [23] but not with that of Papamichael *et al.* [22]. We also discovered that, compared with younger patients, older patients were more likely to experience lung metastasis, which is consistent with the findings of two studies [22, 24]. In addition, we determined that liver metastasis was less

likely in older patients, which is consistent with the findings of one study [24] but not those of another study [23]. Moreover, we noticed no significant between-group differences were observed in two or more metastatic sites, which is consistent with the results of other studies [22-24]. In our previous study, we reported that patients who received 14 cycles or more of treatment had a significantly higher metastasectomy rate, as well as longer OS and PFS [25]. In the present study, no significant between-group difference was found in the ratio of patients who received 14 cycles or more of first-line cetuximab. However, in older patients, the median PFS and CSS were significantly longer for patients who received 14 cycles or more of first-line cetuximab than for those who received fewer than 14 cycles of first-line cetuximab. Therefore, we suggest that even older patients with mCRC receive more than 14 cycles first-line cetuximab to improve their survival outcomes.

In terms of treatment efficacy, the ORR and DCR were similar in the two age groups, consistent with the findings of studies reporting similar efficacy of cetuximab-based regimens in older versus younger patients with mCRC [19-21]. Although older patients had a significantly shorter DoR compared with younger patients (15.1 vs. 17.7 months, P = 0.016), the median PFS in the two groups was almost identical (14.0 vs. 14.0 months, P = 0.098). These results indicate that although older patients may experience a slightly shorter survival with cetuximab-based treatment, the effect of age on cancer survival outcomes of cancers is relatively weak.

Subgroup analyses based on metastatic status, tumor location, and number of cetuximab cycle count provided additional insights into the survival outcomes of our patients. Notably, no significant differences were discovered in survival outcomes (PFS and CSS) between the two age groups in patients with synchronous or metachronous mCRC, suggesting that older patients with different metastatic patterns respond to cetuximab similarly as younger patients. Analysis of tumor location (right-sided vs. left-sided colon tumors) revealed no significant difference in the survival outcomes between the two age groups, confirming that the biological behavior of a tumor may play a more major role than does age in a patient's prognosis.

In this study, we examined the safety profile of cetuximab-based chemotherapy. We discovered that the incidence of hematological AEs was significantly higher in older patients, particularly those with grade 3 or more severe anemia, than in younger patients (13.3% vs. 5.0%, P = 0.003). These findings suggest that older patients are at increased risk of hematologic toxicities, particularly anemia, a result of age-related changes in their bone marrow function and weaker ability to tolerate chemotherapeutic agents. However, no significant between-group differences were found in nonhematologic AEs, suggesting that the aforementioned increase in the risk of hematological toxicities is the primary safety concern in older patients undergoing cetuximab-based therapy.

Although, the incidence of hematologic AEs was higher in older patients than younger patients, the overall incidence of SAEs did not significantly differ between the two age groups. Our findings are consistent with those of previous studies 16, 28, 29 and they underscore the importance of carefully managing hematologic toxicities in older patients, who are often closely monitored for potential side effects. In older patients, monitoring the levels of hematologic toxicity should therefore be carefully considered when prescribing cetuximab. Clinicians may need to adjust the treatment regimen or provide supportive care to mitigate the risks.

This study has several limitations. First, although this study comprised of a large cohort of patients, it was a retrospective study with potential selection bias, which may have influenced the accuracy and reliability of the collected data. Second, our relatively small sample size of older patients (≥ 70 years) may have influenced the statistical power and generalizability of our findings. Third, other less common genes associated with patient's prognosis, such as *BRAF* and the associated with microsatellite instability, were not analyzed because of the lack of routine testing for these genes in hospitals. Therefore, future prospective studies with larger sample sizes are required to validate our findings.

In conclusion, cetuximab-based chemotherapy is effective for and well tolerated by both young-

er and older patients with *RAS* wild-type mCRC. Although older patients exhibit a slightly shorter treatment duration, their objective and disease control responses were comparable to those of younger patients, and the two age groups had similar CSS. Overall, our subgroup analysis suggests that age alone does not significantly affect patient's survival outcomes, particularly when adequate treatment is administered. However, older patients are typically at an increased risk of hematologic toxicities, which may necessitate more careful monitoring and potential adjustments to treatment regimen. These findings support the use of cetuximab-based chemotherapy in older patients with mCRC, provided that appropriate precautions are taken to manage the increased risk of toxicity. Further research focusing on the optimization of treatment strategies for older patients with mCRC is required to improve the outcomes of this growing patient population.

Acknowledgements

This work was supported by grants through funding from the National Science and Technology Council (MOST 111-2314-B-037-070-MY3, NSTC 112-2314-B-037-050-MY3, NSTC 113-2321-B-037-006, NSTC 113-2314-B-037-057, NSTC 114-2314-B-037-103-MY3, NSTC 114-2321-B-037-003) and the Ministry of Health and Welfare (MOHW113-TDU-B-222-134014) and funded by the health and welfare surcharge of on tobacco products, and the Kaohsiung Medical University Hospital (KMUH112-2R37, KMUH112-2R38, KMUH112-2R39, KMUH112-2M27, KMUH112-2M28, KMUH112-2M29, KMUH113-3R31, KMUH113-3R32, KMUH113-3R33, KMUH113-3M58, KMUH113-3M59, KMUH-S11303, KMUH-SH11309, KMUH-SH11327), Kaohsiung Medical University Research Center Grant (KMU-TC11-3A04) and National Tsing Hua University-Kaohsiung Medical University Joint Research Project (NTHU-KMU-KT114P008). In addition, this study was supported by the Grant of Taiwan Precision Medicine Initiative and Taiwan Biobank, Academia Sinica, Taiwan.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jaw-Yuan Wang, Division of Colorectal Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, No. 100 Tzyou 1st Road, Kaohsiung 80708, Taiwan. Tel: +886-7-3122805; Fax: +886-7-3114679; E-mail: cy6141-12@ms14.hinet.net; Jawyuanwang@gmail.com

References

[1] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024; 74: 229-263.

[2] Ministry of Health and Welfare, the Executive Yuan, Republic of China. Health and vital statistics [cited on 2025 Mar 1]. https://www.hpa.gov.tw/Home/Index.aspx.

[3] Arnold D and Stein A. New developments in the second-line treatment of metastatic colorectal cancer: potential place in therapy. Drugs 2013; 73: 883-891.

[4] Van Cutsem E, Nordlinger B and Cervantes A; ESMO Guidelines Working Group. Advanced colorectal cancer: ESMO clinical practice guidelines for treatment. Ann Oncol 2010; 21 Suppl 5: v93-7.

[5] Papamichael D, Audisio RA, Glimelius B, de Gramont A, Glynne-Jones R, Haller D, Köhne CH, Rostoft S, Lemmens V, Mitry E, Rutten H, Sargent D, Sastre J, Seymour M, Starling N, Van Cutsem E and Aapro M. Treatment of colorectal cancer in older patients: international Society of Geriatric Oncology (SIOG) consensus recommendations 2013. Ann Oncol 2015; 26: 463-476.

[6] Høydahl Ø, Edna TH, Xanthoulis A, Lydersen S and Endreseth BH. Long-term trends in colorectal cancer: incidence, localization, and presentation. BMC Cancer 2020; 20: 1077.

[7] Su WC, Huang CW, Ma CJ, Chen PJ, Tsai HL, Chang TK, Chen YC, Li CC, Yeh YS and Wang JY. Feasibility of robot-assisted surgery in elderly patients with rectal cancer. J Minim Access Surg 2021; 17: 165-174.

[8] Van Cutsem E, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, D'Haens G, Pintér T, Lim R, Bodoky G, Roh JK, Folprecht G, Ruff P, Stroh C, Tejpar S, Schlichting M, Nippgen J and Rougier P. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 2009; 360: 1408-1417.

[9] Heinemann V, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, Heintges T, Lerchenmüller C, Kahl C, Seipelt G, Kullmann F, Stauch M, Scheithauer W, Hielscher J, Scholz M, Müller S, Link H, Niederle N, Rost A, Höffkes HG, Moehler M, Lindig RU, Modest DP,

Rossius L, Kirchner T, Jung A and Stintzing S. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol 2014; 15: 1065-1075.

[10] Ocvirk J, Brodowicz T, Wrba F, Ciuleanu TE, Kurteva G, Beslija S, Koza I, Pápai Z, Messinger D, Yilmaz U, Faluhelyi Z, Yalcin S, Papamichael D, Wenczl M, Mrsic-Krmpotic Z, Shacham-Shmueli E, Vrbanec D, Esser R, Scheithauer W and Zielinski CC. Cetuximab plus FOLFOX6 or FOLFIRI in metastatic colorectal cancer: CECOG trial. World J Gastroenterol 2010; 16: 3133-3143.

[11] Benson AB, Venook AP, Al-Hawary MM, Arain MA, Chen YJ, Ciombor KK, Cohen S, Cooper HS, Deming D, Farkas L, Garrido-Laguna I, Grem JL, Gunn A, Hecht JR, Hoffe S, Hubbard J, Hunt S, Johung KL, Kirilcuk N, Krishnamurthi S, Messersmith WA, Meyerhardt J, Miller ED, Mulcahy MF, Nurkin S, Overman MJ, Parikh A, Patel H, Pedersen K, Saltz L, Schneider C, Shibata D, Skibber JM, Sofocleous CT, Stoffel EM, Stotsky-Himelfarb E, Willett CG, Gregory KM and Gurski LA. Colon cancer, version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2021; 19: 329-359.

[12] Benson AB, Venook AP, Al-Hawary MM, Azad N, Chen YJ, Ciombor KK, Cohen S, Cooper HS, Deming D, Garrido-Laguna I, Grem JL, Gunn A, Hecht JR, Hoffe S, Hubbard J, Hunt S, Jeck W, Johung KL, Kirilcuk N, Krishnamurthi S, Maratt JK, Messersmith WA, Meyerhardt J, Miller ED, Mulcahy MF, Nurkin S, Overman MJ, Parikh A, Patel H, Pedersen K, Saltz L, Schneider C, Shibata D, Skibber JM, Sofocleous CT, Stotsky-Himelfarb E, Tavakkoli A, Willett CG, Gregory K and Gurski LA. Rectal cancer, version 2.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2022; 20: 1139-1167.

[13] Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, Aranda Aguilar E, Bardelli A, Benson A, Bodoky G, Ciardiello F, D'Hoore A, Diaz-Rubio E, Douillard JY, Ducreux M, Falcone A, Grothey A, Gruenberger T, Haustermans K, Heinemann V, Hoff P, Köhne CH, Labianca R, Laurent-Puig P, Ma B, Maughan T, Muro K, Normanno N, Österlund P, Oyen WJ, Papamichael D, Pentheroudakis G, Pfeiffer P, Price TJ, Punt C, Ricke J, Roth A, Salazar R, Scheithauer W, Schmoll HJ, Tabernero J, Taïeb J, Tejpar S, Wasan H, Yoshino T, Zaanan A and Arnold D. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016; 27: 1386-1422.

[14] Morris VK, Kennedy EB, Baxter NN, Benson AB 3rd, Cercek A, Cho M, Ciombor KK, Cremolini C, Davis A, Deming DA, Fakih MG, Gholami S, Hong TS, Jaiyesimi I, Klute K, Lieu C, Sanoff H, Strickler JH, White S, Willis JA and Eng C. Treatment of metastatic colorectal cancer: ASCO guideline. J Clin Oncol 2023; 41: 678-700.

[15] Chen HH, Ke TW, Huang CW, Jiang JK, Chen CC, Hsieh YY, Teng HW, Lin BW, Liang YH, Su YL, Hsu HC, Kuan FC, Chou YH, Lin J, Lin BR, Chang YY and Wang JY. Taiwan society of colon and rectal surgeons consensus on mCRC treatment. Front Oncol 2021; 11: 764912.

[16] Bouchahda M, Macarulla T, Spano JP, Bachet JB, Lledo G, Andre T, Landi B, Tabernero J, Karaboué A, Domont J, Levi F and Rougier P. Cetuximab efficacy and safety in a retrospective cohort of elderly patients with heavily pretreated metastatic colorectal cancer. Crit Rev Oncol Hematol 2008; 67: 255-262.

[17] Gouverneur A, Salvo F, Berdaï D, Moore N, Fourrier-Réglat A and Noize P. Inclusion of elderly or frail patients in randomized controlled trials of targeted therapies for the treatment of metastatic colorectal cancer: a systematic review. J Geriatr Oncol 2018; 9: 15-23.

[18] Soler-González G, Sastre-Valera J, Viana-Alonso A, Aparicio-Urtasun J, García-Escobar I, Gómez-España MA, Guillén-Ponce C, Molina-Garrido MJ and Gironés-Sarrió R. Update on the management of elderly patients with colorectal cancer. Clin Transl Oncol 2024; 26: 69-84.

[19] Jehn CF, Böning L, Kröning H, Possinger K and Lüftner D. Cetuximab-based therapy in elderly comorbid patients with metastatic colorectal cancer. Br J Cancer 2012; 106: 274-278.

[20] Jehn CF, Böning L, Kröning H, Pezzutto A and Lüftner D. Influence of comorbidity, age and performance status on treatment efficacy and safety of cetuximab plus irinotecan in irinotecan-refractory elderly patients with metastatic colorectal cancer. Eur J Cancer 2014; 50: 1269-1275.

[21] Rouyer M, Fourrier-Réglat A, Smith D, Becouarn Y, Guimbaud R, Tubiana-Mathieu N, Robinson P, Jové J, Grelaud A, Noize P, Moore N and Ravaud A. Effectiveness and safety of first-line bevacizumab plus FOLFIRI in elderly patients with metastatic colorectal cancer: results of the ETNA observational cohort. J Geriatr Oncol 2016; 7: 187-194.

[22] Papamichael D, Lopes GS, Olswold CL, Douillard JY, Adams RA, Maughan TS, Van Cutsem E, Venook AP, Lenz HJ, Heinemann V, Kaplan R, Bokemeyer C, Chibaudel B, Grothey A, Yoshino T, Zalcberg J, De Gramont A and Shi Q. Efficacy of anti-epidermal growth factor receptor agents in patients with RAS wild-type metastatic colorectal cancer ≥70 years. Eur J Cancer 2022; 163: 1-15.

[23] Wells JC, Tu D, Siu LL, Shapiro JD, Jonker DJ, Karapetis C, Simes J, Liu G, Price TJ, Tebbutt NC and O'Callaghan CJ. Outcomes of older patients (≥70 Years) treated with targeted therapy in metastatic chemorefractory colorectal cancer: retrospective analysis of NCIC CTG CO.17 and CO.20. Clin Colorectal Cancer 2019; 18: e140-e149.

[24] Rosati G, Pinto C, Di Fabio F, Chiara S, Lolli IR, Ruggeri EM, Ciuffreda L, Ferrara R, Antonuzzo L, Adua D, Racca P, Bilancia D, Benincasa E, Stroppolo ME and Di Costanzo F. Quality of life, compliance, safety and effectiveness in fit older metastatic colorectal patients with cancer treated in first-line with chemotherapy plus cetuximab: a restrospective analysis from the ObservEr study. J Geriatr Oncol 2018; 9: 243-248.

[25] Chen CC, Chang SC, Chang YY, Lin BW, Chen HH, Hsieh YY, Hsu HC, Hsieh MC, Ke TW, Kuan FC, Wu CC, Lu WC, Su YL, Liang YH, Chen JB, Huang HY, Tsai HL and Wang JY. Survival benefit of metastasectomy in first-line cetuximab therapy in patients with RAS wild-type metastatic colorectal cancer: a nationwide registry. Am J Cancer Res 2023; 13: 6333-6345.

[26] Abdelwahab S, Azmy A, Abdel-Aziz H, Salim H and Mahmoud A. Anti-EGFR (cetuximab) combined with irinotecan for treatment of elderly patients with metastatic colorectal cancer (mCRC). J Cancer Res Clin Oncol 2012; 138: 1487-1492.

[27] Sastre J, Aranda E, Grávalos C, Massutí B, Varella-Garcia M, Rivera F, Soler G, Carrato A, Manzano JL, Díaz-Rubio E and Hidalgo M. First-line single-agent cetuximab in elderly patients with metastatic colorectal cancer. A phase II clinical and molecular study of the Spanish group for digestive tumor therapy (TTD). Crit Rev Oncol Hematol 2011; 77: 78-84.

[28] McCleary NJ, Hubbard J, Mahoney MR, Meyerhardt JA, Sargent D, Venook A and Grothey A. Challenges of conducting a prospective clinical trial for older patients: lessons learned from NCCTG N0949 (alliance). J Geriatr Oncol 2018; 9: 24-31.

[29] Tsai HL, Chen YC, Yin TC, Su WC, Chen PJ, Chang TK, Li CC, Huang CW and Wang JY. Comparison of UGT1A1 polymorphism as guidance of irinotecan dose escalation in ras wild-type metastatic colorectal cancer patients treated with cetuximab or bevacizumab plus FOLFIRI as the first-line therapy. Oncol Res 2022; 29: 47-61.

[30] Yeh YS, Tsai HL, Chen YC, Su WC, Chen PJ, Chang TK, Li CC, Huang CW and Wang JY. Effects of the number of neoadjuvant therapy cycles on clinical outcomes, safety, and survival in patients with metastatic colorectal cancer undergoing metastasectomy. Oncol Res 2023; 30: 65-76.

[31] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-247.